Research Article

Anti-inflammatory and antidiabetic of *Channa striata* powder and *Nephelium lappaceum* fruit peel ethanolic extracts on albino Wistar mice

Andi Suhendi[1], Muhtadi Muhtadi[1]*, Em. Sutrisna[2]

ABSTRACT

Aim: *Channa striata* powder (CSP) and *Nephelium lappaceum* fruit peel extract (NLPE) were studied for anti-inflammatory and antidiabetic activities. **Materials and Methods:** The investigations on albino Wistar mice for anti-inflammatory action by injecting 0.2 ml of 2% w/v carrageenan sodium subcutaneously in the sub-plantar of the mice right hind paw. Meanwhile, antidiabetic activity performed on animal model diabetic by injected alloxan. **Result:** The results showed that CSP, NLPE, and their combinations at dose 150 mg/kg.bw proved to significantly decreased the volume of mouse foot edema ($P < 0.05$). Antidiabetic activity of the combination had best activity of lowering blood glucose level of 55.6%, while CSP and NLPE could decrease blood glucose level successively 27.4% and 71.2% in mice alloxan-induced diabetic. **Conclusion:** The combination of CSP and NLPE has anti-inflammatory effect lower than a single extract, has antidiabetic activity in alloxan induced mice but did not show synergistic effect.

KEY WORDS: Antidiabetic activity, Anti-inflammatory activity, *Channa striata*, *Nephellium lappaceum*

INTRODUCTION

Inflammation is a normal response to tissue injury caused by physical trauma, hazardous chemicals, and microbiological agents. Inflammation is the body's attempt to activate invading organisms, eliminate wounds, and preparation for improvement in tissues.[1] Somchit *et al*.[2] stated that snakehead fish had activity as an inhibitor of chronic inflammation. The compounds in snakehead fish that play a role are albumin and fatty acids.[3,4] These compounds are able to reduce the production of pro-inflammatory cytokines, inhibit cyclooxygenase enzymes and inhibit the formation of nitric oxide (NO).[5,6] Research conducted by Hassan[7] resulted that snakehead fish extract could inhibit prostaglandin D2-induced edema by 78.7%. Meanwhile, rambutan fruit peel's extract, which was found to contain high phenolic compounds (anthocyanins, flavonoids, tannins, ellagic acid, corilagin, and geraniin), has antioxidant and anti-inflammatory activities.[8] Ellagic acid had activity in reduce cyclooxygenase-2 induction by decreasing Interleukin (IL)-6 levels and increasing IL-10 levels in acute inflammation.[9] Chao *et al*.[10] stated that ellagic acid could reduce pro-inflammatory cytokines, namely, IL-1β, IL-6, TNF-α, and monocyte chemoattractant protein-1. Thus, snakehead fish extract and rambutan fruit peel extract have anti-inflammatory activity with different mechanisms, and a combination of both extracts would be expected to have a better anti-inflammatory agent.

On the other hand, diabetes mellitus is a degenerative disease with increasing prevalence rates, particularly in Indonesia, in which around 50% cases have not been diagnosed.[11] The increasing incidence of diabetes has an impact on the decline in the quality of life of the community and health costs.[11] Muhtadi *et al*.[12] reported that rambutan fruit peel's extract has the potential as an antidiabetic. Rambutan fruit peel's extract has the action as an inhibitor of α-amylase and α-glucosidase.[13] Snakehead fish extract was also reported to have activity in lowering blood glucose levels. Based on the mechanism of action, the extract

Access this article online

Website: jprsolutions.info | ISSN: 0975-7619

[1]Depatment of Pharmaceutical Chemistry, Faculty of Pharmacy, Universitas Muhammadiyah Surakarta, Jl. A. Yani Tromol Pos I, Kartasura, Surakarta, Indonesia, [2]Department of Pharmacology, Faculty of Medicine, Universitas Muhammadiyah Surakarta, Jl. A. Yani Tromol Pos I, Kartasura, Surakarta, Indonesia

***Corresponding author:** Muhtadi Muhtadi, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Universitas Muhammadiyah Surakarta, Jl. A. Yani Tromol Pos I, Pabelan, Kartasura, Surakarta 57102, Indonesia. E-mail: muhtadi@ums.ac.id

Received on: 21-03-2019; Revised on: 24-05-2019; Accepted on: 21-06-2019

could regenerate pancreatic Langerhans Island tissue.[14] Therefore, based on these facts, the research was aimed to determine the anti-inflammatory and antidiabetics activities of a combination of snakehead fish and rambutan fruit peel's extracts as herbal medicine.

MATERIALS AND METHODS

Materials

Spektrofotometer ultraviolet (UV)-visible (Star Dust MC 15), glassware, scalpel no.20, analytical balance (Ohaus), micropipette, vortex, centrifuge Minispin (Eppendorf), rotary evaporator, snakehead fish extract (CV. Jadiid Herbal Solo), rambutan fruit peel extract, mice (Wistar, 2–3 months and weight 180–300 g from Rumah Tiput Klaten), aloksan (Sigma-Aldrich), glibenclamide (PT. First Medipharma), reagent kit *Glucose* PAP SL (ELITech Clinical System).

Methods

This study was an experimental study with post-test with control group design method using five treatment groups, Group I as a negative control was given 0.5% CMC, Group II as a positive control was given diclofenac sodium dose of 4.5 mg/kg BW, Group III was given snakehead fish extract, Group IV was given rambutan fruit peel extract, and Group V was given a combination of snakehead fish extract and rambutan fruit peel extract. The induction of inflammation was using carrageenan 2%, whereas diabetic mice model was induced by alloxan 150 mg/kgBW intraperitoneal.

Mice were divided into five groups, namely, negative control was given 0.5% CMC-Na solution, positive control was given a dose of 4.5 mg/kgBW of diclofenac sodium, *Channa striata* powder (CSP) at dose 150 mg/kgBW, group *Nephelium lappaceum* fruit peel extract (NLPE) at dose 150 mg/kgBW, and group combination of CSP and NLPE at dose 150 mg/kgBB.

After 30 min, the treatment was injected with 0.2 mL subplantar carrageenan 2%; the volume of edema of rat feet was measured with a plethysmometer shortly after induction and every 1 h for 6 h.

Blood glucose levels are read every 24 h until day 4. Mice were considered to be diabetic if in the 4th-day blood glucose level was > 200 mg/dL. The hyperglycemic mice were divided into five groups, namely:

Group negative control was given 2.5 mL aquadest p.o
Group positive control was given glibenclamide 5 mg/kgBW
Group CSP at dose 300 mg/kgBW
Group NLPE at dose 300 mg/kgBW
Group combination of CSP: NLPE (1:1) at dose 300 mg/kg BW.

The treatment was given p.o for 10 days, and the blood glucose level of the test animals was read again every 3 × 24 h.

A total of 0.5 mL of blood was taken from the lateral vein of the tail of mice and then centrifuged at a speed of 13,400 rpm. A total of 5 µL of the supernatant was put into the cuvette, and glucose PAP SL reagent was added as much as 500 µL, then incubated for 10 min. The solution was read using a UV-visible spectrophotometer (Star Dust MC 15 Diasys).

Data Analysis

Data on blood glucose levels were tested for normality distribution and homogeneity. The data obtained were normally distributed and homogeneous ($P > 0.05$) then followed by analysis of variance (ANOVA). Baseline blood glucose data, pre-test, and post-test were tested with a paired sample *t*-test. The percentage decrease in blood glucose levels is calculated using the formula:

$$\%\text{Reduction glucose level} = \frac{\text{Blood glucose level (at pretest} - \text{postest)}}{\text{Blood glucose level at pretest}} \times 100\%$$

The volume of edema is calculated from the difference in volume of the rat's feet before and after carrageenan induction. The results of the edema volume calculated by the area under the curve (AUC) value versus time of observation. The AUC value is calculated based on the trapezoid method.

$$AUC_{tn-1}^{tn} = \frac{Vtn-1+Vtn}{2}$$

Information:

Vtn–1 = Average edema volume in tn–1
Vtn = Average edema volume at n
Percentage of anti-inflammatory power (inhibition of edema volume) is calculated by the formula:

$$\%\text{ Anti-Inflammatory Power} = \frac{(AUC_{0\text{-}x})0 - (AUC_{0\text{-}x})n}{(AUC_{0\text{-}x})0} \times 100$$

Information:

0 = AUC negative control average
n = AUC for the treatment group in each individual.

RESULTS AND DISCUSSION

Preliminary tests showed that maximum formation of edema volume in the 5th h [Figure 1]. This finding was consistent with previous studies, namely, edema

develops rapidly 3 h after induction and persists at maximum volume about 5 h after induction.[15,16] In this study, the measurement of edema volume was carried out until the 6th h because, according to Rosa[17], carrageenan triggers release of inflammatory mediators through three phases. The third phase releases inflammatory mediators until the 6th h.

The results of the anti-inflammatory activity test [Table 1] showed that the treatment groups had AUC_{0-6} values smaller than the negative control. It could be concluded that the extract has an effect to reduce edema volume. Based on statistical tests showed that diclofenac sodium, CSP, NLPE, and combination showed significantly different results ($P < 0.05$) compared with negative controls.

The percentage of anti-inflammation power of diclofenac sodium had a greater value than the three extract groups; value was 44.70 ± 6.17%. Statistical tests showed that CSP, NLPE, and the combination not significant to diclofenac sodium ($P > 0.05$). It can be said that the effect of the three treatment groups was the same as diclofenac sodium. NLPE has several compounds that are efficacious as anti-inflammatory. Phytochemical tests conducted by Muhtadi *et al*.[12] stated that NLPE has flavonoid and phenolic compounds. Ethanol extract of rambutan fruit peel contains quercetin, geranin,[13] and elagitanin.[8] Previous research said that quercetin could inhibit cyclooxygenase-2[18] and ethyl gallate can inhibit NO formation by weakening inducible nitrite oxide synthetase activity.[19] The combination of CSP and NLPE did not show an increase in anti-inflammatory activity compared to a single extract. It could be due to interactions between quercetin and albumin, which bond affinity was strong.[20]

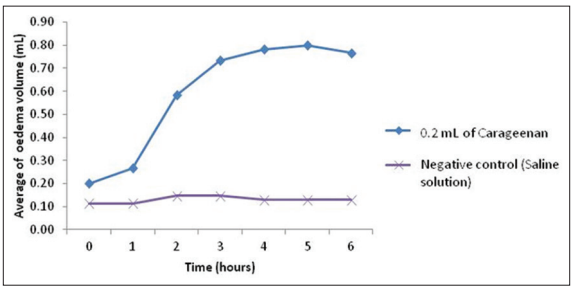

Figure 1: Profile of edema volume of mice after induction of carrageenan and control

Data on measurements of rat blood glucose levels are shown in Table 2. Based on these data, the combined extract reduced blood glucose levels to 123.3 ± 15.5 mg/dL.

Based on the paired *t*-test with $P < 0.05$, there was a significant difference in the group before treatment (pre-test) and after treatment (post-test) based on one-way ANOVA test showed significant results ($P < 0.05$) on day 9. The oral administration of extract CSP and NLPE on diabetic mice showed significant differences in blood glucose levels with negative control. The results of decreasing blood glucose levels between treatments were not significantly different from the glibenclamide, so it can be concluded that the activity CSP, NLPE, and their combination were the same as glibenclamide.

Based on Figure 2, the percentage of decreasing blood glucose levels from high to low, respectively, were glibenclamide, combination of CSP and NLPE, NLPE, and CSP. A combination of CSP-NLPE was expected to increase its anti-diabetic activity, but it is no better than the NLPE.

Table 1: AUC values and percentage of anti-inflammation power of treatment

Treatment	Average of AUC (mL.h) (±SEM)	Average of anti-inflammation power (%) (±SEM)
Negative control (CMC 0,5%)	2.29±0.31	-
Diclofenac sodium at dose 4.5 mg/kgBW	1.27±0.14*	44.70±6.17
CSP at dose 150 mg/kgBW	1.69±0.19*	26.25±8.48
NLPE at dose 150 mg/kgBW	1.37±0.13*	40.17±5.82
Combination CSP- NLPE at dose 150 mg/kgBW	1.60±0.15*	30.14±6.42

CSP: *Channa striata* powder, NLPE: *Nephelium lappaceum* fruit peel extract. SEM: Standard Error of Mean *Statistically different (P<0,05) with negative control

Table 2: Average of the blood glucose level of diabetic mice (mg/dL) (n=3)

Groups	Baseline (mg/dL)	Pre-test (post aloksan) (mg/dL)	Post-test (mg/dL)		
			Days at 3	Days at 6	Days at 9
Negative control	105.7±5.5	412.7±75.9	249.0±20.7	196.0±15.7	315.7±17.8
Glibenclamide	107.0±4.6	562.3±68.8	280.0±137.3	257.7±140.1	118.7±31.1
CSP at dose 300 mg/kgBW	85.0±15.0	217.0±15.5	220.7±98.3	172.0±10.6	157.0±2.0
NLPE at dose 300 mg/kgBW	95.0±14.5	515.0±106.1	205.7±56.6	247.0±172.4	150.0±67.1
Combination of CSP- NLPE at dose 300 mg/kgBW	115.0±19.2	286.0±62.4	171.7±30.9	155.3±20.2	123.3±15.5

CSP: *Channa striata* powder, NLPE: *Nephelium lappaceum* fruit peel extract

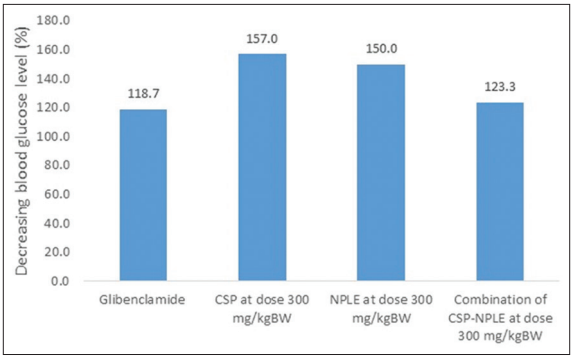

Figure 2: Percentage of decreasing of the blood glucose level of glibenclamide, CSP, NLPE, and their combination at days 9

The ability of CSP in decreasing blood glucose activity was due to the content of amino acid compounds, arginine, and leucine, which plays a role in the regulation of blood glucose levels.[21] Amino acids reduce post-prandial plasma glucose without changes in plasma insulin levels.[22] Stancic *et al*.[23] explained that L-arginine improves beta-cell function, energy expenditure, and insulin sensitivity. Leucine plays a role in gene transcription and protein synthesis in pancreatic beta cells.[24] Leucine increases insulin secretion and improves glycemic control in humans and mice of type 2 diabetes.[24] Albumin also reported has antioxidant activity with the action of multiple-binding sites and capturing free radicals.[25] Antioxidants will reduce the rate of lipid peroxidation and thiobarbituric acid reactive substance.[26] In addition, albumin can also repair damaged pancreatic beta cells by regenerating them.[14]

NLPE contains high phenolic compounds,[27] which could act as antioxidants and hypoglycemic.[26] The mechanism of plants that have potential as antidiabetic works through inhibiting carbohydrate hydrolysis and absorption of glucose, increasing insulin by regenerating pancreatic beta cells, inhibiting aldol reductase, and controlling blood glucose levels. The other compounds were flavonoids, isolate isoflavones.[28] Vinayagam and Xu[29] explained that the antidiabetic activity of flavonoids works by repairing beta cells, reducing insulin resistance, reducing glucose auto-oxidation, thereby reducing free radicals and lipid peroxidation and regulating carbohydrate metabolism. Ellagic acid[8] increases glucose uptake and reduces glucose transport.[30] Ellagic acid can normalize parameters: Insulin and peptide-C, plasma glucose, glycogen and carbohydrate metabolic enzymes, hemoglobin, and glycosylated hemoglobin.[31] Geranin was known have greater antioxidant activity than butylated hydroxyanisole and 2,2-diphenyl-1-picrylhydrazyl[8] and also could inhibit the enzymes α-glucosidase and α-amylase, aldol reductase and the formation of AGEs.[13] With these three abilities, geranin can reduce blood glucose levels.

CONCLUSION

1. The combination of CSP and NLPE has a lower effect than a single extract with a percentage of anti-inflammatory power 30.14 ± 6.42 and 40.17 ± 5.82, respectively
2. The combination of CSP and NLPE at dose 300 mg/kgBW has antidiabetic activity in alloxan-induced mice
3. The combination of CS and NLP did not show synergistic effect.

REFERENCES

1. Finkel R, Clark AM, Luigi XC. Farmakologi. Jakarta: EGC; 2013.
2. Somchit MN, Solihah MH, Israf DA, Zuraini A, Kadir AA, Jais AM. Effects of three local Malaysian *Channa* spp. Fish on chronic inflammation. Orient Pharm Exp Med 2004;4:91-4.
3. Dahlan-Daud CK, Jais AM, Ahmad Z, Akim AM, Adam A. Amino and fatty acid compositions in haruan traditional extract (HTE). Bol Latinoam Caribe Plantas Med Aromáticas 2010;9:414-29.
4. Mustafa A, Widodo MA, Kristianto Y. Albumin and zinc content of snakehead fish(*Channa striata*) extract and its role in health. Int J Sci Technol 2012;1:1-8.
5. Paliliewu N, Datau E, Matheos J, Surachmanto E. *Channa striatus* capsules induces cytokine conversion in pulmonary tuberculosis patients. J Exp Integr Med 2013;3:237.
6. Lee JY, Lee HJ, Jeong JA, Jung JW. Palmitic acid inhibits inflammatory responses in lipopolysaccharide-stimulated mouse peritoneal macrophages. Orient Pharm Exp Med 2010;10:37-43.
7. Hasan I, Indra TA. Peran albumin pada penyakit kritis, dalam konsensus pemberian albumin pada sirosis hati. Maj Med 2008;21:3-6.
8. Thitilertdecha N, Teerawutgulrag A, Kilburn JD, Rakariyatham N. Identification of major phenolic compounds from *Nephelium lappaceum* L. And their antioxidant activities. Molecules 2010;15:1453-65.
9. Favarin DC, Teixeira MM, Andrade EL, Alves C, Chica JE, Sorgi CA, *et al*. Anti-inflammatory effects of ellagic acid on acute lung injury induced by acid in mice. Mediators Inflamm 2013;2013:1-13.
10. Chao PC, Hsu CC, Yin MC. Anti-inflammatory and anti-coagulatory activities of caffeic acid and ellagic acid in cardiac tissue of diabetic mice. Nutr Metab (Lond) 2009;6:33.
11. PERKENI. Konsensus Pengendalian dan Pencegahan Diabetes Melitus Tipe 2 di Indonesia. Jakarta: PERKENI; 2011.
12. Muhtadi, Hidayati AL, Suhendi A, Sudjono TA, Haryoto. Pengujian Daya Antioksidan Dari Beberapa Ekstrak Kulit Buah Asli Indonesia dengan Metode FTC. Symposium; 2014.
13. Palanisamy UD, Ling LT, Manaharan T, Appleton D. Rapid isolation of geraniin from *Nephelium lappaceum* rind waste and its anti-hyperglycemic activity. Food Chem 2011;127:21-7.
14. Abdulgani N, Trisnawati I, Hidayati D, Aisyatussoffi N. Snakehead (*Channa striata*) extracts treatment towards hyperglycemic mice (*Mus musculus*) blood glucose levels and pancreatic histology structure. J Appl Environ Biol Sci 2014;4:1-6.
15. Morris CJ. Carrageenan-induced paw edema in the rat and mouse. Methods Mol Biol 2003;225:115-21.
16. Zubaidi Y. Mekanisme Kerja Obat Antiinflamasi,Obat dan Pembangunan Masyarakat Sehat,Kuat dan Cerdas. Jakarta: Bagian Farmakologi Fakultas Kedoketeran UI; 1975. p. 168-78.

17. Di Rosa M. Biological properties of carrageenan. J Pharm Pharmacol 1972;24:89-102.
18. Cheong E, Ivory K, Doleman J, Parker ML, Rhodes M, Johnson IT, *et al.* Synthetic and naturally occurring COX-2 inhibitors suppress proliferation in a human oesophageal adenocarcinoma cell line (OE33) by inducing apoptosis and cell cycle arrest. Carcinogenesis 2004;25:1945-52.
19. Park PH, Hur J, Kim YC, An RB, Sohn DH. Involvement of heme oxygenase-1 induction in inhibitory effect of ethyl gallate isolated from galla rhois on nitric oxide production in RAW 264.7 macrophages. Arch Pharm Res 2011;34:1545-52.
20. Papadopoulou A, Green RJ, Frazier RA. Interaction of flavonoids with bovine serum albumin: A fluorescence quenching study. J Agric Food Chem 2005;53:158-63.
21. MacKay D, Miller AL. Nutritional support for wound healing. Altern Med Rev 2003;8:359-77.
22. Natarajan Sulochana K, Lakshmi S, Punitham R, Arokiasamy T, Sukumar B, Ramakrishnan S, *et al.* Effect of oral supplementation of free amino acids in Type 2 diabetic patients--a pilot clinical trial. Med Sci Monit 2002;8:CR131-7.
23. Stancic A, Korac A, Buzadzic B, Otasevic V, Jankovic A, Vucetic M, *et al*. L-arginine in nutrition: Multiple beneficial effects in the etiopathology of diabetes. J Nutr Ther 2011;1:114-31.
24. Yang J, Chi Y, Burkhardt BR, Guan Y, Wolf BA. Leucine metabolism in regulation of insulin secretion from pancreatic beta cells. Nutr Rev 2010;68:270-9.
25. Roche M, Rondeau P, Singh NR, Tarnus E, Bourdon E. The antioxidant properties of serum albumin. FEBS Lett 2008;582:1783-7.
26. Widowati W. Potensi Antioksidan Sebagai Antidiabetes. JKM 2008;7:1-11.
27. Tjandra O, Rusliati RT, Zulhipri. Uji Aktivitas Antioksidan dan Profil Fitokimia Kulit Rambutan Rapiah (*Nephelium lappaceum*). Indonesia: UNS Press; 2011.
28. Siringoringo DF. Isolasi Senyawa Flavonoida Dari Kulit Buah Rambutan (*Nephelium lappaceum* L.). Program Studi; 2015.
29. Vinayagam R, Xu B. Antidiabetic properties of dietary flavonoids: A cellular mechanism review. Nutr Metab (Lond) 2015;12:60.
30. Jadhav R, Puchchakayala G. Hypoglycemic and antidiabetic activity of flavonoids: Boswellic acid, ellagic acid, quercetin, rutin on streptozotocin-nicotinamide induced Type 2 diabetic rats. Int J Pharm Pharm Sci 2012;4:251-6.
31. Malini P, Kanchana G, Rajadurai M. Antibiabetic efficacy of allagic acid instreptozotocin induced diabetes mellitus in albino Wistar rats. Asian J Pharm Clin Res 2011;4:127-8.

Source of support: Nil; Conflict of interest: None Declared