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FULL PAPER

Hypocholesterolemic effects of noodles prepared from sago, sorghum and mung bean flours in hyperglycemic rats

*Wahjuningsih, S.B. and Azkia, M.N.

Department of Agricultural Products Technology, Universitas Semarang, Soekarno-Hatta Street, Tlogosari, Semarang, Central Java 50196, Indonesia

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Abstract

Nowadays food development is not only for fulfilling nutritional needs, but food can also have functional properties that are beneficial to health. This study aimed to determine the potential of noodles based on local food ingredients to be developed as a functional food. The functional properties of noodles were observed through blood serum cholesterol profile and SCFA (Short Chain Fatty Acid) levels in the caecum. The in vivo studies used 5 groups of Sprague Dawley rats, namely healthy rats, hyperglycemic rats, hyperglycemic rats with F1 diet, hyperglycemic rats with F2 diet, and hyperglycemic with F3 diet. Data were analysed in triplicates using a completely randomized design and post analysed using Duncan multiple range test. The results showed that the F1-F3 diet could improve blood cholesterol profile by decreasing total cholesterol 16.90-33.69%, triglycerides 30.41-35.64%, Low density lipoprotein (LDL) 37.52-46.48%, and increasing High density lipoprotein (HDL) 103.92-127.47%. Caecum samples in rats with an F1-F3 diet contained acetic acid 5.35-9.28 mMol, propionic acid 3.56-6.39 mMol, and butyric acid 1.97-4.05 mMol. This can conclude that noodles based on sago, sorghum, and mung bean flour (F1-F3) can improve blood cholesterol profile and increase the SCFA levels of hyperglycemic rat caecum.

1. Introduction

Hyperglycemia is associated with the risk of degenerative diseases such as type 2 diabetes mellitus. Diabetes Mellitus (DM) is a non-communicable disease that causes a high risk of death. According to World Health Organization (WHO) (2021), about 1.5 million cases of death in the world are directly caused by diabetes, with a global total of people with diabetes estimated at 463 million people (Saeedi *et al*., 2019). Based on data from International Diabetes Federation (IDF) (2017), Indonesia is included in the top ten countries with the highest diabetes case in the world with 6th place after China, India, the US, Brazil, and Mexico. This risk can be continued to increase from year to year if not controlled properly.

Insulin resistance has a major role in the development of diabetes. Poorly controlled diabetes, altered insulin signaling, hyperglycemia, or both can promote imbalanced lipid metabolism and hypertriglyceridemia (Sacks *et al*., 2014). Type-2 diabetes is associated with dyslipidemia, which is a synergistic risk factor for cardiovascular disease (CVD) (Fan, 2017). Dyslipidemia occurs in 90.1% of patients with coronary heart disease. Dyslipidemia of lipoprotein metabolism, including lipoprotein excess or deficiency. Dyslipidemia can be manifested by an increase in total cholesterol, LDL cholesterol, triglyceride concentrations, and a decrease in HDL cholesterol in the blood (Fodor *et al*., 2008). The incidence of dyslipidemia in Indonesia is quite high. In Indonesia, coronary heart disease (CHD) and stroke are estimated to cause more than 470,000 deaths annually. Five major and modifiable vascular risk factors: smoking, hypertension, diabetes, elevated total cholesterol, and being overweight (Hussain *et al*., 2016).

The low risk of diabetes can be maintained with a healthy diet, including by consuming foods rich in functional properties, such as foods high in dietary fiber. In previous studies, noodles based on sorghum, sago, and mung bean flour had dietary fiber content of 6.48 – 13.16% and resistant starch 16.35 – 21.57 mg/100 g (Azkia *et al*., 2021). Dietary fiber and resistant starch have been studied to provide good health benefits, especially reducing the risk of developing diabetes mellitus. Sunarti *et al*. (2019) studied a high-fiber diet can increase endogenous insulin secretion and reduce insulin resistance in patients with type-2 diabetes

*Corresponding author.
Email: *sribudiwahjuningsih5678@gmail.com*

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mellitus. Dietary fiber at dose 10 g/day for intervention duration of 8 weeks significantly reduced HbA1c, fasting blood glucose (FBG), fasting insulin, and insulin resistance. Soluble dietary fiber is effective in improving glycemic control and insulin sensitivity in T2DM patients (Mao *et al*., 2021). In previous studies, the functional properties of noodles based on sago, sorghum and green beans have been studied, including the content of dietary fiber, resistant starch and phenolic compounds. This study aimed to learn the effect of noodles based on sago, sorghum and mung bean flour consumption on the lipid profile of rats induced by hyperglycemia, to further provide important information for the development of functional foods.

2. Materials and methods

2.1 Materials

The noodles were prepared with sago, sorghum, and mung bean flour obtained from local Indonesian farmers. *In vivo* study using standard feed based on AIN 93 with modifications, the composition is shown in Table 1. Other materials for analysis using analytical standards were purchased from Sigma-Aldrich, Co. (USA).

Table 1. Composition of fed standard AIN-93 feed in percentage.

Ingredients	Percentage (%)
Corn starch	62.07
Casein	14
Sucrose	10
Soybean oil	4
CMC	5
Mineral mix	3.5
L-Cystine	0.18
Vitamin mix	1
Choline Bitartrate	0.25

Source: Reeves *et al*. (1993)

2.2 Noodle preparation

Noodles made by mixing raw materials according to the following formula: F1 (50% Sago: 20% Sorghum: 30% Mung Bean), F2 (20% Sago: 50% Sorghum: 30% Mung Bean), F3 (10% Sago: 60% Sorghum: 30% Mung Bean). The mixture was added to 30% water, then steamed for 35 min, and cooled to room temperature. Furthermore, the mold was shaped using an extruder and dried at 50°C for 17 hrs. The dried noodles were stored in a dry and closed container for *in vivo* study.

2.3 Experimental design

Thirty Sprague Dawley rats aged 2 months with a bodyweight of 150-210 g were randomly divided into 5 groups, there was one normal control group (healthy rats) and four groups of STZ-NA-induced diabetic rats. The group of rats induced by STZ-NA consisted of a group with standard feed AIN-93, standard feed and 1.5 gram/day Noodle F1, standard feed and 1.5 g/day Noodle F2, as well as standard feed and 1.5 g/day Noodle F3. The intervention was carried out for 6 weeks with an adaptation time of 5 days. Weighing of each rat was carried out to ensure that there was no significant decrease and that the condition of the rats remained stable. This study was approved by the health research ethics commission Dr. Moewardi General Hospital No. 811 / VI / HREC / 2020.

2.4 Total cholesterol levels

Total cholesterol levels in the blood serum were measured with the kit (DiaSys diagnostic systems GmbH, Alte Strasse 9 Holzheim Germany). The analytical procedure used the cholesterol oxidase-p-aminophenozone (CHOD-PAP) method. A total of 10 µL of sample was mixed with 1000 µL of kit reagent, then incubated at 37°C for 5 mins. Then the absorbance (A) was measured at wavelength 546 nm. Standards were made using the same method without the addition of samples. Calculation of total cholesterol levels as follows:

$$\text{Total cholesterol level}\left(\frac{\text{mg}}{\text{dL}}\right)=\frac{A_{\text{sample}}}{A_{\text{standard}}}\times\text{standard concentration}\left(\frac{\text{mg}}{\text{dL}}\right)$$

2.5 High-density lipoprotein levels

HDL levels were determined by precipitation of low-density lipoprotein (LDL) and chylomicrons through the addition of phosphotungstic acid and $MgCl_2$. Then the mixture was centrifuged, HDL levels in the supernatant were measured using the p-aminophenozone oxidase kit (CHOD-PAP). 200 µL of blood serum was added to 500 µL of the precipitation reagent which was diluted in a ratio of 4:1, incubated for 10 mins at room temperature. The mixture was centrifuged at 4000 rpm for 10 mins. The supernatant was reacted with a p-aminophenozone oxidase kit (CHOD-PAP) similar to the total cholesterol analysis step.

$$\text{HDL level}\left(\frac{\text{mg}}{\text{dL}}\right)=\frac{A_{\text{sample}}}{A_{\text{standard}}}\times\text{standard concentration}\left(\frac{\text{mg}}{\text{dL}}\right)$$

2.6 Low density lipoprotein levels

LDL levels were measured using the CHOD-PAP reagent kit. blood serum as much as 200 µL of blood serum added 500 µL of precipitation reagent diluted in a ratio of 4:1, incubated for 10 mins at room temperature. Next the mixture was centrifuged at 1074×*g* for 10 mins. The precipitation reagent contains heparin and sodium citrate. The supernatant obtained was analyzed using the CHOD-PAP reagent kit with a procedure similar to that of total cholesterol analysis.

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$$\text{LDL level}\left(\frac{\text{mg}}{\text{dL}}\right) = \frac{A_{\text{sample}}}{A_{\text{standard}}} \times \text{standard concentration}\left(\frac{\text{mg}}{\text{dL}}\right)$$

2.7 Triglyceride levels

Determination of triglyceride levels using the glycerol phosphate oxidase-aminophenozone (GPO-PAP) kit method. The 10 µL sample was mixed with 1000 µL of kit reagent, incubated at 37°C for 5 mins. Standards were made without the addition of samples. The absorbance was measured at a wavelength of 546 nm.

$$\text{TG level}\left(\frac{\text{mg}}{\text{dL}}\right) = \frac{A_{\text{sample}}}{A_{\text{standard}}} \times \text{standard concentration}\left(\frac{\text{mg}}{\text{dL}}\right)$$

2.8 Short chain fatty acid levels

Determination of short chain fatty acid (SCFA) levels refers to the method of Harmayani *et al*. (2014). Cecal content was diluted in 1:10 distilled water, then centrifuged at 3500 rpm for 20 mins. The supernatant obtained was analyzed by gas chromatography (Shimadzu GC-8A) using a capillary column (Φ180 cm × 4 mm).

2.9 Data analysis

The experimental data were analyzed using one-way ANOVA (SPSS 23.0). The significant differences were tested using Duncan's Multiple Range Test (DMRT) ($p<0.05$).

3. Results and discussion

To determine the status of the blood lipid profile of the experimental mice during the diet treatment, we have evaluated their levels of total cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL).

3.1 Total cholesterol

At week 0, the negative control group (healthy) had blood cholesterol levels that were significantly different from the other groups induced by STZ-NA (Table 2). This indicates that STZ-NA induction causes an increase in blood cholesterol. In addition to degradation by β-oxidase, the degradation is also caused by a reduction in the hormone lipoprotein lipase (LPL) whose activity is stimulated by insulin. Insulin resistance is characterized by an increase in glucose that exceeds normal limits (hyperglycemia) and leads to abnormalities in fat metabolism, one of which is hypercholesterolemia (Tomás *et al*., 2006). From week 2 until the end of the intervention, we observed a reduction in the blood cholesterol levels in the sago noodle diet group with formula F1-F3 compared to the STZ-NA induction group. The F1 group had a 33.69% decrease in blood cholesterol levels, higher than the F2 and the F3, while the group induced by STZ-NA had a 3.69% increase in blood cholesterol (Table 2). Diets containing high levels of resistant starch have been studied to effectively reduce total blood cholesterol (Bindels *et al*., 2015; Wahjuningsih *et al*., 2018). Those diets increase insulin secretion (Kim *et al*., 2003), which plays a role in reducing lipolysis and inhibiting the expression of the lipoprotein lipase hormone (LPH) (Ormazabal *et al*., 2018; Zhao *et al*., 2020).

The mechanism of resistant starch in lowering cholesterol levels also occurs through the binding of bile acids and increasing the excretion of bile acids through feces. Thus, to replenish the excreted bile acids, the liver synthesizes new bile acids from cholesterol that eventually leads to lower cholesterol levels (Nugraheni *et al*., 2014). In addition, resistant starch diets can stimulate the conversion of bile acids from cholic acid to chenodeoxycholic acid through microbiome activity. Chenodeoxycholic acid inhibits the activity of 3-Hydroxy-3-Methylglutaryl (HMG)-CoA reductase, an enzyme required for cholesterol biosynthesis. HMG-CoA reductase activity results in a decrease in cholesterol production and causes a decrease in blood cholesterol (Pi *et al*., 2020).

3.2 Triglycerides

Triglycerides are fatty acids that are esterified into glycerol; they are neutral fats synthesized from carbohydrates and are stored in adipose cells. Triglycerides are produced in the liver. Ideally, blood triglyceride levels are below 100 mg/dL. High triglyceride levels can lead to heart disease, such as coronary heart disease.

At the beginning of the intervention (Week 0), the triglyceride levels of the healthy group were significantly different from the other groups. This happened because, in the group induced by STZ-NA, the triglycerides were degraded from the adipose tissue to be further converted into energy. Insulin resistance causes energy conversion from fatty acids which will trigger the accumulation of fat in the liver, thereby increasing the production of triglycerides from the liver cells. The groups fed by Sago Noodle (F1-F3) had a high blood triglyceride level reduction of 30.41-35.64% (Table 3). Resistant starch can be fermented in the large intestine and produce short -chain fatty acids (SCFA), such as propionic acid, butyric acid, and acetic acid. Propionic acid has a role in inhibiting the synthesis of hepatic triglycerides and reducing blood serum lipid levels. Propionic acid can inhibit pyruvate dehydrogenase activity in the liver thereby reducing fatty acid synthesis (Cheng and Lai,

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Table 2. Change of total cholesterol in the blood serum of experimental mice.

Group	Total blood cholesterol levels (mg/dL)					Percentage of change (%)
	Week 0	Week 1	Week 2	Week 3	Week 4	
Control (-)	88.89[a]	93.41[a]	95.67[a]	96.97[a]	98.91[a]	+11.27
Control (+)	175.22[c]	175.58[d]	178.48[d]	179.61[e]	181.69[e]	+3.69
F1	160.28[b]	151.28[b]	165.03[b]	146.65[b]	106.28[b]	-33.69
F2	161.81[b]	154.21[b]	171.46[c]	158.22[c]	112.57[c]	-30.43
F3	159.13[b]	153.36[b]	186.55[e]	166.39[d]	132.24[d]	-16.90

Values with different superscripts within the same column are statistically significantly different (p<0.05). Control (-): healthy mice, Control (+): STZ-NA-induced mice, F1: Sago Noodle 50%: Sorghum 20%, F2: Sago Noodle 20%: Sorghum 50%, F3: Sago Noodle 10%: Sorghum 60%.

Table 3. Change of triglycerides in the blood serum of experimental mice.

Group	Blood triglycerides level (mg/mL)					Percentage of change (%)
	Week 0	Week 1	Week 2	Week 3	Week 4	
Control (-)	79.73[a]	80.97[a]	84.04[a]	84.45[a]	86.19[a]	+8.10
Control (+)	133.82[bc]	137.26[c]	138.42[c]	140.18[d]	142.04[c]	+6.14
F1	134.31[bc]	120.53[b]	108.16[b]	93.81[b]	86.44[a]	-35.64
F2	137.73[c]	122.03[b]	108.51[b]	96.84[b]	88.93[a]	-35.43
F3	136.02[bc]	118.80[b]	108.51[b]	103.56[c]	94.65[b]	-30.41

Values with different superscripts within the same column are statistically significantly different (p<0.05). Control (-): healthy mice, Control (+): STZ-NA-induced mice, F1: Sago Noodle 50%: Sorghum 20%, F2: Sago Noodle 20%: Sorghum 50%, F3: Sago Noodle 10%: Sorghum 60%.

2000). Diets containing high levels of resistant starch are also effective in lowering blood triglyceride levels by lowering levels of Fatty Acid Synthase (FAS) in the liver which has an association with Sterol Regulatory Element -Binding Protein-1c (SREBP-1c) mRNA levels, thereby causing a decrease in blood triglycerides (Hashimoto *et al*., 2006).

3.3 Low-density lipoprotein

The LDL levels of mice at several stages of the study are shown in Table 4. LDL is a lipoprotein that carries cholesterol to tissues including arteries. LDL is often referred to as bad cholesterol or the type of cholesterol that has deteriorating effects on health. Blood LDL levels should be kept below 100 mg/dL. When blood LDL levels are above 130 mg/dL, the risk of getting heart diseases increases.

The group of healthy mice had significantly lower baseline cholesterol levels compared to mice that had been induced by STZ-NA. During the intervention until the 4th week, the groups fed by sago noodle formula (F1 -F3) showed a fairly high decrease in triglyceride levels (37.52-46.89%). According to Ormazabal *et al*. (2018), increased activity of lipids in the liver to produce energy due to insulin resistance will generate smaller and denser LDL particles (small dense LDL). These small dense LDL particles are intrinsically atherogenic than larger LDL particles. Meanwhile, in the sago noodle groups, the reduction in LDL levels may be influenced by the beneficial effects of the sago noodles' metabolism process. Resistant starch can reduce LDL levels by increasing liver LDL receptor mRNA (Fukushima *et al*., 2001). Improvement of insulin resistance in hyperglycaemic conditions can prevent lipid oxidation which produces more LDL.

3.4 High-density lipoprotein

The HDL levels of mice at several stages of the study are shown in Table 5. HDL or High-Density Lipoprotein is in charge of excreting lipoprotein cholesterol from liver tissue. HDL levels should ideally be above 60 mg/dL. HDL levels that are low or below 40 mg/dL can increase the risk of heart diseases.

Table 4. Change of LDL concentration in the blood serum of experimental mice.

Group	Blood LDL level (mg/mL)					Percentage of change (%)
	Week 0	Week 1	Week 2	Week 3	Week 4	
Control (-)	25.94[a]	27.84[a]	28.96[a]	30.34[a]	35.68[a]	-
Control (+)	77.47[d]	79.15[e]	80.14[e]	80.78[e]	81.98[d]	+5.82
F1	66.67[b]	68.66[c]	54.21[bc]	48.52[b]	35.68[a]	-46.48
F2	70.66[c]	69.79[c]	55.44[bc]	51.72[c]	37.53[a]	-46.89
F3	71.13[c]	64.67[b]	58.03[c]	54.09[c]	44.44[b]	-37.52

Values with different superscripts within the same column are statistically significantly different (p<0.05). Control (-): healthy mice, Control (+): STZ-NA-induced mice, F1: Sago Noodle 50%: Sorghum 20%, F2: Sago Noodle 20%: Sorghum 50%, F3: Sago Noodle 10%: Sorghum 60%.

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Table 5. Change of HDL concentration in the blood serum of experimental mice.

Group	Blood HDL level (mg/dL)					Percentage of change (%)
	Week 0	Week 1	Week 2	Week 3	Week 4	
Control (-)	84.20[c]	81.94[d]	79.93[e]	79.14[e]	76.47[f]	-
Control (+)	26.18[a]	24.97[a]	24.34[a]	23.78[a]	23.53[a]	-10.12
F1	32.18[b]	39.84[c]	45.44[d]	58.97[d]	73.20[e]	+127.47
F2	32.53[b]	40.90[c]	40.95[c]	58.28[d]	69.67[d]	+114.17
F3	31.60[b]	40.51[c]	23.07[a]	50.93[c]	64.44[c]	+103.92

Values with different superscripts within the same column are statistically significantly different ($p<0.05$). Control (-): healthy mice, Control (+): STZ-NA-induced mice, F1: Sago Noodle 50%: Sorghum 20%, F2: Sago Noodle 20%: Sorghum 50%, F3: Sago Noodle 10%: Sorghum 60%.

At week 0, the blood HDL levels in the healthy group were significantly higher than in the STZ-NA-induced group. According to Ormazabal *et al*. (2018), increased activity of lipids in the liver to produce energy due to insulin resistance will reduce HDL particles, which happens because of an increase in VLDL and leading to form LDL cholesterol. The group of mice induced by STZ-NA with a standard diet showed a decrease in HDL by 10.12%. The groups fed by sago noodle (F1-F3) showed an effective improvement in blood HDL values, an increase in HDL of 103.92-127.47%, with HDL values at the end of the intervention similar to that of the healthy mice group. Zhou *et al*. (2015) also studied a diet containing high levels of resistant starch that was able to increase blood HDL up to 78% in diabetic mice. Improvement of insulin resistance also contributes to an increase in blood HDL levels (Sadur and Eckel, 1983).

3.5 Cecum short-chain fatty acid levels

Intestinal microbiota plays a role in metabolism and immune response, mainly because of the contribution of its fermentation products such as SCFA. SCFAs have a role in regulating glucose and lipid metabolism through activation of SCFA receptors in the liver, adipose tissue, brain, and pancreas. Table 6 shows SCFA levels in the caecum samples of each treatment group.

SCFA levels of caecum samples in each group illustrate the results of microbiota fermentation in the large intestine (colon) against resistant starch or dietary fiber, some of which are acetic acid, propionic acid, and butyric acid. The group of healthy mice had a higher SCFA level compared to the group of diabetic mice without sago noodle intervention. However, in the diabetic mice group fed by sago noodle (F1-F3), an increase in the SCFA levels in the caecum sample was observed. This is in line with the previous study showing that sago noodle contains high levels of resistant starch and dietary fiber as much as 16.35-21.57 mg/100g and 6.48-13.16%, respectively. Resistant starch is a type of dietary fiber, which includes all starch and its degradation products that are not absorbed in the small intestine of healthy humans. Resistant starch is fermented mostly by the microbiota in the large intestine, resulting in the production of SCFA. These SCFAs can diffuse across epithelial cell membranes, and their absorption is also mediated by monocarboxylate transporter 1 (MCT1) and monocarboxylate sodium-coupled transporter 1 (SLC5A8 or SMCT1) (Haenen *et al*., 2013).

Increased SCFA production is associated with the consumption of dietary fiber and resistant starch, as well as its health benefits. SCFA lowers the pH in the colon, which can prevent the overgrowth of pathogenic bacteria. Acetic, propionic, and butyric acids are the main SCFA products produced in the large intestine. Butyric acid is considered the most beneficial for health (Nugent, 2005). SCFA has an important role in improving blood glucose regulation. SCFA was studied to increase insulin secretion through induction of GLP1 and amylin secretion through activation of FFAR2 (SCFA receptor). SCFA also increases beta-cell mass in the pancreas, reduces glucagon secretion, and regulates the metabolism of glucose (Mandaliya and Seshadri, 2019).

Table 6. Change of SCFA concentration in the caecum of experimental mice

Group	Concentration of SCFA (mMol)		
	Acetic acid	Propionic acid	Butyric acid
Control (-)	5.27[abc]	3.52[bc]	2.20[b]
Control (+)	1.57[a]	0.52[a]	0.16[a]
F1	9.28[c]	6.39[c]	4.05[c]
F2	6.88[bc]	4.53[bc]	2.59[bc]
F3	5.35[abc]	3.56[bc]	1.97[ab]

Values with different superscripts within the same column are statistically significantly different ($p<0.05$). Control (-): healthy mice, Control (+): STZ-NA-induced mice, F1: Sago Noodle 50%: Sorghum 20%, F2: Sago Noodle 20%: Sorghum 50%, F3: Sago Noodle 10%: Sorghum 60%.

4. Conclusion

The increased risk of non-communicable diseases encourages the need to develop food that supports body

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health to control risk. Healthy food ingredients can affect an individual's health status. Diets high in resistant starch can improve the risk of hyperlipidemia complications in diabetic conditions. A noodle diet based on sago, sorghum, and mung bean flour can reduce total cholesterol 16.90-33.69%, triglycerides 30.41-35.64%, LDL 37.52-46.48%, increase HDL 103.92-127.47% and improve the SCFA profile of cecum samples in STZ-Na induced hyperglycemia rats. Noodles based on sago, sorghum, and mung bean flour have the potential value to be developed as a functional food.

Conflict of interest

The authors declare no conflict of interest.

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