



## **Effects of Cinnamon Bark Extract, Moderate Intensity Exercise, Intermittent Fasting, Metformin on Fasting Blood Glucose Levels, Lipid Profile and Malondialdehyde in DMT2 Rats: Case Study**

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### **Abstract**

Diabetes is *a silent killer*. Diabetes mellitus (DM) occurs when the pancreas does not produce enough insulin or the body cannot use insulin effectively. DM is often characterised by chronic hyperglycemia. Diabetes Mellitus (DM) is one of the Non-Communicable Diseases (NCDs), which is a public health problem and has a relatively high number of sufferers in the world. Many ways are used to treat and prevent DM, including changing to a healthier lifestyle and using modern medicine or herbal medicine that can improve hyperglycemia in DM patients. This study was conducted to determine the effects of cinnamon extract with a dose of 120 mg / kgBW / day orally, moderate swimming exercise, and intermittent fasting for 19 days on T2DM Rats. The study shows that there was a significant increase ( $p < 0.005$ ) in Fasting Blood Glucose (FBG) between day 1 and day 4 in the untreated group. In the group given metformin, there was a significant change in FBS on day 1 and day 4. In the group given cinnamon extract, there was a change in FBG on days 1 and 4 (increase) and days 10 and 13 (decrease). In the swimming group, there was an increase in FBG on day 1 and day 4 and a significant decrease in FBS on days 10 and 14, while in intermittent fasting, there was an increase in FBS on day 1 and day 4, which was statistically significant. Increases and decreases in lipid and Malondialdehyde (MDA) profiles were also present in each treatment group. The conclusion is that cinnamon bark extract, moderate-intensity swimming exercise, and intermittent fasting impact fasting blood glucose levels, lipid profiles, and MDA in Diabetes induced rats.

**Keywords:** Diabetes induced rats, Cinnamon extract, moderate exercise swimming, intermittent fasting

### **Introduction**

Diabetes is *a silent killer*. Diabetes Mellitus (DM) is caused by pancreatic dysfunction, where the pancreas does not produce enough insulin or the body cannot use insulin effectively. This is characterised by chronic hyperglycemia (Dr. Berbadetta Dian Nivita Dewi, et al., 2019)

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Diabetes mellitus can be classified into two types, namely Type I DM and Type II DM. Type I DM is a chronic hyperglycemia due to insulin insufficiency; sufferers of this disease are dependent on insulin. The causative agents are genetic factor, immune factor, environmental factor, decreased beta cells, population, pregnancy, and other factors that are not directly to the ability of the pancreas to produce insulin (Aklia Suslia, 2016).

Non-insulin-dependent Type II DM is caused by relative beta-cell failure and insulin resistance. Causative factors are age, obesity, family history, and lifestyle (Bruuer and Suddarth, 2002 and (Nuari, 2017).

The World Health Organisation reported that between 2000 and 2016, there was a 5% increase in premature deaths due to diabetes. In 2019, diabetes was the ninth leading cause of death, with an estimated 1.5 million deaths directly due to diabetes (WHO 2021).

*The International Diabetes Federation* (IDF) noted that 537 million adults (aged 20-79 years), or 1 in 10 people, are living with diabetes, which causes 6.7 million deaths, or one in every 5 seconds. China is the country with the largest number of adults with diabetes in the world. 140.87 million Chinese people live with diabetes in 2021, and Indonesia is in fifth place with 19.47 million people with diabetes. With a population of 179.72 million, the prevalence of diabetes in Indonesia is 10.6%.

It has been reported that prevalence of DM 2018 in Indonesia, the highest is the capital city of Indonesia DKI Jakarta with 3.4%, and the lowest is East Nusa Tenggara with 0.9% while the Riau Islands province are at sixth place at 1.6% (Ministry of Health, 2020). The prevalence of Diabetes Mellitus based on a doctor's diagnosis in residents of all ages according to district/city, Riau Islands Province are Karimun 1,271 sufferers, Tanjung Pinang City 1,150 sufferers and Batam City 7,263 sufferers (Riskesdas RI, 2019).

DM has the potential to cause various complications, from acute complications in the form of diabetic ketoacidosis to chronic complications such as neuropathy as well as to an increased risk of coronary heart disease. Diabetes complications can be prevented by optimal glycemic control (Soelistijo SA, 2019).

Various pharmacological and non-pharmacological therapies have been developed to control blood sugar levels (Pagliari et al., 2023). Diabetes mellitus patients require long-term treatment, which will certainly affect the quality of life both in terms of health and economy. (Suriadi et.al, 2013). Drugs for diabetes with fewer side effects and lower costs is still a major challenge in its development (Wang et al., 2013). Traditional medicine using herbs can be a good alternative in replacing or complementing Western medicine so that it can provide optimal therapeutic results (Jia et al., 2003; Li et al., 2004; Prabhakar and Doble, 2011; Yang et al., 2011; Wang et al., 2013).

Traditional plants and spices are easily found in society and used as herbal medicine, some of which are used to control blood sugar levels (Ega Priani et al., 2022). One of them is cinnamon (Ahuokpeme et al., 2023). Cinnamon (scientific name) is known to be effective in controlling blood sugar in healthy people and people with diabetes mellitus. So, the effect of

lowering blood sugar levels with cinnamon is worth considering as a treatment for diabetes mellitus. (Priani et al., 2020)

Cinnamon is a species of *Cinnamomum*, a local Indonesian plant with an active substance, polyphenols, which can increase insulin receptors in people with type 2 diabetes mellitus. Increasing the sensitivity of these receptors can increase the effectiveness of glucose absorption, ultimately reducing blood glucose levels to near normal (Prettika Juhan Arini, 2016).

In addition to herbal medicines, moderate exercise can control blood glucose levels in DMT2 patients (Munawarah & Segita, 2023). According to WHO, the recommended dose for moderate-intensity exercise is 30 minutes daily (WHO, 2021).

Physical exercise or sports facilitates the transfer of Glucose into cells and increases insulin sensitivity (Price & Wilson, 2005). For both types of diabetes, doing physical exercise or sports has been shown to increase glucose utilisation by cells so that blood glucose levels decrease (Corwin, 2009). In T2DM, physical exercise activities can improve overall glucose control by decreasing HbA1c concentration, which can be an indicator for reducing the risk of complications from diabetes. While in T1DM, physical exercise will make metabolic regulation difficult; therefore, blood sugar control is not the goal of exercise (Sudoyo et al. 2015).

*Intermittent* fasting is one of the pillars that can control blood sugar levels. *Intermittent* fasting is known to reduce adiposity, which causes a reduction in insulin resistance. This is due to reduced calorie intake and metabolic reprogramming that occurs due to the effects of intermittent fasting. In addition, reduced calorie intake can increase *healthier ageing* and reduce the occurrence of chronic diseases due to increased Adenosine Monophosphate Protein Kinase (AMPK). This has similarities with the mechanism of action of the drug metformin. In essence, reduced energy intake through *intermittent fasting* will cause increased AMPK levels, which improve insulin sensitivity and blood sugar homeostasis (Albosta, M., and Bakke, J. 2021).

One study was conducted by Furmli et al. (2018), who studied three type 2 DM patients who did intermittent fasting for several months. During the study, all patients experienced a decrease in HbA1C, which is a blood test that can measure average blood sugar levels over the past 3 months, weight loss, and being able to stop insulin therapy within 1 month.

## **Research Method**

### **Materials**

This study used 25 male Wistar rats (150–200 g). Primary materials included: cinnamon bark extract, metformin, streptozotocin (STZ 45 mg/kg BW), high-fat diet (HFD), glucometer strips, lipid and MDA assay kits. Rats were housed under controlled conditions with food and water ad libitum.

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## **Methods of Functionalization**

Rats were acclimatised for 7 days, then induced with HFD and STZ to develop type-2 diabetes. Diabetic rats (FBG  $\geq 200$  mg/dL) were divided into five groups (n=5):

- a) T-Ct: control (no treatment)
- b) T-St: cinnamon extract
- c) T-Sw: moderate swimming (30 min/day)
- d) T-If: intermittent fasting
- e) T-Me: metformin

Treatments were given for 19 days while rats remained on HFD.

## **Characterization**

- a) Fasting Blood Glucose (FBG): measured on days 1, 4, 7, 10, 13, 16, 19.
- b) Lipid Profile: cholesterol, HDL, LDL, triglycerides (pre- and post-treatment).
- c) Malondialdehyde (MDA): oxidative stress marker (pre- and post-treatment).
- d) Statistical Analysis: Shapiro–Wilk, Levene, t-test or Wilcoxon, significance at  $p < 0.05$ .

## **Methods**

This study used a pretest-posttest experimental laboratory with control and treatment groups. The study's experimental laboratory used a pretest-posttest comparison group design. This research was conducted in the UNPRI laboratory in collaboration with the Integrated Laboratory and Laboratory of the Universitas Sumatera Utara and Ethical Clearance at the Health Research Ethics Commission, Universitas Prima Indonesia. The subjects of this study were twenty-five rats induced with Type-2 Diabetes Mellitus, divided into five groups: the control group, the treatment group without treatment, the cinnamon extract group, the moderate-intensity swimming group, the intermittent fasting group, and the metformin group. The experimental treatment was carried out for three weeks after one week of acclimatisation. As for the ethical consideration, the study was approved by the university research ethical committee (Number: 014/KEPK/UNPRI/XII/2023).

This study used adult male Wistar (*Rattus norvegicus*) rats weighing 150-200 grams, who were in good health and doing regular activity.

Before the experimentation, the animals underwent a one-week acclimatisation in the research animal centre of the university, during which the animals were fed commercial pellets and water ad libitum. The animals were caged in stainless steel cages with ventilation in a room with a temperature of 20–26°C and 40–70% humidity and lighting with a 12-hour light/dark cycle. Rats are adapted to their new living space, and feeding and drinking are equalised for all rats. The purpose of this adaptation is so that all rats are not in a state of stress and are in the same condition before being given treatment.

Before the study began, the rats were divided into five groups, each group of 5 rats, one group for each treatment, grouping the rats randomly.

Rats were given a high-fat diet before and during treatment. The HFD diabetogenic rat feed was made to induce type 2 diabetes by mixing 200 g of goat fat, 100 g of boiled egg yolk, 100 g of sucrose, and 1000 g of corn rice. Goat fat is heated first until it melts, and egg yolk is obtained from boiled eggs. Goat fat and egg yolk are mixed into 1000 g of corn rice (Gani et al., 2013).

### **Diabetes Induction**

In this study, rats were induced with 45 mg/kgBW streptozotocin (STZ) after one week of acclimatisation and fed a high-fat diet (HFD) throughout the acclimatisation and treatment period to develop a model of metabolic dysfunction, including diabetes and obesity. Streptozotocin, administered via intraperitoneal injection at a specific dosage, selectively destroyed pancreatic  $\beta$ -cells, leading to insulin deficiency and hyperglycemia. The high-fat diet, rich in saturated fats, exacerbated metabolic disturbances by promoting weight gain, insulin resistance, and dyslipidemia. This combination effectively mimicked the pathological conditions observed in type 2 diabetes and obesity, allowing for an in-depth investigation of therapeutic interventions and metabolic alterations in the experimental subjects.

After the adaptation process accompanied by the provision of HFD, the rats were induced with STZ 45 mg/kg bw intraperitoneally (Halim S., 2023). Take a syringe and then fill it with ketamine (HCl 100mg /1ml) at a dose of 20-40 mg /kg to anaesthetise the rats. Injection is done in the intraperitoneal (IP) area, puncture in the 2/3 back of the abdomen, before injection, sterilise first with 70% alcohol.

After STZ induction, the rats were left for 48 hours and kept on HFD. Measurement of blood sugar levels began on the first day after STZ injection was performed on the rats. After STZ induction, on day 4, the rats were subjected to DM. Treatment for each group of rats began on day 1 after STZ injection. This study was conducted on 25 diabetes induced rats in 1 group without treatment, namely the control group (CG).

Moreover, four groups of diabetes induced rats were given the following treatments:

- a) Treatment 1 (T1): The rats were given Cinnamon Bark Extract
- b) Treatment 2 (T2): The rats were forced to do moderate-intensity swimming exercises
- c) Treatment 3 (T3): The rats underwent intermittent fasting
- d) Treatment 4 (T4): The rats were given Metformin

In this study, the experimental group was treated for 19 days.

### **Statistical Analysis**

The results' data were subjected to the Shapiro-Wilk and Levene Test homogeneity tests. The normality test of the five groups showed that only the T-Sw group was normally distributed, whereas the data of the T-Ct, T-Me, T-St, and T-If groups were not normally distributed. Thus, the Wilcoxon test was used to compare means for these four groups and the Student t-test for the T-Sw.

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## Results

Fasting blood glucose (FBG) examination of all groups began from the beginning of treatment for the experimental group on day 1 when the rats were more injected with Streptozotocin (STZ), then on day 4, 7, 10, 13, 16, and 19.

The experimental rats were declared DM on day 4. Lipid profile examination was conducted on days 1 and 19, while MDA blood sampling was checked on days 1, 19 and 21. The fasting blood glucose in the control group was compared to that of each treatment group

Statistical homogeneity test of fasting blood glucose (FBG) should indicate that the data were homogeneous. So, statistical calculations were continued using a *nonparametric test*, namely the *Wilcoxon test*.

Table 4.2 fasting blood glucose profile in DMT2 rats before and after treatment

NO	Group	H-1		H-4		H-7		H-10		H-13		H-16		H-19	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	Un-treat	95.40 <sup>a</sup>	13.54	256.80 <sup>a</sup>	81.52	423.60	132.35	350.25	91.00	259.75	138.84	290.00	151.71	302.67	104.41
2	Metformin	94.20 <sup>a</sup>	15.79	208.80 <sup>a</sup>	78.85	220.80	96.49	177.80	87.50	212.40	193.23	156.80	106.09	154.40	108.30
3	Cinnamon	100.40 <sup>a</sup>	11.65	275.80 <sup>a</sup>	78.90	246.60	163.88	267.80 <sup>b</sup>	113.45	197.60 <sup>b</sup>	124.16	200.40	185.51	197.60	124.16
4	Swim	100.00 <sup>a</sup>	6.44	305.20 <sup>a</sup>	159.37	179.20	82.03	247.20 <sup>b</sup>	106.86	141.00 <sup>b</sup>	90.37	158.20	60.47	105.33	20.84
5	IF	94.00 <sup>a</sup>	12.31	283.20 <sup>a</sup>	115.93	235.80	150.89	217.00	42.92	96.25	29.39	101.50	25.28	86.33	29.16

There were insignificant changes in the average FBG at each measurement point, but there was a significant increase in FBG ( $p < 0.005$ ) between day 1 and day 4 in the control group. There was a significant change in FBG in the Metformin group on days 1 and 4. In the cinnamon extract group, there was a significant increase in FBG on days 1 and 4 and a significant decrease on days 10 and 13. There was also a significant increase in FBG in the swimming group on days 1 and 4. And a statistically significant decrease in FBG on days 10 and 14. In the intermittent fasting group, there was a significant FBG on days 1 and 4, which was statistically significant.

Table 4.3 Lipid Profile in T2DM Rats before and after Treatment

NO	Lipid	Pre		Post	
		Mean	SD	Mean	SD
1	Un-treat	103.8	3.11	109.33	9.02
2	Metformin	103.80 <sup>a</sup>	3.11	127.80 <sup>a</sup>	25.21
3	Cinnamon	107.20	3.49	117.33	6.66
4	Swim	105.20	3.56	127.33	10.07
5	IF	109.6	3.44	135.2	15.22

Note: Pre = Before Treatment, Post = After Treatment. ( $p < 0,05$ )

Table 4.3 shows a change in the average lipid profile in the treatment group given metformin. The lipid profile of the treatment group given metformin. The lipid profile examination was carried out at the beginning and end. Significant changes can be seen. Based

on the analysis of the results of the statistical test, a *p-value* of 0.042 was obtained, which means that this value is significant at ( $p < 0.05$ ), so that it can be concluded that there is a significant difference between the beginning of treatment and the end of treatment in the group given metformin.

Table 4.4. MDA in T2DM Rats before and after Treatment

NO	MDA	Pre		Post	
		Mean	SD	Mean	SD
1	Un-treat	2.06	0.61	2.20	0.42
2	Metformin	1.42	0.32	2.48	0.71
3	Cinnamon	1.98	0.63	2.28	0.60
4	Swim	1.40	0.23	2.95	0.10
5	IF	2.04	0.32	2	0.11

Note: Pre = Before Treatment, Post = After Treatment Sig. =  $\leq 0,05$

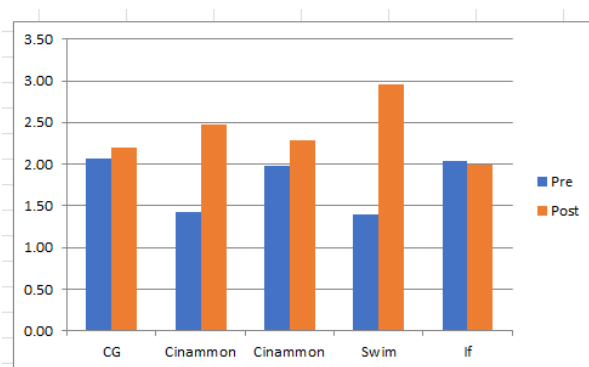


Table 4.4 and Figure 4.3 showed a change in the average MDA at each measurement point. MDA examination was carried out at the beginning and the end of treatment. The changes obtained were insignificant, either an increase or a decrease in each treatment group. This means there is no effect of cell damage on mice treated for 19 days.

## Discussion

Based on the results of this study, when cinnamon extract was given, there was a change in FBG on days 1 and 4 (increase) and on days 10 and 13 (decrease), where the increase and decrease that occurred were statistically significant.

This aligns with *in vitro* studies showing that cinnamon increases glucose uptake by activating insulin receptors (IR), autophosphorylation of insulin receptors, glycogen synthesis, and its enzymes. *In vivo*, cinnamon extract increases glucose utilisation in mice (Plantamor. Information species: Wood Sweet Cinnamon cassia, 2016)

Furthermore, cinnamon has high levels of polyphenols and flavonoids as antioxidant agents (Chan KW. 2014). Polyphenols. This can lower blood glucose levels through several mechanisms, namely increasing the entry of Glucose into cells by inducing insulin receptor phosphorylation and GLUT 4 translocation. In addition, it increases the expression of the Peroxisome Proliferator-Activated Receptor (PPAR), which increases insulin sensitivity. Some studies explain that the polyphenol content in cinnamon also has antioxidants, which can repair damaged cells due to oxidative stress that occurs in hyperglycemic conditions, which is seen in the increase in glutathione serum (GSH) levels in

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DM patients who were given cinnamon extract therapy for 12 weeks (Sahib, AS.2016)

There was a significant change in the swimming treatment: an increase in FBG on days 1 and 4 and a statistically significant decrease in FBG on days 10 and 14. This is in line with the research conducted.

Jones, Meredith-Jones, and Legge (2009) showed that good glucose and insulin responses during physical activity occur in water. Water play is any physical activity done in water, be it a swimming pool, river or ocean (Susanto, 2016)

From the research of Bayu Agung Pramono et al. (2020). Water Activity: Recommendations for Lowering Blood Glucose. This study has a pre-post design. The number of samples involved in this study were active adults aged 19 years, with 27 people. The sample was divided into three groups: nine people in the water game activity group, nine in the swimming activity group, and nine in the jogging activity group. All physical activities will be carried out for 30 minutes. First, all samples will have their blood taken to see blood glucose levels before physical activity, and after doing physical activity for 30 minutes, their blood glucose levels will be rechecked.

Water game activities consist of ball throwing and catching games, running, and jogging, all done in the pool within 30 minutes. Swimming activities include freestyle and breaststroke swimming in a 25 x 10-meter pool for 30 minutes. Jogging activities are done for 30 minutes.

The study showed that water activity significantly reduced blood glucose levels in all sample groups.

In intermittent fasting, there increased a statistically significant increase in FBG on days 1 and 4.

This is in line with the research results conducted by Dr. John Berardi, who himself obtained results in the form of psychological and physiological changes. For nine months, Dr John lost weight from 190 Pounds to 170 Pounds, if converted to kilograms, approximately 9 Kilograms, and reduced body fat from 10% to 4%.

In this study, there was also a change in the average lipid profile in all treatment groups; examining the lipid profile at the beginning and end of the treatment, significant changes can be seen. Based on the analysis of the results of the statistical test, a *p-value* of 0.042 was obtained, which means that this value is significant at ( $p < 0.005$ ), so that it can be concluded that there is a significant difference between the beginning of treatment and the end of treatment in the group given metformin.

There is also a change in the average MDA at each measurement point; an MDA examination was conducted at the beginning and the end of treatment. The changes obtained were insignificant, either an increase or a decrease in each treatment group. This means there is no effect of cell damage on mice treated for 19 days.

MDA is a stable and accurate component for measuring lipid peroxidation. MDA also contributes to oxidative damage to DNA (this DNA damage is called oxidative stress).



## **Conclusion**

Cinnamon Bark Extract in this study indicates that cinnamon has natural compounds that can affect fasting blood glucose levels in T2DM-induced rats. The results of this study indicate that cinnamon extract affects fasting blood glucose levels in T2DM rats. Moderate-intensity exercise in the form of swimming also reduces fasting blood glucose levels in rats with T2DM. Intermittent fasting in this study also impacted the fasting blood glucose level profile in T2DM rats. The results of this study indicate that intermittent fasting affects fasting blood glucose levels,

In this experiment, cinnamon bark extract, moderate swimming exercise, and intermittent fasting also affected MDA and lipid profiles in T2DM rats. So overall, this study shows that cinnamon, moderate-intensity exercise, and intermittent fasting impact the fasting blood glucose profile, lipid profile, and MDA in T2DM rats.

## **Suggestion**

1. Further research is needed on the effects of *Cinnamomum sp cinnamon* by comparing several doses to determine the best level for therapy in DM patients.
2. Further research is needed to evaluate the optimal dose of cinnamon and its long-term effects.
3. Moderate swimming exercise can be a choice for T2DM sufferers to reduce their fasting blood glucose levels.
4. Because this research was conducted on mice and not humans, further research is needed on humans to evaluate the effectiveness and safety of using cinnamon bark extract, moderate swimming exercise, intermittent fasting, or a combination of the three.

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