

RESEARCH ARTICLE

Effect of Gooseberry (*Physalis angulata*) Ethanol Extract in Wistar Rats Carrageenan-Induced Paw Oedema

Ami Nurlatifah,¹ Eka Hendryanny,² Yuniarti³¹Medical Undergraduate Study Program, Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia,²Department of Physiology, Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia,³Department of Anatomy, Faculty of Medicine, Universitas Islam Bandung, Bandung, Indonesia

Abstract

Gooseberry is an herbaceous plant that contains flavonoids. Flavonoid is one of the secondary metabolites that have an anti-inflammatory effect. This study aims to determine the effect of using ethanol extract of gooseberry as an anti-inflammatory in carrageenan-induced paw edema. This study was in vivo experimental laboratory using a completely randomized design of 25 Wistar rats and divided into five groups. The negative control group was given carboxymethylcellulose. The positive control group has given diclofenac sodium 27 mg/200 gBW. The sample test group has given ethanol extract of gooseberry with 3.6 mg/200 gBW, 5.4 mg/200 gBW, and 7.2 mg/200 gBW dosage. Paw rat's inflammation induced by injecting carrageenan and measured from 1st to 6th hour using a pletismometer. This study has conducted at Pharmacology Laboratory, Universitas Islam Bandung, and the Laboratory of Therapy and Pharmacology, Universitas Padjajaran, from June to September 2019. The result of average edema volume paw rats using the Kruskal-Wallis test on the 6th hour was $p=0.02$ ($p<0.05$). The Mann-Whitney test was $p<0.05$, showing differences between negative control and positive control and sample test groups. One-way ANOVA test on the percentage of edema inhibition between positive control and sample test group had $p=0.107$. It shows no significant difference. An effect of ethanol of extract of gooseberries as an anti-inflammatory with the highest percentage of edema inhibition is 5.4 mg/200 gBW dosage. The flavonoid content in gooseberries is thought to inhibit the formation of prostaglandins by inhibiting the cyclooxygenase enzyme. In conclusion, the ethanol extract of gooseberry can be anti-inflammatory.

Key words: Anti-inflammatory, diclofenac sodium, gooseberry ethanol extract, Wistar rat

Efek Ekstrak Etanol Ciplukan (*Physalis angulata*) terhadap Edema Telapak Kaki Tikus Galur Wistar yang Diinduksi Karagenan

Abstrak

Ciplukan adalah tanaman herbal yang mengandung flavonoid. Flavonoid merupakan salah satu metabolit sekunder yang dapat memberikan efek antiinflamasi. Penelitian ini bertujuan mengetahui pengaruh penggunaan ekstrak etanol *ciplukan* sebagai antiinflamasi pada tikus yang diinduksi karagenan. Penelitian ini merupakan penelitian laboratorium eksperimental *in vivo* menggunakan desain rancangan acak lengkap pada 25 ekor tikus galur Wistar yang terbagi ke dalam lima kelompok. Kelompok kontrol negatif diberi *carboxymethylcellulose*. Kontrol positif diberi sodium diklofenak 27 mg/200 gBB. Kelompok uji diberi ekstrak etanol *ciplukan* dengan dosis 3,6 mg/200 gBB; 5,4 mg/200 gBB; dan 7,2 mg/200 gBB. Induksi inflamasi dilakukan dengan menginjektikan karagenan pada telapak kaki tikus, lalu diukur menggunakan pletismometer dari jam ke-1 hingga jam ke-6. Penelitian ini dilakukan di Laboratorium Farmasi, Universitas Islam Bandung dan Laboratorium Farmasi dan Terapi, Universitas Padjajaran dari bulan Juni hingga September 2019. Volume rerata telapak kaki tikus pada jam ke-6 menggunakan Uji Kruskal-Wallis adalah $p=0,02$ ($p<0,05$). Hasil Uji Mann-Whitney diperoleh $p<0,05$ yang menunjukkan terdapat perbedaan bermakna antara kontrol negatif dan kontrol positif serta kelompok uji. Uji *one-way* ANOVA pada persentase penghambatan edema antara kontrol positif dan kelompok uji diperoleh $p=0,107$ yang menunjukkan tidak terdapat perbedaan yang bermakna. Terdapat pengaruh ekstrak etanol *ciplukan* sebagai antiinflamasi dengan persentase penghambatan edema tertinggi pada dosis 5,4 mg/200 gBB. Kandungan flavonoid pada *ciplukan* diduga mampu menghambat pembentukan prostaglandin dengan menghambat enzim siklooksigenase. Simpulan penelitian ini adalah ekstrak etanol *ciplukan* dapat digunakan sebagai antiinflamasi.

Kata kunci: Antiinflamasi, ekstrak etanol *ciplukan*, sodium diklofenak, tikus galur Wistar

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Correspondence: Ami Nurlatifah. Medical Undergraduate Study Program, Faculty of Medicine, Universitas Islam Bandung. Jln. Tamansari No. 22, Bandung 40116, West Java, Indonesia. E-mail: ami19nurlatifah@gmail.com

Introduction

The human body has a protective response to the dangerous agent that works when there is an infection, physical pressure, and injury. The protection response is called inflammation. Inflammation is signed by rubor, calor, dolor, tumor, and functio laesa. Several studies have provided evidence that inflammation is involved in the pathogenesis of various diseases, including aging, cancer, and cardiovascular dysfunction. Inflammation can be divided into acute and chronic phases. Acute inflammation cannot be sustainable because it can cause a chronic condition that triggers the chronic inflammatory disease. Chronic inflammation that arises in certain areas can result in a dangerous disease, such as if it occurs in a blood vessel, it will increase the risk of atherosclerosis. If it occurs in the joint area, it can cause rheumatic disease.¹⁻¹¹

It is necessary to use anti-inflammatory to reduce the sign of inflammation and tissue damage. Anti-inflammation commonly used in modern medicine is divided into two different types: glucocorticoid and nonsteroidal anti-inflammatory drugs (NSAIDs). Diclofenac sodium is one of the NSAIDs types commonly used, but this one can cause ulceration in the digestive tract and inhibit blood coagulation if consumed for long periods.¹²⁻¹⁵

Many people choose to use bioactive molecular medicinal plants in medicine throughout the country, especially in rural areas in developing countries with low socio-economic factors that make it difficult to access the health care system and modern medicines. One of the medicinal plants which have anti-inflammatory properties is gooseberry (*Physalis angulata*).^{16,17}

Gooseberry is an herbaceous plant that is easily obtained and can be purchased at low prices in Indonesia. All of the gooseberries, such as the roots, stems, fruits, and leaves, are rich in chemical compounds beneficial for therapy. The content of gooseberry, which provides an anti-inflammatory effect, comes from flavonoids. Flavonoids are secondary metabolites formed through fatty acid metabolism that can inhibit the cyclo-oxygenase (COX) enzyme. Flavonoids also inhibit xanthine oxidase (XO), lipoxygenase, and phosphoinositide-3-kinase.¹⁶⁻²⁰

One study mentioned that ethanol had the highest percentage in attracting active flavonoid substances from gooseberry.¹⁰ For this reason, this

research use ethanol as a solvent from gooseberry extract. Based on this background, the purpose of this study was to determine the effect of ethanol extract of gooseberry as an anti-inflammation in carrageenan-induced rats, to know the concentration of ethanol extract of gooseberry, which faster to eliminate inflammation, and to analyze the difference of anti-inflammatory effects between ethanol extract of gooseberry and diclofenac sodium on carrageenan-induced paw edema in Wistar rats.

Methods

The research was conducted from June to September 2019 after received ethical clearance from the Health Research Ethics Committee of Faculty Medicine, Universitas Islam Bandung, Number: 039/Komite Etik FK/IV/2019. This research method was purely in vivo experiments conducted in a laboratory using a complete randomized design. It began with collecting gooseberry plant from Yogyakarta and then determining it in Institut Teknologi Bandung by a process called determination plants to ensure the plants were *Physalis angulata* species. The gooseberry ethanol extract was made using one kilogram of dried gooseberry leaves processed into powder using an electric blender and dissolved with 95% ethanol in 3 days. The extract filtered then evaporated using a vacuum rotary evaporator to separate the solvent from the extract. This process is repeated three times, with the result was a brown paste. The phytochemical screening was conducted in Pharmacology Laboratory Universitas Islam Bandung to ensure that the extract contained flavonoids. In this study, both extract ethanol of gooseberry and diclofenac sodium diluted with carboxymethyl cellulose 0.5% to make sure it had a similar liquid type with the negative control group. The suspension of λ carrageenan was from the Laboratory of Therapy and Pharmacology Universitas Padjajaran. It is made from 5-gram carrageenan powder and diluted with 500 mL saline 0.9%. Randomization of 25 rats used paper shuffle for five numbers of groups and five numbers of rats. The adaptation rats' period was carried out for seven days on the cage in the Laboratory of Therapy and Pharmacology Universitas Padjajaran with research standards, 12 hours in a dark room and 12 hours in a bright room. It was given standard feed and water. A

day after the rats' adaptation period completed, the study was carried out by conducting initial measurements on the volume of rats paw, followed by 0.5% carboxymethylcellulose administration with 2 mL/200 gBW to the negative control group, sodium diclofenac 27 mg/200 gBW to the positive control group, and gooseberry ethanol extract with the dosages of 3.6 mg/200 gBW, 5.4 mg/200 gBW, and 7.2 mg/200 gBW to the first, second and third groups. Thirty minutes after oral treatment, all of the rats were induced to inflammation by injecting 0.1 mL subplantar carrageenan (Figure 1).

The measurements were retaken after carrageenan induction and continued every hour, started from the first hour until 6 hours after carrageenan induction.²¹⁻²⁴ After all the research step was done, to fulfill a good animal ethical procedure, the rats have been euthanasia with injected 1 mL of ketamine then buried the rats.

The results were displayed by the average edema volume of rats paw in the 1st, 2nd, 3rd, 4th, 5th, and 6th hours. The study's normality used the Shapiro-Wilk test, and the homogeneity used the Levene test on IBM SPSS statistics 25 application with a confidence interval of 95%. The normal and homogenous data used a one-way ANOVA test, while the abnormal nor homogenous data used the Kruskal-Wallis test. The Mann-Whitney test tested the significant result of Kruskal-Wallis..

Results

Institut Teknologi Bandung gave the result of the determination, and it showed the gooseberry's type we brought was *Physalis angulata*. The production of ethanol extract of gooseberry was carried out in the Laboratory of Therapy and Pharmacology Universitas Padjajaran, followed by a phytochemical screening in Pharmacology Laboratory Universitas Islam Bandung, which showed that the extract contained flavonoid. Research on the anti-inflammatory activity of ethanol extract of gooseberry was conducted on 25 carrageenan-induced male Wistar rats. All of the anti-inflammatory samples tests were given 30 minutes before carrageenan induction to see the percentage of edema inhibition and the measurement as in Figure 2.

The measurements were taken every hour for 6 hours by dipping the paw rats into the tube of the pletismometer. The measurement result of the paw rat volume was in Table 1.



Figure 1 Injection of Carrageenan



Figure 2 Measurement of Paw Rats Volume

In the 4th hours, the rat's paw volume from all groups was at the edema peak. The volume of paw rats in the positive control group, the first sample test, the second sample test, and the third sample test decreased than the negative control group at the 6th hours. Comparing the average paw rat volume at the initial measurements and the 6th hours showed the highest increase in the negative control group and the lowest in the second sample test group. There was a difference in rat paw edema volume of about two μ L between the second sample test group and the positive control group.

Table 1 Result of Paw Rat Volume Measurement

Rat Groups	Volume of Rat Paw (µL)							
	IM*	BCI**	Hour					
			1	2	3	4	5	6
Negative control	56.0±13.4	80.0±12.3	108.0±16.4	114.0±8.2	122.0±13.0	134.0±8.9	128.0±13.0	132.0±16.4
Positive control	82.0±8.4	96.0±8.9	124.0±11.4	122.0±13.0	116.0±13.4	132.0±8.4	114.0±11.4	104.0±5.5
1 st sample test	70.0±10.0	96.0±13.4	124.0±16.7	124.0±15.2	122.0±14.8	128.0±19.2	120.0±12.3	104.0±8.9
2 nd sample test	76.0±5.5	90.0±7.1	112.0±14.8	114.0±15.2	118.0±16.4	124.0±16.7	110.0±12.3	100.0±12.3
3 rd sample test	64.0±11.4	82.0±8.4	100.0±7.1	106.0±5.5	114.0±11.4	124.0±8.94	110.0±7.2	102.0±4.5

Note: *initial measurement, **before carrageenan induction

Based on Table 1, it can be calculated the percentage of the average edema inhibition on the rat paw through the formula:²⁵

$$\% \text{ edema inhibition average} = \left\{ 1 - \left(\frac{a-x}{b-y} \right) \right\} \times 100\%$$

Description: a=the rat's paw average volume at a certain hour in the positive control group and the test group, x=the rat's paw average volume at the positive control group's initial measurements and the test group, b=the rat's paw's average volume at a certain hour in the negative control group, y=the average volume of the rat's paw at the negative control group's initial measurements

The percentage of rat's paw edema inhibition is shown in Figure 3.

In Figure 3, in the 1st hours of measurement, the highest percentage of inhibition came from the second sample test group (30.77%) and the third sample test (30.77%), followed by the positive control group (19.23%) and the first sample test group (-3.85%). While the edema peaked in the 4th hours, the percentage edema inhibition in the positive control group (35.9%) and the third sample test (23.08%) decreased.

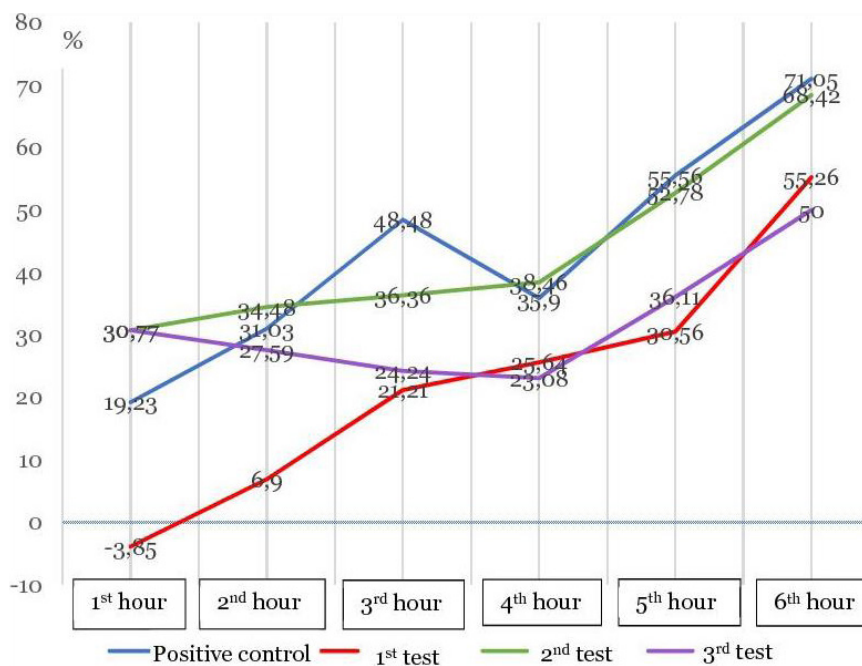


Figure 3 Percentage of Paw Rat Edema Inhibition

Table 2 Volume Difference on Paw Rats

Measurement Time	p*	p**
1 st		0.068
2 nd		0.260
3 rd	0.855	
4 th		0.651
5 th		0.100
6 th		0.022

Note: *one-way ANNOVA test, $p < 0.05$ significant, **Kruskal-Wallis test, $p < 0.05$ significant

However, it turned back to the extreme increase in edema inhibition until the last hour, followed by the second sample test group (68.47%). In the 5th hours, the first sample test group's percentage edema inhibition increased (30.56%). In the 6th hours, the positive control group (71.05%) showed the highest percentage of edema inhibition, followed by the second sample test group (68.42%), the first sample test (55.26%), and the third sample test (50%). When the sample test compared to the positive control, the first sample test group's edema inhibition rate was 16% lower than the positive control. The second sample test was 3% lower than the positive control, and the third sample test was 21% lower than the positive control.

The normality and homogeneity tests were performed on the edema volume. It showed normal and homogeneous distributed data only in the third hour. Then one-way ANOVA test was performed with a value of $p = 0.855$ ($p < 0.05$), which meant there was no significance. In the 6th hour measurement, data were not distributed normally nor homogenous, and it continued with the Kruskal-Wallis test with p value = 0.022 ($p < 0.05$). The difference between the one-way ANOVA test and the Kruskal-Wallis test in Table 2. Data in the 6th hour had a significant result—the Mann-Whitney test showing a significant difference between negative control and positive control and sample test groups. Also, there was no significant difference between the positive control and sample test group.

The normality and homogeneity tests were also performed on the edema inhibition percentage data, and the results showed normal and homogeneous distribution. A one-way ANOVA test was then performed with a value of $p = 0.107$ ($p < 0.05$), which meant no significant difference

from the percentage of inhibition edema in the positive control group with the first, second and third sample tests group. It showed that ethanol extract of gooseberry provides anti-inflammatory effects such as diclofenac sodium.

Discussion

Induction of inflammation using carrageenan on the paw to make edema. In Table 1, the volume of the paw increased immediately after carrageenan injection. The peak of edema occurs at the 4th hour when carrageenan triggers maximal prostaglandin release. The process consists of the first phase mediated by histamine and 5-hydroxytryptamine, followed by a second phase mediated by kinin triggering the activation of the enzyme cyclooxygenase and the third phase of local prostaglandin production. The prostaglandin precursor is a derivative of arachidonic acid, which is activated by the enzyme cyclooxygenase.^{2,3}

Gooseberry is an herbaceous plant that has various substances, one of that is a flavonoid.^{15,17,18} The role of flavonoids in inhibiting the cyclooxygenase enzyme can be used as an anti-inflammatory. Flavonoid will break the chain of inflammation by inhibiting the cyclooxygenase enzyme so that prostaglandins will not be formed. Flavonoid is COX-2 selective, so it can be used as an anti-inflammatory that reduces the effects of ulceration in the digestive tract and bleeding.³ In bio-molecular studies, the marker used in anti-inflammatory testing is nuclear factor-kappaB (NF- κ B). Research shows the content of physalin E (a type of secosteroid that can form flavonoids through fatty acid metabolism in physalis plants (gooseberry) can inhibit the transcription factor NF- κ B which plays an essential role in the inflammatory process. When NF- κ B bind to tumor necrosis factor- α (TNF- α) and interferon- γ (IFN- γ), it can induce the transcription of pro-inflammatory genes, so that inhibition of NF- κ B can prevent inflammation. These studies support that the reduced edema volume in the sample test group comes from flavonoid in ethanol extract of gooseberry.²⁶

Gooseberry (*Physalis angulata*) has active substances such as physalin 9 and 10 that act as antiproliferative, and physalin 1, 3, 4, 9, 10, 13, 14, 16 act as an anti-inflammatory which works by inhibiting the production of nitrite oxide. The damage of deoxyribonucleic acid (DNA) and cell membranes is mediated by nitric oxide to trigger

nuclear pro-inflammatory cytokines, which can activate and recruit inflammatory cells. If nitric oxide production is inhibited, the inflammatory process can be stopped.²⁷

Dosage of 400 mg/kgBW of methanol extract of gooseberries by Ukwubile and Oise¹⁸ showed the same anti-inflammatory effect as ethanol extract of gooseberries in this research. The percentage of edema inhibition produced in Ukwubile and Oise's¹⁸ study was 62.7%. This is different from the research results that gooseberry's ethanol extract gave the highest percentage of edema inhibition, with 68.4% from the second sample test group given a dosage of 5.4 mg/200 gBW (300 mg/kgBW). It can be caused by the differences in the solvent so that the binding of flavonoids non-optimal.

Conclusions

We conclude an anti-inflammatory effect of ethanol extract of gooseberry on carrageenan-induced paw edema in Wistar rats. There was no significant difference between the diclofenac sodium group and the gooseberry ethanol extract, which meant both had anti-inflammatory effects on edema.

Conflict of Interest

There is not any conflict of interest in this research.

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