jffn Journal of Functional Food and Nutraceutical

HYPOGLYCEMIC AND ANTIOXIDATIVE EFFECTS OF CHROMIUM, MAGNESIUM, AND CINNAMON FORTIFIED PARBOILED RICE ON DIABETIC RATS

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ABSTRACT

One of the strategies to manage diabetic blood glucose is through the consumption of foods with a low glycemic index (GI) such as parboiled rice with adequate chromium and magnesium. In diabetes, insulin resistance leads to impaired glucose metabolism and oxidative stress. This oxidative rate can be prevented by adding to the intake of antioxidants from cinnamon. Therefore, this research aimed to determine the effect of chromium, magnesium, and cinnamon fortified parboiled rice on hypoglycemic and antioxidant activities in diabetic rats. The clinical trial treatments on rats with dietary intake were given for 28 days in 6 groups, namely healthy rats with standard feed and diabetic rats with standard feed milled or non-parboiled rice, non-fortified parboiled rice Cr and Mg fortified parboiled rice as well as Cr, Mg, and cinnamon fortified parboiled rice (DRFCP). The analysis carried out included glucose, insulin, malondialdehyde (MDA) levels, and statistical analysis using One-Way Annova. The results showed that in the DRFCP group, glucose and MDA levels decreased significantly ($p < 0.05$) from 258.63 mg/dL to 111.19 mg/dL (57%) and 9.28 ng/mL to 1.96 ng/mL (78.87%), while the insulin levels increased significantly ($p < 0.05$) from 413.97 ug/dL to 540.65 ug/dL (30.60%). This type of feed (DRFCP) can be used as a diet for diabetes because it can reduce blood glucose and malondialdehyde levels.

Keywords: antioxidative; diabetic; hypoglycemic; malondialdehyde; parboiled rice

ABSTRAK

Salah satu strategi untuk mengelola gula darah diabetesi ialah mengonsumsi makanan berindeks glikemik (IG) rendah seperti beras *parboiled*. Selain itu, diabetesi perlu kecukupan kromium dan magnesium. Resistensi insulin pada diabetesi mengakibatkan gangguan metabolisme gula darah, dan *stress oxidative*. Untuk mencegah atau menahan laju oksidatif tersebut dapat ditambahkan asupan antioksidan dari kayu manis. Tujuan penelitian ini untuk mengetahui efek pemberian beras *parboiled* terfortifikasi kromium, magnesium dan kayu manis terhadap efek hipoglikemik dan antioksidatif pada tikus diabetes. Perlakuan uji klinis pada tikus dengan asupan diet diberikan selama 28 hari pada 6 kelompok, yaitu tikus sehat dengan pakan standar, tikus diabetes dengan pakan standar, tikus diabetes dengan beras giling atau *non parboiled*, tikus diabetes dengan beras *parboiled* non-fortifikasi, tikus diabetes dengan beras *parboiled* terfortifikasi Cr, Mg, dan tikus diabetes dengan beras *parboiled* fortifikasi Cr, Mg, kayu manis (DRFCP). Analisis yang dilakukan meliputi kadar glukosa, insulin dan Malondialdehid (MDA). Analisis statistik data menggunakan *One Way Anova*. Hasil penelitian menunjukkan bahwa pada kelompok DRFCP kadar glukosa dan MDA berturut-turut menurun secara nyata ($p < 0,05$) dari 258,63 mg/dL menjadi 111,19 mg/dL (57%) dan 9,28 ng/mL menjadi 1,96 ng/mL (78,87%), sedangkan kadar insulin meningkat secara nyata ($p < 0,05$) dari 413,97 ug/dL menjadi 540,65 ug/dL (30,60%). Pemberian asupan DRFCP dapat menurunkan kadar glukosa darah, dan malondialdehid. Jenis pakan ini dapat digunakan untuk diet penderita diabetes.

Kata kunci: antioksidatif; beras *parboiled*; diabetes; hipoglikemik; malondialdehid

Article Information

Article Type: Research Article
Journal Type: Open Access
Volume: 4 Issue 1

Manuscript ID
V4n11050-1

Received Date
14 July 2022

Accepted Date
05 September 2022

Published Date
20 September 2022

DOI: 10.33555/jffn.v4i1.97

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Citation:
Leba, H., Yulianto, W.A., Pujimulyani, D. 2022. Hypoglycemic and Antioxidative Effects of Chromium, Magnesium, and Cinnamon Fortified Parboiled Rice on Diabetic Rats. J. Functional Food & Nutraceutical, 4(1), pp.49-55

INTRODUCTION

According to the International Diabetes Federation Diabetes Atlas 2021, the number of people with diabetes in Indonesia in 2021 will reach 19.465 million or 10.8% of the total population and in 2045 it is estimated to reach 28.6 million (IDF, 2021). Due to this large number of patients, there is a need for urgent treatment. One of the strategies to manage diabetes blood sugar is through the consumption of foods with a low glycemic index (GI) (GI < 55) such as rice. Although rice is a staple food with a high GI, its components can be modified to have lower GI by applying several processing methods. These include the parboiling process accompanied by cooling, which can increase the levels of resistant starch (RS). Yulianto et al. (2018) stated that parboiled rice processed by cooling treatment contained RS of 3.75-10.56%. According to Anderson (2008) diabetics are deficient in chromium and magnesium (Dong et al., 2011). Therefore, the availability of these micronutrients is needed to control blood glucose levels and increase insulin action by activating the receptors (Dubey et al., 2020).

The condition of hyperglycemia in diabetes mellitus (DM) patients is indicated by the accumulation of free radicals in the body. This can cause insulin resistance, leading to oxidative stress due to an increase in reactive oxygen species (ROS) with an impact on disrupting the balance of oxidation-reduction reactions (redox), which decreases antioxidants in the body. Therefore, it is necessary to improve glycemic control and antioxidants to inhibit oxidation reactions by free radicals (Réus et al., 2019). One source of high antioxidant food is cinnamon with several main flavonoid contents which are antioxidants, namely cinnamic aldehyde, cinnamyl acetate, and eucalyptol. There are also other chemical compounds in form of phenols, terpenoids, saponins, polyphenols, cinnamaldehyde, and flavonoids as good sources of antioxidants to control blood glucose levels (Talaei et al., 2017).

Yulianto et al (2018) reported that Cr, Mg, and cinnamon fortified parboiled rice soaking at 65°C for 2.5 hours and cooling at 2°C for 12 hours had the lowest GI of 20.03 and the highest RS content of 23.99%. The RS was shown to be negatively correlated with the glycemic index. This indicates the higher the RS in food, the lower the glycemic index. According to Sun et al. (2018), the administration of a high RS type 2 diet, namely a 15 g/kg BW dose can reduce blood glucose levels by 59.65% in STZ-induced rats. Zhu et al. (2017) stated that the cinnamaldehyde in cinnamon reduced glucose and lipid levels, while the presence of polyphenol compounds can prevent insulin resistance in diabetic rats. Therefore, there is a need to investigate the effects of hypoglycemia and antioxidant on diabetic rats fed with chromium, magnesium, and cinnamon fortified parboiled rice.

MATERIALS AND METHOD

Materials and tools.

The main ingredients used to make parboiled rice are prime varieties of Ciherang rice obtained from agricultural shop in Sleman, Yogyakarta, $CrCl_3$, magnesium acetate (Sigma Aldrich), and cinnamon powder (Beringharjo market, Yogyakarta). The materials for the treatment of experimental animals include male Wistar rats aged 2 months, weighing 150-200 g, and are obtained from the laboratory of the Center for Food and Nutrition Studies, Gadjah Mada University Yogyakarta (CFNS UGM) for *in vivo* biological testings. Streptozotocin (STZ) and Nicotinamide (NA) were used for diabetes induction. The AIN-93 standard feed formula includes aquadest, cornstarch, casein, sucrose, soybean oil, mineral mix, vitamin mix, L-cystine, and choline bitartrate (Reeves et al., 1993) This research also used GOD-PAP, CHOD-PAP, and Malondialdehyde (MDA) test reagents including phosphoric acid, while standard TEP (Tetraethoxypropane) and TBA (Thiobarbituric acid) were obtained from CFNS UGM. The tools used include glucose, insulin, and cholesterol kits (DiaSys diagnostic system GmbH, Alte Strasse 9 Holzheim, Germany).

Production of chromium (Cr), magnesium (Mg), and cinnamon extract fortified parboiled rice.

The process of making parboiled rice refers to the method of Yulianto et al. (2018) with modified addition of $CrCl_3$ 5.39 mg/L, Mg acetate 1.75 g/L, and 10% cinnamon extract. The extraction process was carried out using 400 g of cinnamon powder with 1 L ml of water and blended for 10 minutes. The solution was filtered using a calico cloth and 40% cinnamon extract was stored in a refrigerator at 4°C. The grain to be used was washed 2 times with plain water and 1 time using distilled water with a 1:1.5 ratio of grain to water. Subsequently, 5 kg of grain was sorted and immersed in 3.75 L of a solution containing 20 mg $CrCl_3$, 6.56 g Mg acetate, and 10% cinnamon extract at a temperature of 65°C for 150 minutes. The fortified grain was cooked (boiled) for 20 minutes at a temperature of 100°C. After cooking, the grain was cooled at 0°C for 12 hours and was dried using a cabinet dryer at a temperature of 50°C until the moisture content of the fortified grain reached 13-14%. The dry grain is ground to produce parboiled rice fortified with Cr, Mg, and cinnamon extract.

Testing parboiled rice fortified Cr, Mg, and cinnamon extract on rats.

The use of experimental animals in this research has received ethical approval from the Health Research Ethics Committee, Universitas Respati Yogyakarta No: 355.3/FIKES/PL/X/2019. The animals used are 24 male Wistar rats aged 2 months, weighing 150-200 g. They were divided into 6 treatment groups, namely healthy rats with standard feed (HRSF), and DM rats with standard feed (DRSF), DM rats with milled or non-parboiled rice (DRNP), DM rats with non-fortified parboiled rice (DRNFP), DM rats with Cr, Mg fortified-parboiled rice (DRFP), and DM rats with Cr, Mg, cinnamon fortified-parboiled rice (DRFCP). Before treatment, the rats were adapted for 7 days by administering standard AIN-93 feed and drinking ad libitum. On the 8th day, STZ injection at a dose of 45 mg/kg BW and NA at 110 mg/kg BW dose was administered intraperitoneally, which had been dissolved in 0.1 mol/L sodium nitrate with a pH of 4.5. The glucose, insulin, and MDA were analyzed on the 8th day as initial, the 11th day as pre-treatment, and the 40th day as treatment data

The standard AIN-93 and treatment feed were given, with approximately 15 g/head/treatment group from the 12th to 40th day, which is the 1st to 28th day of treatment. The composition of standard and treatment feed is shown in Table 1.

Measurement of glucose and insulin analysis.

The glucose levels were analyzed using the *Glucose-Oxidase Peroxidase-Aminoantipyrine-Phenol* (GOD-PAP) method with a glucose kit (Diasys diagnostic systems GmbH, Alte-Strasse 9 Holzheim, Germany). The blood sample was taken from blood vessels around the eyes using microhematocrit and centrifuged at 2600 rpm for 20 minutes to obtain serum. Analysis of serum glucose levels was carried out using a kit consisting of standard solutions and reagents. A total of 10 µl sample was mixed with 1000 µl of reagent and 10 µl of aquadest. Subsequently, the solution was incubated at 37ºC for 10 minutes and measured at a wavelength of 500 nm absorbance. Measurement of insulin was carried out using the enzyme-linked immunosorbent assay (ELISA) method, which was reacted with monoclonal anti-mouse insulin in the ELISA kit and measured with a microplate reader at a wavelength of 450 nm.

Malondialdehyde (MDA) measurement.

The MDA analysis procedure used the thiobarbituric acid reactive substance (TBARs) method. The blood sample was taken from the blood vessels around the eyes using a microhematocrit and centrifuged at 2600 rpm for 20 minutes to obtain serum for analysis. Approximately 0.1 mL of serum was taken and put into a tube containing EDTA (Ethylene diamine tetraacetic acid). A total of 750 µL of phosphoric acid was put into a 13 mL polypropylene tube and 50 µL of plasma sample was added. The mixture was shaken until homogeneous and 250 µL of 40 mM TBA solution was added. Furthermore, 450 µL of distilled water was added to the tube and tightly closed. The mixture is brought to a boil, cooled in an ice bath, and the sample was applied to an 18-column C Package. The absorbance was measured with a spectrophotometer at a wavelength of 532 nm.

Data analysis.

The statistical analysis used was analysis of variance (Annova) at the 95% confidence level ($p < 0.05$) to determine the difference between the treatment and the control group (standard feed). When the results are significantly different, the test was continued with the Duncan Multiple Range Test. Paired T-Test was also conducted to determine the difference before and after treatment. Subsequently, the statistical analysis was carried out using SPSS version 25.0 software.

Table 1. Diet Formulation

Ingredient	Treatment Group					
	HRSF	DRSF	DRNP	DRNFP	DRFP	DRFCP
Cornstarch (g)	620.7	620.7	-	163	218	215
Ciherang rice (g)	-	-	899.28	-	-	-
Parboiled rice (g)	-	-	-	656.16	-	-
Cr, Mg – parboiled rice (g)	-	-	-	-	587.54	-
Cr, Mg, cinnamon-parboiled rice (g)	-	-	-	-	-	559.28
Casein (85% protein) (g)	140	140	55.38	70.19	74.02	75.35
Sucrose (g)	100	100	30	50	50	100
Soybean oil (g)	40	40	31.59	33.3	31.59	30.50
Fibre (g)	50	50	0	0	0	0
Mineral mix (g)	35	35	35	35	35	35
Vitamin mix (g)	10	10	10	10	10	10
L-cysteine (g)	1.8	1,8	1,8	1,8	1,8	1.8
Choline bitartrate (g)	2.5	2.5	2.5	2.5	2.5	2.5
Total (g)	1000	1000	1066.04	1022.67	1010.45	1029.47
Energy (kcal)	3603.63	3603.63	3756.69	3604.58	3603.65	3602.36

The healthy rats with standard feed (HRSF), and DM rats with standard feed (DRSF), DM rats with milled or non-parboiled rice (DRNP), DM rats with non-fortified parboiled rice (DRNFP), DM rats with Cr, Mg fortified parboiled rice (DRFP), and DM rats with Cr, Mg, cinnamon fortified-parboiled rice (DRFCP)

RESULTS AND DISCUSSION

Hypoglycemic effect.

In this study, different amounts of cornstarch and sucrose were added to meet the required number of calories, which was equivalent to AIN-93 (3,603.63 kcal). Therefore, the differences in dietary components can be ignored and the study is aimed at how the effect of the type of diet group on the glucose and insulin levels of rats. The glucose levels of rats in all groups before STZ injection were in the normal range, namely <200 mg/dL. Meanwhile, 3 days after the injection, glucose levels were analyzed, and the results obtained are presented in Table 2. The table shows that in the STZ-injected group, blood glucose levels increased significantly to a hyperglycemic state (glucose >200 mg/dL). Based on the analysis of glucose levels in diabetics rate after 28 days of treatment as shown in Table 2, there are significant differences in glucose and insulin levels (Table 3) between the treatment and the control groups ($p<0.05$). The decrease in glucose levels with the highest percentage was in DRFCP at 57.00%, followed by DRFP, DRNFP, and DRNP at 50%, 46.23%, and 32.80%, respectively (Table 2). The largest increase in insulin levels was in DRFCP, which was 30.60%, followed by DRFP, DRNFP, and DRNP at 25.82%, 16.47%, and 11.62%, respectively (Table 3). These results showed the roles of parboiled rice, magnesium, and cinnamon bioactive components. This is in line with the research conducted by Hamad et al (2017), which stated that the administration of parboiled rice can reduce post-prandial blood glucose levels in type 2

Table 2. Glucose Levels Before and After Treatment

Glucose (mg/dL)					
Group	Before STZ Injection	3 Days Post STZ Injection/Before Treatment	Changes After STZ Injection (%)	28 Days of Treatment	Changes After Treatment (%)
HRSF	70.71 ± 5.47	74.70 ± 2.47[a]	+5.6	77.22 ± 1.56[aA]	+3.37
DRSF	68.56 ± 4.28	263.19 ± 7.00[b]	+183.88	269.76 ± 5.23[fF]	+2.49
DRNP	73.39 ± 2.21	258.03 ± 1.34[b]	+251.58	139.31 ± 1.49[dD]	-46.23
DRNFP	71.24 ± 1.56	259.13 ± 5.27[b]	+263.74	130.54 ± 4.13[cC]	-50.00
DRFP	73.60 ± 4.18	261.11 ± 2.80[b]	+254.76	139.31 ± 1.49[dD]	-46.23
DRFCP	72.85 ± 2.41	258.63 ± 3.61[b]	+255.01	111.19 ± 4.09[bB]	-57.00

Notation with different lowercase letters in the same row shows significant differences between treatment groups (One Way Annova, p<0.05). Notation with different capital letters on the same column shows a significant difference before and after treatment (Paired T-Test, p<0.05).
The healthy rats with standard feed (HRSF), and DM rats with standard feed (DRSF), DM rats with milled or non-parboiled rice (DRNP), DM rats with non-fortified parboiled rice (DRNFP), DM rats with Cr, Mg fortified parboiled rice (DRFP), and DM rats with Cr, Mg, cinnamon fortified-parboiled rice (DRFCP)

Table 3. Insulin Levels Before and After Treatment

Insulin (ug/dL)					
Group	Before STZ Injection	3 Days Post STZ Injection/Before Treatment	Changes After STZ Injection (%)	28 Days of Treatment	Changes After Treatment (%)
HRSF	566.80 ± 7.81[a]	563.39 ± 7.73[b]	-0.60	552.86 ± 8.20[fF]	-1.86
DRSF	566.80 ± 7.81[a]	422.11 ± 11.77[a]	-26.24	405.51 ± 7.98[aA]	-3.93
DRNP	566.28 ± 2.18[a]	419.75 ± 6.35[a]	-2587	484.91 ± 3.04[cC]	+16.47
DRNFP	577.31 ± 2.71[b]	415.81 ± 2.32[a]	-27.97	517.24 ± 6.77[cC]	+25.82
DRFP	571.01 ± 6.18[ab]	411.08 ± 4.23[a]	-28.00	484.91 ± 3.04[cC]	+16.47
DRFCP	573.89 ± 2.71[ab]	413.97 ± 7.50[a]	-27.86	540.65 ± 2.69[dD]	+30.60

Notation with different lowercase letters in the same row shows significant differences between treatment groups (One Way Anova, p<0.05). Notation with different capital letters on the same column shows a significant difference before and after treatment (Paired T-Test, p<0.05). The healthy rats with standard feed (HRSF), and DM rats with standard feed (DRSF), DM rats with milled or non-parboiled rice (DRNP), DM rats with non-fortified parboiled rice (DRNFP), DM rats with Cr, Mg fortified parboiled rice (DRFP), and DM rats with Cr, Mg, cinnamon fortified-parboiled rice (DRFCP)

DM patients (p <0.05). It has a high RS content and can slow down carbohydrate digestion, thereby increasing satiety and inhibiting motility in the body's gastrointestinal tract. Rouhi et al (2017) discovered that giving magnesium supplements for 4 weeks in DM rats improved insulin resistance, sensitivity, as well as glucose metabolism and also prevent lipid disorders due to diabetes. A previous investigation identified the role of magnesium in insulin receptor phosphorylation and translocation of GLUT-4 from intracellular to plasma membrane. This indicated that magnesium can control blood glucose and has a direct effect on insulin receptors (Morakinyo et al., 2018). Zhu et al. (2017) stated that cinnamaldehyde and polyphenol compounds in cinnamon have the potential to reduce glucose levels and prevent insulin resistance in diabetic rats. Meanwhile, Talaei et al. (2017) reported that giving a cinnamon diet at a dose of 3 g/day for 3 weeks can reduce blood glucose and malondialdehyde and increase insulin levels by activating receptor proteins on cells. This process increases insulin sensitivity and lowers blood glucose levels to near normal. Foods that have dietary fiber and are rich in antioxidants play a role in reducing insulin resistance by capturing free radicals and reducing inflammation. Therefore, -4 expression increases and causes a GLUT reduction in blood glucose levels (Beji et al., 2018).

Antioxidative effect.

Table 4 showed that there is a significant difference (p<0.05) in MDA levels between the treatment group and the control group. The highest decrease in MDA levels was discovered in DRFCP at 78.87%. This is because, in the DRFCP group treated with fortified parboiled rice with chromium, magnesium, and cinnamon, there are phenolic compounds obtained from the addition of 10% cinnamon extract. These results are in line with the research of Tuzcu et al. (2017), where the administration of polyphenols from cinnamon had a significant effect on MDA levels (p < 0.05) in rats. The cinnamon extract contains polyphenols that can stimulate antioxidant enzyme activity, thereby preventing oxidative stress and increasing nuclear factor-erythroid-2 related factor 2 (NrF2). Higher activity of NrF2 can also improve the production of antioxidants. Polyphenols have the potential to activate extracellular signal regulatory kinase (ERK) and NrF2, leading to an increase in endogenous antioxidant gene expression (Beji et al., 2018).

Table 4. MDA Levels Before and After Treatment

	MDA (ng/mL)				
Group	Before STZ Injection	3 Days Post STZ Injection/Before Treatment	Changes After STZ Injection (%)	28 Days of Treatment	Changes After Treatment (%)
HRSF	1.09 ± 0.16^{ab}	1.27 ± 0.13^{a}	+16.5	1.64 ± 0.25^{aA}	+29.13
DRSF	1.00 ± 0.34^{a}	8.76 ± 0.42^{b}	+776	9.28 ± 0.36^{dD}	+5.93
DRNP	1.54 ± 0.24^{c}	9.22 ± 0.54^{b}	+498.70	4.91 ± 0.17^{Cc}	-46.74
DRNFP	1.27 ± 0.23^{abc}	9.10 ± 0.51^{b}	+616.53	2.57 ± 0.27^{bB}	-71.75
DRFP	1.23 ± 0.21^{abc}	8.92 ± 0.20^{b}	+625.20	2.73 ± 0.15^{bB}	-69.39
DRFCP	1.41 ± 0.25^{bc}	9.28 ± 0.33^{b}	+558.15	1.96 ± 0.13^{aA}	-78.87

Notation with different lowercase letters in the same row shows significant differences between treatment groups (One Way Anova, p<0.05). Notation with different capital letters on the same column shows a significant difference before and after treatment (Paired T-Test, p<0.05). The healthy rats with standard feed (HRSF), and DM rats with standard feed (DRSF), DM rats with milled or non-parboiled rice (DRNP), DM rats with non-fortified parboiled rice (DRNFP), DM rats with Cr, Mg fortified parboiled rice (DRFP), and DM rats with Cr, Mg, cinnamon fortified-parboiled rice (DRFCP)

CONCLUSION

Dietary intake of parboiled rice fortified with chromium, magnesium, and cinnamon fortified-parboiled rice (DRFCP) significantly affected glucose, insulin, and malondialdehyde levels of rats. It shows that the administration of the feed to DM rats was best for lowering glucose and MDA levels, and increasing insulin levels. This type of food is suitable as a diet for diabetics.

ACKNOWLEDGEMENT

The authors would like to thank the Directorate General of Higher Education, Ministry of Research, Technology and Higher Education of Indonesia which has funded this research through the Master Thesis Research Program in 2019 with contract number: DIPA-042.06.1.401516/2019, 5 December 2018.

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