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Original Research

Effectiveness of *Moringa oleifera* extract supplementation in increasing Glucagon-like peptide-1 (GLP-1) in prediabetic model

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Abstract
Prediabetes is a serious global health problem. The prevalence of prediabetes is estimated to be higher than that of diabetes mellitus (DM), and 5%-12.5% of prediabetic patients will develop DM. Epidemiological studies showed that consumption of polyphenol-rich foods impacts blood glucose control and improves insulin resistance. Moringa leaves contain high levels of flavonoids that are effective in glucose control. This study aimed to determine the effect of moringa leaf extract supplementation on increasing GLP-1 levels in prediabetes models. This study used a randomized controlled trial-post-test-only design. Twenty-five male Rattus norvegicus were divided into five groups, namely the normal group, the prediabetes group, and three intervention groups, each given moringa leaf extract at a dose of 75 mg/kgbb, 150 mg / kgbb and 225 mg / kgbb. After 4 weeks of intervention, a GLP-1 examination was conducted. Data analysis using the ANOVA test. There was a significant difference in GLP-1 levels in the intervention group compared to the prediabetes control group ($p<0.05$). GLP-1 levels increased as the dose given increased. In the intervention group, the dose of 225 mg/kg bw showed the highest increase in GLP-1 levels, but there was no significant difference compared to the 150 mg/kg bw dose group. Moringa leaf extract supplementation is proven to increase GLP-1 in the Rattus norvegicus model. The effect gets better with increasing doses. Further development and testing related to this supplementation are needed so it can be used as a safe non-pharmacological treatment for prediabetes and DM patients.

Keywords: *Glucagon-like peptide-1; Moringa oleifera leaf extract*; prediabetes

1. Introduction

Diabetes is a global health emergency in the 21st century. International Diabetes Federation (IDF) reported that in 2021 the number of diabetics increased sharply, in the age range of 20-79 years there were 537 million, which means that for every 10 people there is 1 person with diabetes (IDF, 2022). Indonesia has the largest number of diabetics, with a sharp increase of 167% in the last ten years (IDF, 2022). Diabetes is a development of a previous prediabetic condition. Estimating that 5% to 12.5% percent of prediabetic patients will progress to DM (Anthony et al., 2021; Lee et al., 2022). Prediabetes is a serious global health problem, and it is estimated that the prevalence of prediabetes is much higher than that of diabetes, but comprehensive data are not yet adequate (Kusumawati, 2023). The prevalence of prediabetes globally is increasing rapidly (Lee et al., 2022). Prediabetes by value *Impaired Glucose Tolerance* (IGT) in individuals aged 20-79 years of age of 7.3% equivalent to 352.1 million people in 2017 and is estimated to increase to 8.3% equivalent to 586 million people in 2045 (IDF, 2017).

Prediabetes is a condition that is at high risk for the development of diabetes in the future. Incretin abnormalities are important in the development of pancreatic β cell damage in T2DM. Patients with

prediabetes are found to have changes in circulating concentrations of incretin. Incretin is a hormone produced by the intestinal mucosa in response to oral nutrient intake by increasing insulin secretion stimulated by increased glucose and lowering blood glucose levels. The hormone incretin consists of: *glucagon like peptide-1* (GLP-1) and *glucose-dependent insulinotropic peptide* (GIP) has a useful effect in the therapy of diabetes. The hormone incretin will be rapidly degraded by the enzyme dipeptidyl peptidase IV (DPP-IV) which has an impact on decreasing insulinotropic activity (Husna et al., 2019). GLP-1 is an incretin hormone that has the effect of lowering glucose, slowing gastric emptying and suppressing glucagon secretion (Bell & Watts, 2015). Incretin deficits are associated with decreased effects of GLP-1, impaired insulin secretion capacity, increased insulin resistance, and hyperglycemia. (Hinnen, 2017). The new approach to controlling diabetes is based on the use of GLP-1, an incretin hormone, which has been shown to reduce postprandial glycemia and fasting in T2DM (Singh et al., 2021).

Previous research revealed in prediabetic individuals found a decrease in GLP-1 concentrations. A decrease in GLP-1 in patients with impaired glucose tolerance leads to insulin resistance. Damage to GLP-1 secretion contributes to the pathogenesis of prediabetes. Incretin-based therapies have been shown to increase β cell mass, glycemic control, weight loss and improve liver cells and the cardiovascular system. Incretin-based therapies (DPP IV inhibitors and GLP-1 agonists) have been shown to improve β cell function and mass in experimental animals and clinical trials (Ahmadieh & Azar, 2014). GLP-1 increases pancreatic cell mass and inhibits cell apoptosis and increases insulin secretion. GLP-1 agonists can normalize hyperglycemia, delay gastric emptying, increase insulin release, decrease glucagon, decrease food intake and improve cell function (Pegah et al., 2021). GLP-1 is highly unstable in vivo with a very short half-life, and is easily degraded and inactivated by the enzyme dipeptidyl peptidase (DPP-IV). Prolonging the hypoglycemic effects of GLP-1 by inhibiting DPP-IV is one of the key mechanisms of DMT2 treatment. DPP-IV inhibitors currently present are sitagliptin and vitagliptin which have significant hypoglycemic effects, but have side effects such as hypersensitivity reactions, rashes and upper respiratory tract infections (Yang et al., 2020).

Conventionally, prediabetes is managed by a combination of pharmacotherapy and lifestyle modifications such as dietary interventions (Gamede et al., 2021). Epidemiological studies show that consumption of polyphenol-rich foods has an impact on blood glucose control and improves insulin resistance. A healthy diet rich in vegetables, fruits, whole grains containing polyphenols can reduce the risk of DMT2 by 14% (Maghsoudi et al., 2016; Zamora-Ros et al., 2013). Natural flavonoids and alkaloids have DPP-IV inhibiting activity can be used as a drug source (Yang et al., 2020). Moringa leaves (*Moringa oleifera*) contains polyphenols especially the most important are flavonoids quercetin, kaempferol, phenolic acids, chlorogenic acid and caffeoylquinic acid which are antihyperglycemic acting as competitive inhibitors of SGLT 1 in the mucosa of the small intestine (duodenum and jejenum) thereby reducing the absorption of glucose in the intestine (Vargas-Sánchez et al., 2019). Although many non-pharmacological treatments related to diabetes have been developed, studies related to the effects of moringa leaves on increasing GLP-1 in prediabetes are currently very limited. This study aims to determine the effect of Moringa leaf extract supplementation on increasing GLP-1 levels in the prediabetic models *Rattus norvegicus.*

2. Research Methods

2.1.Research Design

This study used design *Randomized Controled Trial Post Test Only*. The research protocol has been approved by the health research ethics committee of Diponegoro University with number 25/EC/H/FK-UNDIP/IV/2022. The sample in this study was 25 heads *Rattus norvegicus* male, age 8 weeks, average body weight 179+4 grams. Rats were divided into five groups randomly, namely the normal control

group (K1), the prediabetes control group (K2), and three treatment groups each given Moringa leaf extract doses of 75 mg / kgbb (P1), doses of 150 mg / kgbb (P2) and 225 mg / kgbb (P3).

Making a high fat diet: the high-fat diet mass is compacted and ovened in pellet form at 1800C for 2 hours. The high-fat diet was adopted from previous studies with minor modifications (Huda et al., 2020). Making moringa leaf extract: moringa leaves are taken from the Klaten region, Central Java. Moringa leaves that have been picked are then sorted, washed and drained, then in the oven at 500C for 2x24 hours until the leaves dry. Dried Moringa leaves are then ground and sieved using mesh 40. Moringa leaf powder is then macerated with 96% ethanol in a ratio of 1: 5 for 3 days. Every day stirring is carried out for + 10 minutes. After the third day the maceration results are filtered, then evaporation is carried out with a *rotary evaporator*, to get a viscous extract not dripping.

Induction of prediabetes is done by administering a high-fat diet (DTL) for 4 weeks. The composition of a high-fat diet consists of Comfeed PAR-s 60%, wheat 27.8%, cholesterol 2%, cholic acid 0.2%, lard 10% in 100 grams of feed. Determination of the prediabetic mouse model was carried out when the results of the fasting glucose level examination were 100 -160 mg / dL (Abdel-Hamid & Firgany, 2019). In the treatment group, Moringa leaf extract was given through sonde according to the dose in each group for 4 weeks. At the end of week 4, blood samples were taken through retro-orbitals for GLP-1 examination. Data analysis using ANOVA, if the results of the $p< 0.05$ value are continued *Post-Hoc Least Significant Difference* (LSD).

3. Results and Discussion

3.1.Characteristics of Experimental Animals

Prediabetes is characterized by mild hyperglycemia and is a high risk factor for diabetes. The most common changes in prediabetes are evidenced by the presence of impaired fasting glucose and/or glucose intolerance due to deregulation of glucose control as well as cell dysfunction (Zborowski et al., 2021). Maintaining glycemic control is a major treatment goal in prediabetes and diabetes because it can reduce the risk of health complications and death (Ahmad et al., 2019). In this study, making a prediabetes model *Rattus norvegicus* performed with the administration of a high-fat diet (DTL) for 4 weeks *ad libitum*. The prediabetes model is determined if blood glucose after an 8-hour fast is 100 -160 mg/dL (Abdel-Hamid & Firgany, 2019). DTL induction results in the prediabetes group (K2, P1, P2, and P3) showed an average fasting blood glucose of 131.68±3.201mg/dL. In line with previous research showing that administering a high-fat diet improves serum glucose levels, insulin resistance and impaired glucose metabolism metabolism (Balakumar et al., 2016; Hassan-Danboyi et al., 2021).

The results of this study also proved that administering a high-fat diet increased body weight and Lee index > 300 in the prediabetes control group (K2) and intervention group (P1,P2,P3) as shown in Table 1. This condition is likely due to an increase in fat mass and a decrease in lean mass simultaneously (Lee et al., 2022). A high-fat diet induces a positive energy balance resulting in visceral fat deposits (El-Shehawi et al., 2021). Previous research has shown that feeding a high-fat diet improves serum glucose levels, insulin resistance and impaired glucose metabolism (Balakumar et al., 2016; Hassan-Danboyi et al., 2021).

Table 1. Characteristics of Experimental Animals Before and After the 4-Week Intervention

Variable	Measurement period	Control Groups		Treatment Groups		
		Normal (K1)	Prediabetes (K2)	EMo75 (P1)	EMo150 (P2)	EMo225 (P3)
Body weight (g)	Before	212±3.16	238.8±3.11	234.8±4.81	233.6±3.20	232.2±3.70
	After	235.4±2.70	295.4±3.43	270.6±5.31	262.6±3.64	260.4±4.39
Length of body (cm)	Before	20.07±0.11	18.80±0.37	18.72±0.12	18.53±0.12	18.42±0.15
	After	20.73±0.12	18.98±0.21	20.61±0.14	20.90±0.15	21.30±0.06

Variable	Measurement period	Control Groups		Treatment Groups		
		Normal (K1)	Prediabetes (K2)	EMo75 (P1)	EMo150 (P2)	EMo225 (P3)
Indeks Lee	Before	296.9±0.80	330.09±5.97	329.7±5.99	332.2±4.13	333.6±6.92
	After	297.7±1.18	350.8±3.48	313.7±2.44	306.37±2.17	299.7±1.58

Source: Primary Data, 2022

Normal (K1) : Normal Mouse (Negative Control)
Prediabetes (K2) : Prediabetic Rats (Positive Control)
EMo75 (P1) :Extract *M. oleifera* 75 mg/kgbb (Treat 1)
EMo 150 (P2) :Extract *M. oleifera* 150 mg/kgbb (Treat 2)
EMo 225 (P3) : M. oleifera extract 225 mg/kgbb (Treat 3)

After 4 weeks of intervention there was an increase in body weight (g) in all groups as shown in Table 1. The highest increase in body weight was found in the K2 group (prediabetic control group), while the lowest body weight and Lee index were found in the EMo dose group of 225 mg / kgbb (P3). When compared to the prediabetes control group (K2), the EMo treatment group (P1, P2, P3) showed lower body weight. This is in line with previous research that states the provision of Moringa leaf extract significantly reduces body weight in experimental animals given a high-fat diet (Monraz-Méndez et al., 2022). GLP-1 has effects on various organ systems, most relevantly causing a decrease in body weight in the long term (Popoviciu et al., 2023).

3.2.Differences in GLP-1 Levels Between the Intervention Group and the Control Group

Table 2. The difference in GLP-1 levels between groups after 4 weeks of intervention

Group	n	Mean±SD	*p-value*
K1	5	19.8±0.76	0,000
K2	5	5.86±0.52	
P1 (EMo 75)	5	11.73±0.80	
P2 (EMo 150)	5	13.73±0.80	
P3 (EMo 225)	5	14.66±0.96	

Source: Primary Data, 2022

Table 2 shows GLP-1 levels in the normal control group, prediabetes control and EMo intervention group. The highest GLP-1 levels (19.8±0.76) were found in the normal control group. The lowest GLP-1 levels (5.86±0.526) were found in the prediabetes group and the highest GLP-1 levels (14.668±0.962) were found in the Emo 225 intervention group. The results of the analysis using *one way ANOVA* showed a significant difference in GLP-1 levels in the normal control group (K1), prediabetes control (K2), EMo (P1, P2, P3).

GPL-1 is a powerful stimulator of insulin secretion. GLP-1 stimulates insulin gene expression and proinsulin biosynthesis. GLP-1 has an anti-apotosis effect on β cells. Incretin, especially GLP-1, is secreted by enteroendocrine L cells in the intestine in response to regulation of postprandial glucose levels. GLP-1 increases pancreatic cell mass and inhibits cell apoptosis and increases insulin secretion. In patients with T2DM, GLP-1 secretion is reduced compared to healthy people (Pegah et al., 2021). This is consistent with the results of the study that GLP-1 levels in the prediabetes control group (K2) showed the lowest value on average 5.86±0.526 pg/mL.

The results of this study showed that after 4 weeks of EMo administration Doses of 75 mg/kgbb, 150 mg/kgbb, and 225 mg/kgbb cause significant increase in GLP-1 levels compared to prediabetes control group (ρ <0,05). This is likely to exist proteins/peptides contained in leaf extracts *M. oleifera*

which has an insulin-mimetic effect. The GLP-1 hormone is secreted by cells in the gastrointestinal tract in response to the presence of carbohydrates in food. GLP-1 helps promote glycemic normalization after carbohydrate consumption by stimulating insulin secretion by cells. This mechanism is the basis of therapeutic treatment of hypoglycemic in T2DM known as dipeptidyl peptidase 4 (DPP-IV) inhibitors by increasing the half-life of the GLP-1 hormone and triggering the secretagogue effect of insulin. Moringa contains insulin-like proteins detectable from seed coats, seedless fruits and leaves. Moringa leaves contain promising sources of protein/peptides with relevant in vivo insulin mimetic effects (Paula et al., 2017).

3.3.Differences in GLP-1 Levels in Each Group

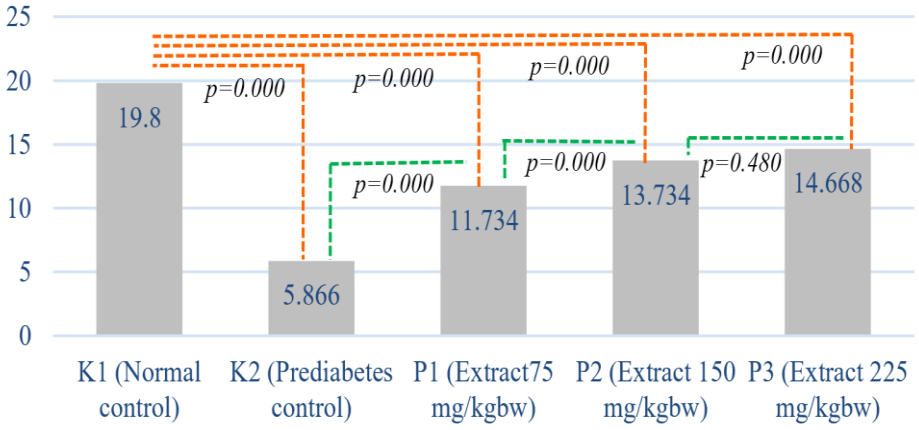

Figure 1. Differences in GLP-1 Levels After 4 Weeks of Intervention

Figure 1 shows differences in GLP-1 levels in the control, prediabetes and EMo treatment groups (P1,P2,P3). The results showed that GLP-1 levels in the prediabetes group (K2) significantly decreased ($p<0.05$) when compared to the control group (K1). In the P1,P2 group, P3 showed a significant increase in GLP-1 when compared to prediabetes controls. Changes in EMo 150 to 225 dose did not show a statistically significant increase in GLP-1 ($p>0.05$) but descriptively still showed an increase in GLP-1 levels.

Elevated GLP-1 levels affect the improvement of blood glucose control through mechanisms of action, namely: 1) glucose-dependent insulinotropic action, 2) suppress glucagon secretion (except during hypoglycemia episodes), 3) slow gastric emptying. Changes in appetite, satiety, reduction in calorie intake (Nauck et al., 2021). Moringa leaves likely play a role in delaying gastric emptying, inhibiting intestinal glucose uptake, increased glucose uptake in muscles and liver contributing to hypoglycemic effects (Gómez-Martínez et al., 2022). Alkaloids, phenolic acids, amino acid polysaccharides, peptidoglycan, and glycopeptides in Moringa leaves contain antioxidant properties that function as DPP-4 inhibitors. The mechanism of action of DPP4 inhibitors through blocking enzyme activity, increasing the half-life of GLP-1, increasing insulin secretion and limiting glucagon secretion (Singh et al., 2021).

The results of this study are different from previous studies that stated that supplementation *M. oleifera* potential as a blood glucose controlling agent in prediabetic patients, but supplementation *M. oleifera* has no effect on intestinal hormones (GLP-1) (Gómez-Martínez et al., 2022). Other studies mention quercetin content in *M. oleifera* has the ability to inhibit *α-glucosidase* by increasing GLP-1 secretion in healthy individuals as well as T2DM patients (Ganjayi et al., 2023). Inhibition *α-*

glucosidase causes a delay in the breakdown of carbohydrates in the small intestine by intensifying glucose absorption in the lower intestine thereby reducing glucose levels (Hossain et al., 2020).

Administration of Moringa leaf extract dose of 225 mg / kgbb increased the highest GLP-1 levels. Alkaloids, phenolic acids, amino acid polysaccharides, peptidoglycan, and glycopeptides contain antioxidant properties that function as DPP-4 inhibitors (Singh et al., 2021). DPP4 inhibitor mechanism through blocking enzyme activity, increasing the half-life of GLP-1, increasing insulin secretion and limiting glucagon secretion (Singh et al., 2021). Moringa leaves also contain compounds O-Ethyl-4-[(α-NS-rhamnosyloksi)benzyl]carbamate which has excellent pharmacokinetic properties and safety and is a potential lead compound against DPP-IV (Yang et al., 2020). Previous research in prediabetes treated with GLP-1 analogues for 24 weeks showed normoglycemia (Farr & Mantzoros, 2017). The hypoglycemic mechanism via the GLP-1 pathway is safe because GLP-1 increases insulin secretion depending on glucose concentration. GLP-1 stimulates increased insulin secretion when blood glucose levels rise, but when blood glucose levels are too low, GLP-1 maintains normal insulin secretion levels (Yang et al., 2020).

4. Conclusion

This study showed that Moringa leaf extract was effective in increasing GLP-1 levels in a prediabetic model of *Rattus norvegicus*. The effect gets better with increasing doses of administration. Further development and testing related to moringa leaf extract supplementation is needed so that it can later be used as a safe non-pharmacological treatment for patients with prediabetes and diabetes mellitus.

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