ETHANOLIC EXTRACT OF *Moringa oleifera* LEAVES IMPROVES GLUCOSE TOLERANCE, GLYCOGEN LEVELS, AND LIVER HEALTH IN ALLOXAN-INDUCED DIABETIC RATS

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Abstract: The moringa plant (*Moringa oleifera*) is a traditional plant that has many health benefits, one of which is as a medicine for diabetes mellitus. This study aims to determine the effect of the leaf ethanol extract of (*Moringa oleifera* L.) on increasing the content of liver glycogen grains in hyperglycemic rats. The research was conducted at the Pathology and Pharmacology Laboratory, Department of Veterinary Clinic, Faculty of Veterinary Medicine, Universitas Syiah Kuala. The method used is an experimental method with a completely randomized design consisting of five treatments and five treatment tests. Treatment A = Negative control (given with distilled water and physiological NaCl), B = Positive control (75 mg/kg of alloxan and incubated for 21 days), C (75 mg/kg of alloxan and 150 mg/kg of *Moringa oleifera* leaf ethanol extract for 21 days), D (75 mg/kg of alloxan and 300 mg/kg of *Moringa oleifera* leaf ethanol extract for 21 days), and E (75 mg/kg of alloxan and 450 mg/kg of *Moringa oleifera* leaf ethanol extract for 21 days). The parameters observed were three factors: blood sugar levels, glycogen levels, and histological images of the liver depicting the condition of either a healthy or diseased liver. The results of statistical analysis showed that there was a significant effect, namely the administration of Moringa oleifera leaf extract at a dose of 450 mg/kg was able to reduce blood glucose levels, increase liver glycogen content and repair liver cell damage in hyperglycemic rats ($P<0.01$).
Keywords: *Moringa oleifera*; Hyperglycemic; Liver Glycogen Grains

Abstrak: Tanaman kelor (*Moringa oleifera*) merupakan tanaman tradisional yang memiliki banyak manfaat bagi kesehatan, salah satunya sebagai obat diabetes mellitus. Penelitian ini bertujuan untuk mengetahui pengaruh pemberian ekstrak daun kelor (*Moringa oleifera*) terhadap peningkatan kandungan butir glikogen hati pada tikus hiperglikemik. Pelaksanaan penelitian dilakukan di Laboratorium Patologi dan Farmakologi Jurusan Klinik Veteriner Fakultas Kedokteran Hewan Universitas Syiah Kuala. Metode yang digunakan adalah metode eksperimen dengan Rancangan Acak Lengkap yang terdiri atas lima perlakuan dan lima ulangan. Perlakuan A = Kontrol negatif (diberi akuades dan NaCl fisiologis), B = Kontrol positif (75 mg/kg aloksan dan diinkubasi selama 21 hari), C (75 mg/kg aloksan dan 150 mg/kg ekstrak daun kelor selama 21 hari), D (75 mg/kg aloksan dan 300 mg/kg ekstrak daun kelor

selama 21 hari), dan E (75 mg/kg aloksan dan 450 mg/kg ekstrak daun kelor selama 21 hari). Parameter yang diamati adalah kadar glukosa darah, kandungan butir glikogen hati dan perbaikan sel hati pada tikus hiperglikemik. Hasil analisis statistik menunjukkan adanya pengaruh yang signifikan yaitu pemberian ekstrak daun kelor (*Moringa oleifera*) pada dosis 450 mg/kg mampu menurunkan kadar glukosa darah, meningkatkan kandungan butir glikogen hati dan memperbaiki kerusakan sel hati pada tikus hiperglikemik (P<0.01).
Kata kunci: *Moringa oleifera*; Hiperglikemik; Butir Glikogen Hati

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Introduction

Moringa (*Moringa oleifera* L.) is a miracle tree with various pharmacological properties and significant nutritional value and has been scientifically evaluated for various medical applications. This plant is a source of protein, carotene, vitamins (A, B, C, E, riboflavin), nicotinic acid, folic acid, pyridoxine, amino acid, minerals, various phenolic compounds (Mallya *et* al., 2017; Bhattacharya *et al.,* 2018). Moringa has natural antioxidants with high concentrations such as vitamins A, C, E, and phenolics also contains 46 antioxidants that help cells neutralize free radicals (Arise *et al.,* 2019). Many studies show that Moringa ethanol extract can act as an anti-inflammatory, iso thiocyanic component, phenolic acids, flavonoids, and terpenoids that have antihyperglycemic activity (Wardhani, 2020).

In other research, it is stated that Moringa leaf extract contains phytochemicals in the form of alkaloids, flavonoids, steroids, glycosides, various important antioxidants, antibiotics and nutrients including vitamins and minerals which can be used as antimicrobial, anticancer and antidiabetic (Berawi *et al*., 2019; Susanti & Nurman, 2022).

Moringa of biological activities evidenced in *invitro* experiments, showing potent anti-oxidative, analgesic, cytoprotective, anti-ulcer, anti-hypertensive and immunomodulatory actions as well as an inhibitory effect on proinflammatory mediators (Anwar *et al.,* 2006; Stohs and Hartman, 2015; Luetragoon *et al.,* 2020; Arulselvan *et al.,* 2016). Moringa is a popular medicine as a cardioprotective, hepatoprotective, neuroprotective, anti-asthmatic, anti-tumour, antimicrobial, hypolipidemic, modulator of intestinal microbiota and anti-diabetic agent derived from its phytochemical constituents such as alkaloids, phenolic compounds and glycosides although the amount of these metabolites varies according to the geographical location and the extraction method used (Anwar *et al.,* 2006; Kou *et al.,* 2018; Dou *et al.,* 2019).

One of the diseases whose number of cases has increased significantly is diabetes mellitus. Diabetes mellitus is a slow damaging disease known worldwide due to the low insulin production or damaged insulin that is unusable for body cells. Diabetes mellitus refers to a group of physiological dysfunctions that are characterized by a hypoglycemic state, insulin deficiency, inadequate insulin secretion, or excessive glucagon secretion (Siddiq *et al*., 2013, Yuan *et al*., 2016, Smeltzer *et al*., 2009). Diabetes mellitus can occur due to several factors including stress factors, the immune system, free radicals, nutritional factors (hyperglycemia), genetics, infection and other factors that result in damage or fatigue of pancreatic beta cells so that they are unable to produce insulin optimally (Stumvoll *et al*., 2005).

In the world, the number of cases of diabetes has increased significantly in the last ten years and is the sixth leading cause of death. The number of cases of diabetes mellitus is expected to increase from 135 million in 1995 to 380 million in 2025. The largest number of this increase occurs in developing countries, one of which is Indonesia (Nwanko *et al.,* 2010). Indonesia is one of the countries that ranks fourth in the number of people with diabetes mellitus after the United States, China, and India. The World Health Organization (WHO) predicts that the number of people with diabetes mellitus in Indonesia will increase from 8.4 million in 2000 to 21.3 million in 2030 (Johnson, 2011). In May 2021, a resolution on diabetes mellitus was adopted at the World Health Assembly. This resolution urges WHO Member States to raise the priority given to the prevention, diagnosis and control of diabetes as well as the prevention and management of risk factors for type 2 diabetes, such as obesity, and recommends the development of pathways for achieving targets for the prevention and control of diabetes (WHO, 2021).

So far, the treatment of diabetes mellitus has been carried out using antidiabetic drugs. Oral antidiabetic treatment in the long term tends to reduce blood glucose levels because resistance occurs, causing hypoglycemia, nausea, dizziness, easy fatigue and anorexia (Dewi *et al.*, 2014). Currently, the lower middle class are using alternative medicine to treat diabetes mellitus. One of the traditional medicines that can be used for diabetes mellitus and its presence is most commonly found in Aceh is the Moringa plant known as Murong (*Moringa oleifera*) (Tende *et al*., 2011).

The administration of Moringa leaf extract at a dose of 300 mg/kg can reduce glucose levels to 44.96%. To see a decrease in blood glucose levels below 44.96%, use a dose of 150 mg/kg and for an increase above 44.96%, use a dose of 450 mg/kg (Edoga *et al.,* 2013). Based on the description above, it is necessary to conduct research on the appropriate dosage from the leaf extract (*Moringa oleifera*) in increasing liver glycogen grains in hyperglycemic rats. This study aims to determine the effect of different doses of Moringa leaf extract on the increase in

liver glycogen grains of hyperglycemic rats. This study is expected to provide information about the effect of giving the right dose of Moringa leaf extract to increase liver glycogen grains in hyperglycemic rats.

Methodology

Tools and Materials

The tools used in this research were OHAUS scales, Sartorius analytical scales, Erlenmeyer flasks, rat cages, rotary microtome, oven, light microscope, slides, cover slips, scissors, tweezers, hot plates, staining jars, block holders, photomicroscopes, GlukoDrTM Blood Glucose Test Meter, GlukoDrTM Test Meter, gavage, and writing tools.

The materials used in this research were 25 three month old male rats (*Rattus wistar*) with a body weight of 200-250 grams from the Pathology Laboratory, Faculty of Veterinary Medicine, Syiah Kuala University, type 789-S pellets produced by PT. Charoen Phokpahan Medan, Indonesia, alloxan monohydrate comes from the Micro technical Laboratory of Faculty of Mathematics and Natural Sciences, Syiah Kuala University, Moringa leaves (*Moringa oleifera*) comes from the plantation of Teu Dayah village, Kuta Malaka District, Aceh Besar, ethanol, distilled water, Carnoy's fixative solution, 70% series alcohol up to alcohol absolute, xylol, paraffin 56-58 ^{o}C, Gomori's Chromium Hematoxylin Phloxin dye solution, Best's Carmine dye solution, albumin, acetic acid, entelan and CMC 1% (*Sodium Carboxymethyl Cellulose*).

Extract *Moringa oleifera*

This study is an experimental study to determine the dose of Moringa leaf extract in reducing blood glucose levels in hyperglycemic rats. The manufacture of Moringa leaf ethanol extract is guided by (Gupta *et al*., 2012), air-dried Moringa leaves then crushed as much as 3 kg then mixed into 75% ethanol for 72 hours. The ethanol was then evaporated at a temperature of 35 ± 2 ^{o}C for 48 hours and a net residue of (25.7 g) was obtained which was stored at -4 ^{o}C, this is a liquid extract. Moringa leaf extract was given at different doses, namely 150 mg/kg, 300 mg/kg and 450 mg/kg.

Research Design

Moringa leaf extract was given at different doses, namely 150 mg/kg, 300 mg/kg and 450 mg/kg. This study used a completely randomized design (CRD) consisting of five treatments and each treatment was repeated five times. The treatments consisted of A = negative control (given aquadest and physiological NaCl), B = positive control (75 mg/kg of alloxan and incubated for 21 days), C (75 mg/kg of alloxan and 150 mg/kg of Moringa leaf extract for 21 days), D (75 mg/kg of alloxan and 300 mg/kg of Moringa leaf extract for 21 days) and E (75 mg/kg of

alloxan and 450 mg/kg of Moringa leaf extract for 21 days). Moringa leaf extract was administered orally (oesophageal intubation). The research design can be seen in Table 1.

Table 1. Research Design

Treatment	Test	Alloxan		*Moringa oleifera*	
		Dose (mg/kg)	Giving (time)	Dose (mg/ kg)	Giving (day)
A	5	0	1	0	21
B	5	75	1	0	21
C	5	75	1	150	21
D	5	75	1	300	21
E	5	75	1	450	21

The study used a completely randomized design (CRD) using 25 male rats (Rattus wistar) three months old and weighing 200-250 grams. Rats were obtained from the maintenance cage of the Pathology Laboratory, Department of Veterinary Clinic, Faculty of Veterinary Medicine, Syiah Kuala University. Mice were acclimatized for 7 days in experimental cages, the cages were made of plastic tubs with a size of 70 cm x 44 cm x 20 cm with the top covered with wire netting and the bottom covered with husks with a thickness of 3 cm. Experimental animals were given food in the form of pellets of type 789-S, and food and drink were provided ad libitum.

Alloxan was administered once on the first day of intraperitoneal treatment at a dose of 75 mg/kg for four days referring to (Fauziah, 2010). Moringa leaf extract was administered orally (oesophageal intubation) for 21 days for all treatments. Mice were necropsied one day after treatment ended. After necropsy, the liver was immediately removed and histological preparations were made using the paraffin method. Liver specimens were fixed in Bouin's solution, then dehydrated using 70% alcohol series to absolute alcohol, clearing in xylol, infiltration and embedding in paraffin blocks 56–58 ^{o}C. The embedding preparations were slashed with a thickness of 6 microns using a rotary microtome. Each replication was made in 4 incisions with an interval of 10 incisions and placed on a glass object that had been given an adhesive solution.

Research Parameters

Staining of the glycogen content of rat liver was stained using the Best's Carmine staining method according to (Gridley, 1960). Furthermore, observations of the content of liver glycogen grains were carried out with a light microscope at a magnification of 10 x 40. Each incision was observed in as many as 3 fields of view so that there were 12 observation fields in each replication.

The parameter observed in this study was the content of liver glycogen grains. The total content of liver glycogen grains is calculated in the field of view of the microscope using a scoring system, namely:

a. Score (1): if liver glycogen grains are greater than 10% and seen less than 30% (slightly and unevenly distributed) from the wide field of view.
b. Score (2): if liver glycogen grains are larger than 30% and smaller than 60% (looks a little and spread evenly) from the wide field of view.
c. Score (3): if liver glycogen grains are greater than 60% (looks like many and evenly distributed) from the wide field of view.

Results and Discussion

The average content of liver glycogen grains in various treatments can be seen in Table 2. The average content of rat liver glycogen grains in treatment A was very significantly different from treatments B, C, and D (P<0.01), but significantly different. with treatment D (P<0.05).

Table 2. Average Content of Rat Liver Glycogen Grains in Various Treatments.

	Treatment	Liver Glycogen Grain Average Content (X ± SD)
A.	Aquades + physiological NaCl	2.17 ± 0.14Cc
B.	75 mg/kg alloxan and incubated for 21 days	1.58 ± 0.19Aa
C.	150 mg/kg *Moringa oleifera* leaf ethanol extract + 75 mg/kg alloxan for 21 days	1.75 ±0.23Aab
D.	300 mg/kg *Moringa oleifera* leaf ethanol extract + 75 mg/kg alloxan for 21	1.89 ± 0.26Bbc
E.	450 mg/kg *Moringa oleifera* leaf ethanol extract + 75 mg/kg alloxan for 21	2.10 ± 0.17Cc

Information: Different capital letters superscripts (A, B, C, D) showed a very significant difference (P<0.01); lowercase letters (a, b, c, d) showed significantly different (P<0.05); the same lowercase letters were not significantly different (P>0.05).

Analysis of variance in the content of rat liver glycogen grains in various treatments showed that there was a very significant effect of different treatments (P<0.01). The average content of liver glycogen grains can be seen in Figure 1.

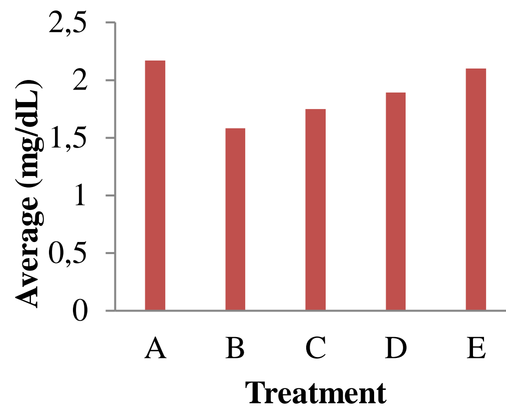

Figure 1. Average Blood Glucose Levels in Various Treatments.

Information :
A = Negative control was given aquadest and physiological NaCl
B = Positive control was given 75 mg/kg of alloxan and incubated for 21 days
C = 75 mg/kg of alloxan and 150 mg/kg of *Moringa oleifera* leaf ethanol extract for 21 days
D = 75 mg/kg of alloxan and 300 mg/kg of *Moringa oleifera* leaf ethanol extract for 21 days
E = 75 mg/kg of alloxan and 450 mg/kg of *Moringa oleifera* leaf ethanol extract for 21 days

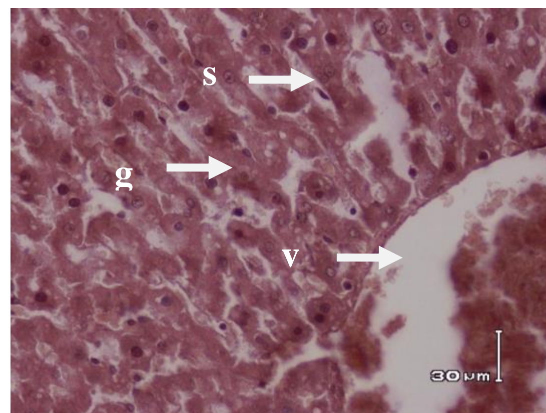

Figure 2. Grain Content of Liver Glycogen in Treatment A; g = normal liver glycogen, s = normal sinusoids and v = central vein, (Best's Carmine stain, 400x magnification).

The mean content of rat liver glycogen grains in treatment B (positive control) which was induced by alloxan and incubated for 21 days was 1.58, which was very significantly different from treatment A, which was 2.17 (Figure 2.). The mean content of rat liver glycogen grains in treatment B (Figure 3.) was lower than the content of rat liver glycogen grains in treatment A. This is seen in Figure 3. (positive control), there is very little content of liver glycogen grains and is not evenly distributed in hepatocyte cells. In addition, the absorption of Best's Carmine dye also looks paler.

The difference with Figure 2. (negative control), there is a lot of content of liver glycogen grains and it is evenly distributed in hepatocyte cells and the absorption of Best's Carmine dye is maximized so that it looks brighter. This indicates that glucose in treatment B mice is not stored in the form of glycogen. The low glycogen content in the liver indicated that the rats in treatment B had hyperglycemia due to being induced by alloxan. Alloxan is thought to play a role in inhibiting glucokinase in the process of energy metabolism (Nugroho, 2006).

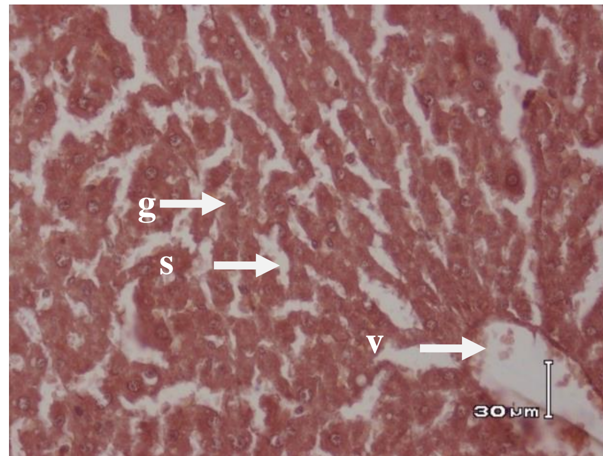

Figure 3. Content of Liver Glycogen Grains in Treatment B; g = low liver glycogen, s = abnormal sinusoids and v = hemolyzed central vein, (Best's Carmine stain, magnification 400x).

Alloxan induction and accompanied by administration of *Moringa oleifera* leaf ethanol extract in treatments C, D, and E with different doses for 21 days showed an increase in the content of liver glycogen grains compared to treatment B (positive control). The rats in treatment C with a mean of 1.75 showed an increase that was not significantly different ($P>0.05$) from treatment B (Figures 3. and 4.). A fairly high increase in liver glycogen content was seen in treatments D and E with a mean of 1.89 and 2.10, respectively (Figures 5 and 6), indicating a very significant increase ($P<0.01$) with treatment B (Figure positive control).

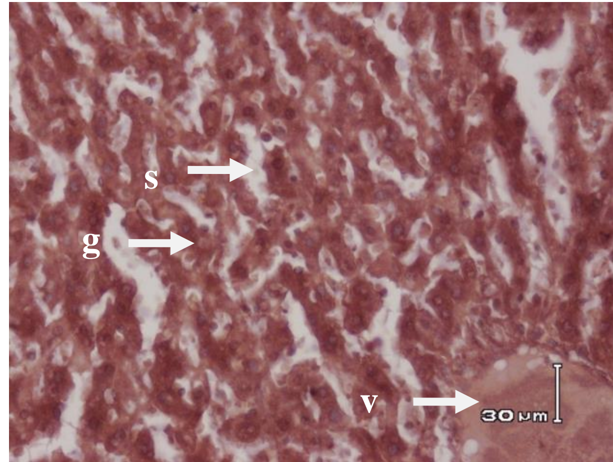

Figure 4. Content of Liver Glycogen Grains in Treatment C; g = low hepatic glycogen, s = abnormal sinusoids and v = central venous hemolysis, (Best's Carmine stain, magnification 400x).

However, treatment E was significantly different from treatment A (P<0.05). The significant increase in the content of liver glycogen grains was due to the effect of secondary metabolites in *Moringa oleifera* leaf ethanol extract which function as antioxidants and antihyperglycemic agents so that pancreatic cells continue to produce insulin. One of the important effects of insulin is that it causes most of the glucose absorbed after eating to be stored immediately in the liver in the form of glycogen. The mechanisms used to induce glucose uptake and storage in the liver include; insulin inhibits hepatic phosphorylase, insulin increases the uptake of glucose from the blood by liver cells, and insulin also increases the activity of enzymes that increase glycogen synthesis (Guyton and Hall, 1997).

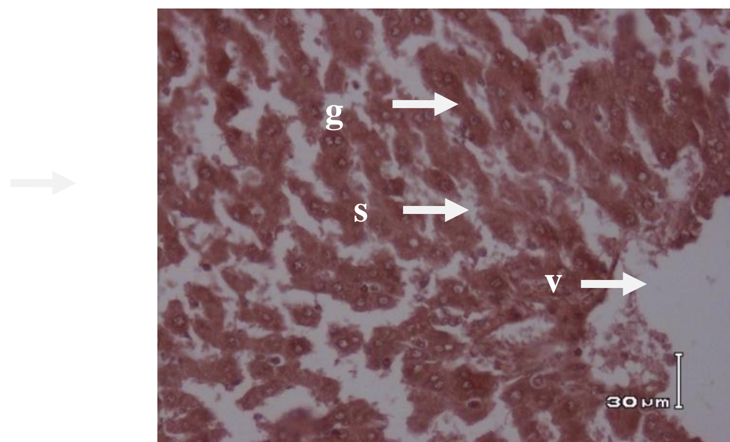

Figure 5. Content of Liver Glycogen Grains in Treatment D; g = low hepatic glycogen, s = abnormal sinusoids and v = central venous hemolysis, (Best's Carmine stain, magnification 400x).

Glycogen is the main source of polysaccharides in human and animal cells. Glycogen is stored by the body to provide a temporary supply of glucose as fuel or

as a high-energy phosphate-producing material. Glycogen anabolism and catabolism in the liver and muscles depend on the availability of glucose and body activity (Mayes, 2003). In people with diabetes mellitus insulin does not work well or insulin resistance occurs because insulin receptors on cell membranes are reduced or their structure changes so that they are not responsive to insulin (Stumvoll *et al.,* 2005).

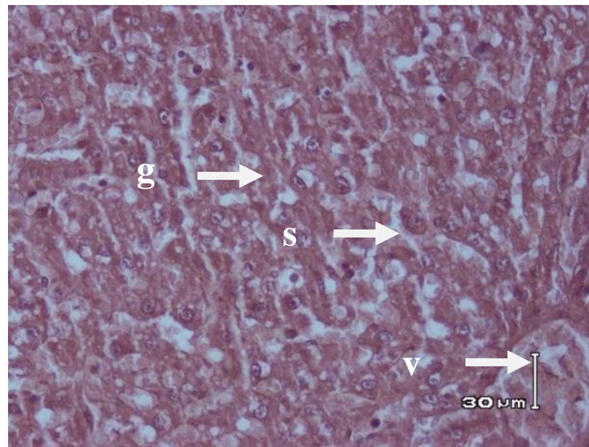

Figure 6. Content of Liver Glycogen Grains in Treatment E; g = normal liver glycogen, s = normal sinusoids and v = normal central vein, (Best's Carmine stain, 400x magnification).

Insulin resistance contributes to increased glucose release in the liver and decreases glucose uptake into adipose tissue. This condition will cause hyperglycemia and failure of glycogen formation. This condition is in line with those who also reported that in Zucker (fa/fa) diabetic rats there was skeletal muscle resistance to glucose transport (Jung *et al*., 2006 and Jin *et al.,* 2007). This is what causes the failure of glucose metabolism and the failure of glycogenesis in the liver and muscles.

The flavonoids contained in *Moringa oleifera* leaf ethanol extract act as insulin secretion or insulin picking, which can affect the pleiotropic mechanism to attenuate diabetic complications. The phytochemical preparation of *Moringa oleifera* revealed the presence of bioflavonoids which are responsible for stimulating glucose uptake in peripheral tissues and the regulatory activity or expression of inhibitory enzymes involved in carbohydrate metabolism (Gupta *et al*., 2012., Gupta *et al*., 2011., and Gupta *et al.,* 2009).

In previous studies, it was said that increased levels of liver enzymes in type 2 DM patients were due to increased effects of glycogen or insulin on liver cells. Increased glycogenolysis and gluconeogenesis from non-carbohydrate precursors into primary metabolic pathways (Balaji *et al.,* 2013). Excess release of free fatty acids due to insulin resistance induces fat mobilization and results in hepatocyte toxicity (Sunitha *et al.,* 2015).

Moringa extract plays a role in increasing the activity of enzymes and restoring hepatocyte cells, causing accelerated regeneration of parenchyma cells and lysosomes (Otomoso *et al.,* 2015). Reduction of ALT and AST activity as a result of Moringa leaf extract indicates an early repair of liver cell membranes from anti-hepatotoxic effects (Elbakry *et al.,* 2016). Recovery of this enzyme to normal levels indicates the return of normal liver function after administration of Moringa leaf extract. This indicates insulin secretion and regenerative activity of pancreatic beta cells in the pancreatic islets of Langerhans cells (Woldekidan *et al*., 2021).

Moringa leaf extract can prevent hepatotoxicity due to DM, among others, as a result of its chemical constituents having hepatoprotective properties. The antioxidant and hepatoprotective activity of M. oleifera leaf extract in DM rats is due to the presence of total active phenolic constituents and the flavonoids sitosterol, quercetin and kaempferol (Singh *et al*., 2014). Moringa leaf extract has a remedial effect on liver damage as a complication by reducing serum ALT and AST levels in the treatment group (Otomoso *et al.*, 2015). Hepatotoxic especially those that follow free radical-mediated mechanisms need material to overcome the wound of the heart. Flavonoids can control blood glucose by increasing glycolysis and glycogenesis by stimulating glucose utilization so that blood glucose levels decrease. This causes glucose to be available in cells so that it can inhibit gluconeogenesis in the liver (Yuneldi *et al*., 2018).

This is in line with research that *Moringa oleifera* leaf extract at a dose of 200 mg/Kg on days 14 and 21 was effective in reducing blood glucose levels in alloxan-induced diabetic mice (Yasaroh, S., *et al.,* 2021). This is in line with research which states that Moringa oleifera leaves contain flavonoid antioxidants which have the function of increasing insulin secretion and increasing glucose uptake. Moringa leaf extract (Moringa oleifera) at doses of 250 mg/kg, 450 mg/kg, and 600 mg/kg has a probability value of <0.05 which indicates a statistically significant reduction in blood sugar levels, so it has an anti-diabetic effect (Toby, T.R. *et al.,* 2020).

Conclusion

The giving of moringa leaf extract at a dose of 450 mg/kg for 21 days was able to significantly increase the content of liver glycogen grains ($P<0.01$).

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