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RESEARCH PAPER

Hypoglycemic and hypolipidemic activity of a catfish oil and *Andrographis paniculata* herb extract combination in diabetic rat model

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Abstract

The single use of natural ingredients for the treatment of diabetes mellitus is considered less optimal compared to the combination of several ingredients which is expected to produce a synergistic effect. Therefore, this study aimed to investigate the combined effect of catfish oil (CFO) and *Andrographis paniculata* ethanolic extract (APE) in reducing blood glucose levels and hyperlipidemia in a diabetic rat model. A total of 30 male Wistar rats were used while diabetes was induced using 50 mg/kg streptozotocin. The rats were randomly divided into six groups consisting of the control, diabetes, and drug control group treated with metformin 120 mg/kg; as well as treatments I, II, and III given CFO 1000 mg/kg, CFO 1000 mg/kg + APE 200 mg/kg, and CFO 1000 mg/kg + APE 400 mg/kg, respectively. The test was carried out for 28 days, then on the 29th day, all the test animals were examined for observation of blood glucose levels and lipid profiles. In the fourth week of testing, all groups showed a significantly different blood glucose profile compared to the diabetes control group with $p<0.05$. The combined administration of 1000 mg/kg CFO and 400 mg/kg APE showed a better reduction in blood glucose compared to the single dose of CFO ($p<0.05$). Furthermore, the lipid profiles showed a significant reduction compared with the diabetes control ($p<0.05$). Except for LDL values, the combination of both doses of CFO+APE showed a better reduction in lipid profile compared to the single CFO. A single dose of CFO and a combination dose of APE provided a beneficial effect by inhibiting the increase in blood glucose levels and lipid profiles in a streptozotocin-induced diabetic rat model. Based on the results, the combined dose of 1000 mg/kg CFO+400 mg APE produced a better effect on most of the blood biochemical parameters than the single administration of CFO.

1. Introduction

Diabetes mellitus is a metabolic disorder caused by problems with insulin secretion (Souza *et al*., 2020), this occurs when the pancreas does not produce normal insulin thereby increasing the level of glucose in the blood (Sasongko *et al*., 2020). In conditions of hyperglycemia with insulin resistance, this might lead to several metabolic disorders, such as increased hyperlipidemia, liver injury, nephropathy and other health problems (Zaccardi *et al*., 2016; Xu, Li, Dai *et al*., 2018). These disorders can be treated by administering therapy with antioxidant and anti-inflammatory properties (Asmat *et al*., 2016; Xu, Bai, Chen *et al*., 2018). Natural ingredients, either singly or in combination, potentially function as an antioxidant and anti-inflammatory agent (Sasongko *et al*., 2020).

Omega-3 fatty acids found in fish oil are anti-inflammatory precursors that can overcome insulin resistance (Gao *et al*., 2017; Jamilian *et al*., 2018). Catfish (*Pangasius micronema* Blkr.) is one of the sources of omega-3 with high productivity worldwide, especially in Indonesia (Sasongko, Nurrochmad, Nugroho *et al*., 2022). They belong to the high protein and medium fat groups of fish, with a 16.1% protein content and 5.7% fat (Hashim *et al*., 2015). Other important contents also include vitamins, minerals and

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omega-3 fatty acids (Sudirman *et al*., 2018). In addition, flavonoids are the largest components in plants often used as antioxidants (Sarker and Oba, 2018; Sasongko *et al*., 2018). *Andrographis paniculata* is a plant that is rich in flavonoid content as well as antidiabetic and antihyperlipidemic activities (Nugroho *et al*., 2014; Arifah *et al*., 2022). Aside from flavonoids, *A. paniculata* also contains several phytoconstituent compounds such as andrographolides, neoandrographolides, saponins, alkaloids, glycosides, diterpenoids and polyphenols (Jaiyesimi *et al*., 2020).

The single use of natural ingredients for treatment is considered less optimal compared to the combination of several ingredients which is expected to produce a more optimal antioxidant effect (Sasongko *et al*., 2020). There are no previous studies on the combined effect of catfish oil and *A. paniculata* extract for antidiabetic and antihyperlipidemic activities. Catfish and *A. paniculata* presumably have good antioxidant and anti-inflammatory activity in improving metabolic disorders caused by diabetes mellitus. In this study, we evaluate the effects of single and combined administration of catfish oil and ethanol extract of *A. paniculata* on blood sugar levels and lipid profiles in a rat model of diabetes mellitus.

2. Materials and methods

2.1 Materials

Catfish were purchased from a traditional market in Surakarta, while *A. paniculata* was obtained from farmers in Karanganyar regency, Central Java Indonesia. Meanwhile, streptozotocin as a diabetogenic agent (Sigma Aldric), metformin (Glucophage® from PT. Merck), and biochemical reagents were obtained from BioSystems S.A, Spain.

2.2 Animals

Wistar rats weighing 180-220 were used in this study. All testing protocols on experimental animals were approved by the health research ethics committee of Dr. Moewardi General Hospital Surakarta Central Java, Indonesia (No: 966/VI/HREC/2022).

2.3 Fish oil extraction

The extraction of catfish oil was conducted using a previous method (Sasongko *et al*., 2017), with slight modifications. About 20 kg of ground catfish meat were boiled in 60 L of distilled water for 15 mins at a temperature of 70°C. Next, the mixture of water and fish oil was separated using a separating funnel. Fish oil was purified using 1% bentonite at an oil temperature of 55-60°C, then the mixture was heated to a temperature of 80°C and filtered using a vacuum filter.

2.4 Andrographis paniculata extraction

The *Andrographis paniculata* herbs were dried are made into powder, then a total of 3 kg was macerated with 9 L of 96% ethanol as the solvent. Maceration was carried out for 3 × 24 hrs, while the residue was concentrated using a rotary evaporator at a temperature of 50°C to obtain a thick extract (APE).

2.5 Total flavonoid and phenolic analysis of APE

The method uses a UV-Vis spectrophotometer to analyze total flavonoids at λ = 510 nm and λ = 760 nm for total phenolics. The standard used to analyze total flavonoids is quercetin equivalent in the concentration series of 6.125, 12.5, 25, 50, and 100 ppm. Then for total phenolic analysis using standard gallic acid equivalents.

2.6 Animal experiment

A total of 30 male Wistar rats were used, while streptozotocin (STZ) at a dose of 50 mg/kg dissolved in citrate buffer, pH 4.5, was injected intraperitoneally on day 1 except for the normal group. After 3 days of fasting, blood glucose levels were measured through the tail vein and those with blood sugar levels of > 200 mg/dL were considered diabetic. Rats with diabetes were randomly divided into 6 groups with 5 members each, consisting of the control group, diabetes and drug control group given metformin 120 mg/kg; as well as treatments I, II, and III given 1000 mg/kg CFO, 1000 mg/kg CFO + 200 mg/kg APE, and 1000 mg/kg + 400 mg/kg APE, respectively. The health condition was monitored by weighing the test animals once a week.

2.7 Blood biochemical analysis

Blood was drawn from the test animals through the tail vein at weeks 0, 2 and 4 to measure glucose levels using a glucometer (EasyTouch). At week 4, all rats were euthanized for blood collection. Next, serum was separated from the blood and analyzed for levels of triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), uric acid (UA), creatinine (Cr) and blood urea nitrogen (BUN) using a biochemistry analyzer (Biosystem®).

2.8 Statistical analysis

The results are presented as the standard error of the mean, while the data were evaluated using one-way analysis of variance (ANOVA) followed by an LSD post test and $P<0.05$ was judged statistically significant.

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3. Results

3.1 Total flavonoid and phenolic analysis

The total flavonoid (quercetin equivalent) of APE was 15.99±0.48% w/w, while the total phenolic (gallic acid equivalent) of APE was 9.83±0.45% w/w.

3.2 Body weight profile

Figure 1 shows the body weight profile for 4 weeks of observation. Three days after STZ injection, the profile showed similar weight homogeneity with 175-210 gram. However, there were already changes in each group caused by diabetes from week 1 to week 4, while body weight increased in normal rats till the completion of the test. The body weight at the end of the test was as follows control group 279.20±43.13, diabetes control 163.00±25.32, drug control 204±37.70, treatment I 195±31.53; II 152.6±23.73; and III 171.2±28.81. The group of rats given metformin at a dose of 120 mg/kg showed a better body weight profile compared to other groups.

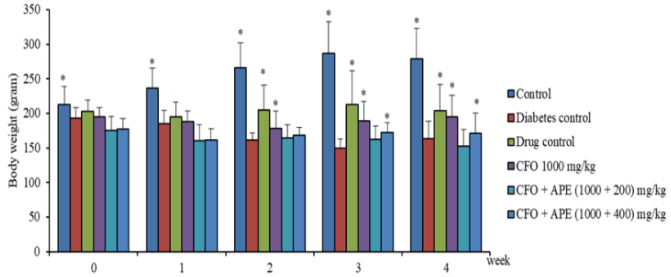

Figure 1. Body weight profile for 4 weeks of testing.
*statistically significantly different (p<0.05) when compared to diabetes control.

3.3 Blood glucose level

Figure 2 shows a graph of changes in blood glucose levels after STZ induction for 4 weeks of the experiment. Injection of 50 mg/kg STZ increased fasting blood glucose levels > 200 mg/dl in the first week. In the second and fourth week, all groups showed a significantly different blood glucose level profile compared to the diabetes control group with p<0.05. The combined administration of 1000 mg/kg CFO and 400 mg/kg APE showed a better reduction in blood glucose compared to the single dose of CFO (p<0.05). Meanwhile, the administration of a lower APE dose did not show a better effect compared to the single CFO treatment.

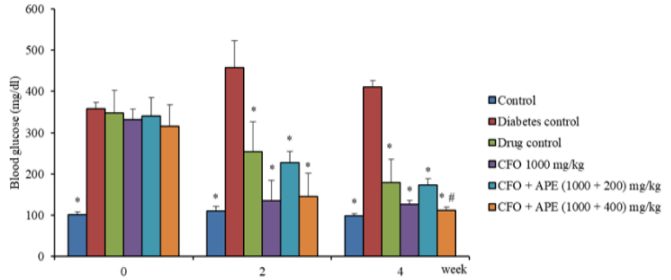

Figure 2. Blood glucose level profile for 4 weeks of testing.
*statistically significantly different (p<0.05) when compared to diabetes control.
#statistically significantly different (p<0.05) when compared to CFO single dose of 1000 mg/kg.

3.4 Blood biochemical profile

Table 1 shows the biochemical profile of rat blood serum at the end of the test (4 weeks), during the testing period, only the levels of TG, AST, and ALT in the control diabetes group were observed to increase above normal blood biochemistry. Although other blood biochemical levels increased, they were still below normal in general. Lipid profiles of TG, TC, and LDL showed a significant reduction compared to the diabetes control with p<0.05. Except for LDL values, the combination of both doses of CFO+APE significantly reduced the lipid profile compared to single CFO. The indirect administration of metformin was able to maintain blood glucose levels and significantly correlated with the inhibition of the increase in TG levels (p<0.05). In other blood biochemical parameters, the administration of CFO and APE inhibited an increase in AST and ALT at all doses. Meanwhile, there was no significant effect on the values of UA, Cr, and BUN except at a dose of 1000 mg/kg CFO+400 mg APE.

4. Discussion

The increase in blood glucose levels in this study was influenced by STZ, because the destruction of pancreatic beta cells, especially by autoimmune damage, culminates in the inability to produce insulin in the pancreas (Sasongko, Nurrochmad, Rohman *et al*., 2022). Diabetic rats often have a lower total body weight than healthy types. Weight loss in diabetes occurs because the body does not get sufficient energy from sugar, thereby causing fat to be processed into energy (Pareek *et al*., 2018). Body weight is linked to an increase in blood glucose levels. When blood glucose is converted into glycogen, muscle mass and body weight simultaneously grow (Guo *et al*., 2018).

The increase in glucose levels at week 0 was demonstrated in the average value of negative control > 200 mg/dL, and this value was higher than normal control glucose levels of ±101.2 mg/dL. The statistical test results showed that at week 0, the test animals experienced an increase in glucose levels 72 hrs after streptozotocin induction, which was marked by a significant difference between the normal and treatment groups. Hyperglycemia conditions cause uncontrolled gluconeogenesis, glycogenolysis, and lipolysis processes to maintain glucose levels in cells (Li *et al*., 2019). In this condition, glucose levels are above normal, i.e.,

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Table 1. Biochemical profile of rat blood serum after testing for 4 weeks.

Group	Biochemical serum profile							
	TG (mg/dL)	TC (mg/dL)	LDL (mg/dL)	ALT (U/L)	AST (U/L)	UA (mg/dL)	Cr (mg/dL)	BUN (mg/dL)
Control	147.20±14.22*	82.40±5.50*	26.68±1.76*	61.00±4.75*	166.40±11.81*	1.58±0.05	0.43±0.04	13.27±1.93*
Diabetes control	292.40±33.13	125.33±4.87	30.48±1.78	267.20±22.87	360.60±26.82	2.54±0.11	0.66±0.07	28.21±4.96
Drug control	141.01±21.48	123.38±2.03	25.86±2.11	65.40±3.20	337.60±37.79	1.53±0.21	0.48±0.02	27.59±6.14
CFO 1000 mg/kg	153.48±35.15*	103.63±4.27*	23.02±1.53*	78.80±5.11*	245.40±8.57*	1.50±0.08	0.50±0.04	23.06±4.11
CFO + APE (1000 + 200) mg/kg	92.00±12.19*#	76.00±4.73*#	25.17±3.01	71.20±4.07*#	325.75±7.67	1.63±0.13	0.52±0.07	24.62±3.95
CFO + APE (1000 + 400) mg/kg	107.27±11.96*#	72.20±5.79*#	25.70±1.54	77.80±3.72*#	263.80±38.32*	1.85±0.14	0.47±0.05	18.25±2.36*#

TG: triglycerides, TC: total cholesterol, LDL: low-density lipoprotein, ALT: alanine aminotransferase, AST: aspartate aminotransferase, UA: uric acid, Cr: creatinine, BUN: blood urea nitrogen.

*statistically significantly different ($p<0.05$) when compared to diabetes control.

#statistically significantly different ($p<0.05$) when compared to CFO single dose of 1000 mg/kg.

blood sugar levels are equal to or more than 200 mg/dL, and fasting levels are above or equal to 126 mg/dL (Sampson *et al*., 2018). Blood glucose levels decreased, with an average of at least 1000 mg/kg in the CFO group for week 2, followed by the 1000 mg/kg CFO+400 mg/kg APE group in week 4. The Omega-3 contained in CFO can increase the insulin sensitivity of diabetic rats thereby reducing blood glucose levels (Keapai *et al*., 2016). Andrographolide compounds from APE facilitate the utilization of glucose in the muscles of induced and diabetic rats through the stimulation of the GLUT-4 transporter. They can also cause an increase in the amount of mRNA expression and levels of the GLUT-4 protein that penetrates cells (Nugroho *et al*., 2012).

Insulin resistance potentially leads to a higher lipid profile in people with diabetes mellitus (Keapai *et al*., 2016). When the condition is resistant, lipolysis rises in the tissues and the activity of lipoprotein lipase decreases gradually (Saadh, 2020), thereby increasing the amount of fat in the blood as well as the total value of cholesterol in the body (Biadgo *et al*., 2017). This is supported by the relationship between DM and increased levels of TG. Insulin resistance that occurs in DM affects fat metabolism by decreasing the activity of lipoprotein lipase (LPL) culminating in chylomicron catabolism and a reduction in very-low-density lipoprotein (VLDL). Consequently, excess fatty acids are produced and cannot be catabolized, causing triglyceride levels to increase in DM patients (Bjornstad and Eckel, 2018). Based on the results, a single dose of CFO and combination with APE can reduce levels of TC and TG in a diabetic rat model at the fourth week. Omega-3 inhibits the increase in total cholesterol by increasing lipid metabolism, inhibiting the formation of triglycerides in VLDL, and elevating the levels of High-Density Lipoprotein (HDL) (Yanai *et al*., 2018). The andrographolide content in APE also plays a role in preventing the increase in hyperlipidemia levels. Andrographolide in APE regulates LDL receptors in the liver, and functions as an inhibitor of the HMG-CoA reductase enzyme. This enzyme plays a role in the formation of mevalonate, which is the raw material for the formation of cholesterol. By inhibiting the activity of this enzyme, the formation of excess cholesterol can also be inhibited (Lakshmia *et al*., 2014).

High glucose levels in diabetics cause liver dysfunction (Yazdi *et al*., 2019), while liver function tests can be performed by measuring ALT and AST levels (Sasongko *et al*., 2021). These enzymes are found in the cytosol and mitochondria of hepatocytes and are released when necrosis occurs in liver cells (Shaaban *et al*., 2014). ALT is found in the cytosol of hepatocytes and converts L-alanine to α-ketoglutarate. The enzyme is released by necrotic hepatocyte cells into the serum, causing ALT levels to increase. A drastically increased AST is caused by hepatitis, iron content, excess body weight, and abnormalities in glucose metabolism (Liu *et al*., 2014). Furthermore, the administration of CFO and APE reduced AST and ALT levels in diabetic rats as shown in Table 1. Fish oil plays a role in inhibiting an increase in blood glucose levels by increasing the body's insulin levels. When the pancreatic cells that produce insulin receive stimulation from omega-3, insulin secretion increases (Hwang *et al*., 2015). Therefore, omega-3 can inhibit pancreatic cell damage that triggers liver cell damage by inhibiting an increase in liver enzymes. APE compounds also play a role in reducing the risk of liver damage (Mehta *et al*., 2021). The bioactive components of lactones and flavones can reduce the production of tumor necrosis factor alpha (TNF-α) triggered by intercellular adhesion molecule-1 (ICAM-1) and endothelial cells when cells undergo an inflammatory process (Dai *et al*., 2019). APE also inhibits inflammation by blocking the production of TNF -kappa and proinflammatory cytokines, which damage hepatocyte cells (Jaiyesimi *et al*., 2020).

5. Conclusion

Based on the results, a single dose of CFO and the combination with APE provide a beneficial effect by inhibiting the increase in blood glucose levels and lipid profiles in a streptozotocin-induced diabetic rat model. The combined administration of medicinal ingredients has a better effect compared to a single component. Further investigations on the target markers in anti-diabetic activities, such as inflammation and oxidative stress up to the molecular level will help the study of CFO and APE.

Conflict of interest

The authors declare no conflict of interest.

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