The Effect of Arrowroot and Casein Diet in Oxidative Stress-induced Rats on Lipid Metabolism

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10.18805/ajdfr.DRF-416

ABSTRACT

Background: Diets rich in complex carbohydrates, such as Arrowroot and diets containing casein have the potential to be effective in preventing disease. This study aims to determine whether the combination of an arrowroot diet, low sugar and added casein in oxidative stress-induced rats on body weight, consumption of feed, glucose levels, lipid profile and expression of the gene that regulates cholesterol synthesis, namely HMGCR.

Methods: The research was experimental on 1-month-old rats. A total of 20 female rats were randomized into four groups, namely 1) standard feed without induction of oxidative stress (normal group), 2) standard feed with induction of oxidative stress, 3) modified feed A (arrowroot 30% and induction of oxidative stress, 4) modified feed B (arrowroot 60% and induction of oxidative stress). After seven months, blood was collected from the orbit to examine lipid profile levels and blood glucose levels. Liver tissue was assessed for HMGCR mRNA expression.

Result: The body weight and feed intake in the normal and modified feed B groups were higher than in the other groups. There were no significant differences between groups' total cholesterol, LDL-C, HDL-C, triglycerides and blood glucose levels. HMGCR expression level measured as 1.05±0.38; 0.926±0.32; 1.24±0.37 and 1.55±0.6 (p=0.17), respectively.

Key words: Arrowroot, Casein, HMGCR, Lipid profile, Oxidative stress.

INTRODUCTION

Foods high in carbohydrates are essential for health. Carbohydrates produce glucose, which is vital for physical activity. Dietary recommendations suggest that carbohydrates should comprise 45% to 65% of total daily calories. However, the quality of carbohydrates determines a person's health. Simple carbohydrates and refined carbohydrates are often associated with degenerative diseases such as diabetes mellitus and even cancer. Conversely, consuming complex carbohydrates with a low glycemic index can improve health, prevent oxidative stress and mitigate disease risk, including cancer (Clemente-Suárez *et al*., 2022). Various types of foods are complex carbohydrates, such as Arrowroot (*Maranta arundinacea* L). Arrowroot has a low glycemic index and high fibre content has health benefits (Fidianingsih *et al*., 2022a) and can even play a role in cancer prevention (Fidianingsih *et al*., 2022b).

One mechanism by which complex carbohydrates can prevent various diseases, including cancer, is their slow absorption, so people feel full. Additionally, the high fibre content of this carbohydrate can inhibit the absorption of glucose and fat, reduce total cholesterol and LDL levels, increase HDL levels and inhibit insulin resistance. The underlying mechanism is that complex carbohydrates can increase the expression of genes that promote lipolysis and inhibit cholesterol synthesis (Salto *et al*., 2020). Previous research shows that arrowroot can reduce blood cholesterol, LDL and triglyceride levels (Damat, 2012). However, according to the researcher's review, there has been no research regarding the effect of a complex carbohydrate diet (especially arrowroot) in oxidative stress conditions and its mechanism in lowering cholesterol.

A protein-rich diet, including essential and non-essential amino acids, is vital for health. A protein diet is necessary to maintain lean body mass throughout life. Animal protein sources contain higher essential amino acids, which are very important (Cena and Calder, 2020). However, animal diets derived from meat cause insulin resistance and are associated with metabolic disorders, increased LDL, inflammation and liver lipid accumulation

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How to cite this article: Fidianingsih, I., Aryandono, T., Widyarini, S., Herwiyanti, S. and Sunarti (2026). The Effect of Arrowroot and Casein Diet in Oxidative Stress-induced Rats on Lipid Metabolism. *Asian Journal of Dairy and Food Research*. **45(3):** 451-457. doi: 10.18805/ajdfr.DRF-416.

Submitted: 18-06-2024 **Accepted:** 22-07-2025 **Online:** 22-08-2025

compared to soy vegetable protein diets. The casein diet, usually from dairy products, has a better lipid profile than meat (Ijaz *et al*., 2018). Casein protein is a protein that contains most of the essential amino acids and non-essential amino acids. This protein is slow to digest and filling. Consumption of this protein is reported to have biological functions for health, such as anti-inflammatory, antioxidant and lowering blood pressure. However, there is no significant difference in lipid profiles and glucose levels (Zhou *et al*., 2022). A systematic review shows that consuming dairy products containing lots of casein protein can prevent diabetes and improve insulin secretion, cardiovascular disease and neurological disorder and also increases the immunity of body disease (Pasin and Comerford, 2015; Chitra, 2021).

A healthy diet should be rich in vegetables, fruits, whole grains, dairy products, lean proteins and vegetable oils. By adhering to these dietary recommendations, individuals can significantly reduce their risk of developing diet-related diseases such as obesity, dyslipidemia, metabolic syndrome, diabetes, osteoporosis, coronary heart disease, stroke and cancer (U.S. Department of Agriculture and U.S. Department of Health and Human Services, 2020). A systematic review and meta-analysis of low-calorie, high-protein combination diets have also demonstrated their effectiveness in cancer prevention (Mittelman, 2020).

Oxidative stress is the underlying cause of many diseases, such as obesity, metabolic syndrome, diabetes and cancer. Oxidative stress, in this case, DMBA, can initiate changes in gene expression related to lipid homeostasis and trigger an increase in cholesterol levels (Khan *et al*., 2012). Cholesterol is synthesized by the enzyme HMGCR, which converts 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) into mevalonate, where the final product of mevalonate is cholesterol (Renno *et al*., 2015).

A varied diet with a diverse nutritional composition is necessary for health. Arrowroot can be served as an alternative functional food. The results of this study are expected to enrich information about the health benefits of arrowroot. This study aims to determine the effect of combining an arrowroot diet, reducing sugar and adding casein in DMBA oxidative stress-induced rats on body weight, feed intake, glucose levels, lipid profiles and the gene expression regulating cholesterol synthesis (HMGCR).

MATERIALS AND METHODS

Animals

This research used 20 Sprague Dawley rats. Calculations are based on the formula E=10-20 = a, where the total number of animals used minus the total number of groups = 20-4=16 (Charan and Biswas, 2013). 4-week-old rats were obtained from PT Bogor Life Science and Technology (BLST) Holding Company of Institut Pertanian Bogor University. The inclusion criteria are being female, active, able to adapt, no signs of illness. Exclusion criteria: The rat died before the end of the study. Rat were randomised using a computer after adaptation for one week and divided into four groups: rats given standard feed and not induced by oxidative stress (normal group), rats given standard feed and induced oxidative stress (negative control group), rats given modified diet A (arrowroot of 30%, low sugar and addition of casein) and rats were given modified diet B (arrowroot 60%, low sugar and addition of casein). Rats were housed in one cage, with two to three rats kept clean daily. The room temperature was 23±2°C, with 12 hours of darkness, 12 hours of bright light and 70-80% air humidity. This research received ethical approval from the UGM FKKMK Ethical Commission.

Oxidative stress induction

All rats were provided with standard feed and allowed to drink ad libitum during the adaptation period. The animals were fed according to their groups starting in the second week. In the third week, the rats from the negative control and modified feed groups underwent oxidative stress induction, a pivotal step in this research. The method used for inducing oxidative stress was the administration of DMBA(@Sigma) orally, twice a week for five weeks, at a dose of 20 mg/kg BW dissolved in corn oil, totalling 0.5-1 ml. Following this, the rat were kept until they reached 8 months of age, allowing for the observation of long-term effects.

Diet and feeding

The normal and negative control groups received standard rat feed (Table 1). Proximate feed testing was conducted at the Faculty of Agricultural Technology, Universitas Gadjah Mada, to determine the nutritional content of the feed, such as carbohydrate, fat and protein content (Table 1). The feed was weighed daily, the rats always had access to food. The rat's body weight was also measured weekly using a mouse scale.

Examination of lipid profile and blood sugar levels

After termination, blood was collected from the rats *via* the orbit and centrifuged to obtain serum. Glucose and lipid levels were assessed using the GOD-PAP and CHOD-PAP enzymatic methods with a MICROLAB 300 spectrophotometer. The lipid profiles included total cholesterol, triglycerides, Low-density lipoprotein cholesterol (LDL-C) and High-density lipoprotein cholesterol (HDL-C). Glucose levels and lipid profiles were measured based on the absorbance of the standard (Astd) and sample (Asp) against the blank (Abl).

Examination of HMGCR expression in the liver

HMGCR mRNA expression was calculated using the relative quantitation method after the mRNA was converted into cDNA and Real-Time PCR was carried out. The relative quantitation value is calculated based on mass units with the ratio of the Cq value of the housekeeping gene (calibrator), in this case, GAPDH, to the Cq of the sample. (Pcr and Pfaffl, 2001). A qualitative real-time polymerase chain reaction was conducted using a Power SYBR Green PCR master mix and an RT-PCR machine (@ABi 7500 fast). The forward and reverse primers of HMGCR are TGTGGGAACGGTGACACTTA and CTTCAAATTTTGGG CACTCA (Wong *et al*., 2011). The primary forward and reverse housekeeping genes (GAPDH) are TGTTCCAGTATGA CTCTACC and TCACCCCATTTGATGTTAGC, respectively (Ren *et al*., 2017).

Data analysis

Differences in feed intake, body weight, lipid profile and HMGCR expression were analyzed using one-way ANOVA. Post hoc LSD tests were also carried out to measure differences between each group regarding feed intake, body weight and HMGCR expression. Analysis of differences in glucose levels was performed using the Kruskal-Wallis test. All statistical tests were carried out with a confidence level of 95%.

RESULTS AND DISCUSSION

Body weight and feed intake

The body weight of all groups continued to increase with age. However, by week 26, the body weight of the standard diet group with oxidative stress and the modified feed A group began to decrease. At the end of treatment, the group of oxidative stress given standard feed and modified feed A had a lighter body weight than the normal and modified feed B group (Fig 1). By the end of treatment, clinically, the normal group and modified feed B group appeared healthier and more active. In contrast, the negative control group and modified feed A group looked sick, weak and inactive. In the fourth week, the feed consumed by the modified feed group was still less than that of the standard feed group. Even though the modified feed group consumed less in the first week, their body weight was not significantly different from the group of test animals that used standard feed. Starting from week 27th, the rats with oxidative stress and standard feed consumed less than the other groups (Fig 2).

The results of this study show that arrowroot consumption has the potential to limit eating. All arrowroot groups exhibited a decreased appetite from weeks two to five compared to standard feed. This can be because the fiber content in arrowroot can form a gel (thick solution) and a large bolus, so gastric emptying is slower, resulting in a feeling of fullness. Soluble fiber and resistant starch in arrowroot, which are not easily digested, will be fermented by the intestinal microbiota into short-chain fatty acids (SCFA). SCFA will bind its receptor on colonic L cells so that these cells secrete the hormones PYY and GLP1. This hormone in the bloodstream will go to the arcuate nucleus in the hypothalamus to increase the activity of appetite-suppressing pro-opiomelanocortin (POMC) and inhibit appetite-stimulating neuropeptide Y (NPY), thereby reducing appetite (Chambers *et al*., 2014).

Even though the feed intake is less, body weight does not significantly differ from standard feed. This modified feed is effective for growth and development. Arrowroot and dairy products have been widely developed as complementary foods to breast milk and have the potential to meet the nutritional adequacy of babies by substituting for other foods (Aini and Wirawan, 2014). At week 22, the oxidative stress induction group with standard feed began to experience a decrease in appetite until the end of treatment. Previous research shows that administering DMBA oxidative stress

Table 1: Composition and nutrients of the experimental diet.

	Standard feed	Modified feed A	Modified feed B
Component, g/kg diet			
Casein	140	200	200
Metionin	3	3	3
Corn starch	619.5	403.65	237.8
Arrowroot starch	0	185.85	371.7
Sucrose	100	70	50
Corn oil	40	40	40
Alfa cell	50	50	50
Mineral mix	35	35	35
Vitamin mix	10	10	10
Choline bitartrate	2.5	2.5	2.5
Analysed crude nutrient			
Water (%)	9.68	9.85	8.54
Abu (%,wt)	4.44	2.94	4.215
Fat (%, wt)	2.24	1.23	2.1
Total protein, Fk:6,25 (%,wt)	10.74	14.71	16.21
Serat kasar (%,wt)	0.01	2.18	0.065
Carbohydrate (Betw diff) (%)	72.91	71.28	68.96
Calorie (kcal/100 g)	331.62	329.49	332.84

Standard feed rodent based AIN93M (Reeves *et al*., 1993).

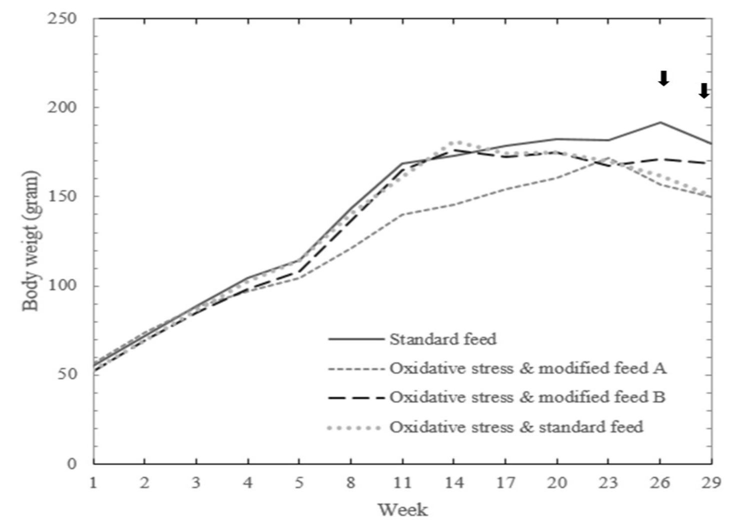
often causes weight loss (Rojas-Armas *et al*., 2020). In the standard feed and stress induction group, the rats looked sick, were less active and had no appetite, so their body weight was lower than the normal and modified B groups.

Lipid profile and glucose levels

The cholesterol, triglyceride, HDL-C and LDL-C levels did not vary significantly across the groups (Table 2). However, a noteworthy observation was the seemingly elevated glucose levels in the negative control group, although this difference was not statistically significant (Table 2).

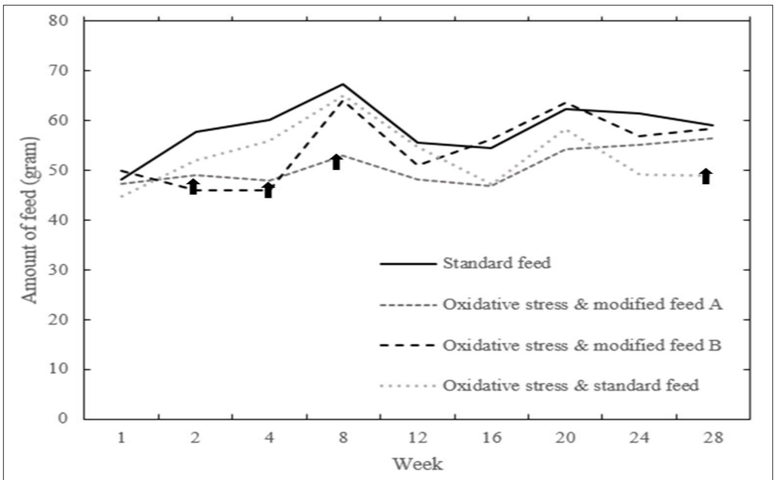
At the end of the treatment in this study, all groups demonstrated that cholesterol, triglyceride and HDL-C levels tended to be low. In contrast, LDL-C levels were found to be normal (Ihedioha *et al*., 2013), with no significant differences. However, although they were not statistically different, the LDL levels in the modified feed B group appeared higher than those in the other groups. It can be explained by the fact that the digestion of mice that consume arrowroot contains more short-chain fatty acids. Short-chain fatty acids, primarily acetate, will enter the bloodstream. After arriving in the liver, these short-chain fatty acids can become an energy source and can be converted into acetyl-coenzyme A. Acetyl-CoA can be converted into acetoacetyl-CoA for cholesterol synthesis and converted into malonyl-CoA for the synthesis of fatty acids and triglycerides (Moffett *et al*., 2020).

Glucose levels at the end of treatment in the modified feed tended to be lower than the standard feed and the oxidative stress group, although this was not statistically significant. The effect of arrowroot in previous research was also indicated by a reduction in glucose levelcompared to mice given standard feed (Pricilla and Buana, 2020). SCFA, produced from bacterial fermentation in the



Black arrows indicate significant differences (p<0.05).

Fig 1: Body weight of rats (grams) during the experimental period.



Arrows indicate significant differences (p<0.05).

Fig 2: Feed intake of weekly test animals during the experimental period.

Table 2: Lipid profile and glucose level at week 29.

	Total cholesterol	Triglyceride	HDL-C	LDL-C	Glucose
Standard feed	54.52±12.89	24.76±8.36	28.36±4.32	22.79±4.56	107.19±16
Oxidative stress and standard feed	54.93±2.35	33.07±0.25	28.63±5.97	17.13±6.32	139.57±35
Oxidative stress and modified feed A	48.70±7.40	30.58±4.90	24.83±3.28	22.56±3.82	91.83±12
Oxidative stress and modified feed B	53.90±6.91	32.72±7.21	26.46±6.88	27.18±7.29	103.72±8
p-value	0.86	0.17	0.8	0.133	0.128

HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol.

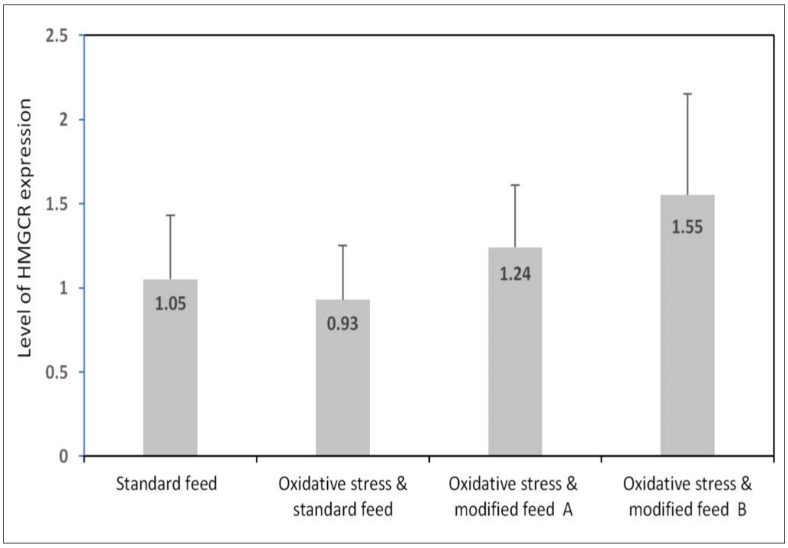


Fig 3: HMGCR expression.

intestine after consumption of arrowroot, can potentially inhibit gluconeogenesis (Tang and Li, 2021). Administration of casein can also reduce glucose levels and increase insulin secretion (Geerts *et al*., 2011).

HMGCR expression

The relative expression of HMGCR was highest in the modified feed B, modified feed A and normal group and lowest in the negative control group, but the statistics were insignificant (p=0.17). Result from post hoc test using the LSD test showed that there was a significant difference (p=0.038) between the modified feed B group and the negative control group (Fig 3).

Cholesterol levels can influence HMGCR expression. Dietary cholesterol will cause a decrease in HMGCR expression (El-Sohemy and Archer, 2000). On the other hand, administering HMGCR inhibitors lowers cholesterol and can trigger a feedback mechanism so that HMGCR expression increases (Bjarnadottir *et al*., 2013). In this study, experimental animals showed normal cholesterol and triglyceride levels. However, this level tended to be low, so there is a possibility of a feedback mechanism that causes an increase in HMGCR expression. Animals in this study experienced oxidative stress and required an enhanced immune response (Naik *et al*., 2024). Immune cells necessitate increased expression of HMGCR for cholesterol synthesis. Cholesterol within the T cell membrane is the main component of the receptor. It is required in the signalling activity of the effector function of TCD8 cells and iNKT cells to increase immune activity (Yu *et al*., 2021). Antioxidant administration can affect lipid metabolism and improve immune function (Li *et al*., 2020). Increased expression of HMGCR is required for insulin secretion, allowing cells to utilize glucose. Conversely, inhibition of HMGCR can lead to insulin resistance (Sarsenbayeva *et al*., 2021).

CONCLUSION

Combining an arrowroot diet (especially at 60%), low sugar and adding casein positively affects oxidative stress-induced rats. Animals appeared healthier, had good feed intake and weighed better than those fed standard feed. However, there was no difference in glucose levels and lipid profiles. In addition, HMGCR expression in liver tissue tended to increase, but it is not statistically significant.

ACKNOWLEDGEMENT

Researchers would like to thank Fatin, who helped in conducting this research. Part of this study was supported by a grant from the Unit of Research and Community Services, Faculty of Medicine, Universitas Islam Indonesia (UPPM FK UII).

Conflict of interest

No conflict of interest.

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