



## Potential Bark *Cinnamomum burmanii* in Regenerating Damaged Liver Cells of Mice (*Mus musculus*) Diabetes Mellitus Model

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### Abstract

Diabetes mellitus is a chronic disease that can quickly increase the prevalence of complications in sufferers, such as liver damage. This study aims to examine the effect of methanol extract cinnamon bark (*Cinnamomum burmanii* Bl) in regenerating liver cell damage mice (*Mus musculus*) Diabetes Mellitus through the histological picture. 20 mice were divided into 5 groups which consisted of a negative control group, Positive control and a group of mice that were given methanol extract bark *Cinnamomum burmannii* dose of 125 mg/head/day, 250 mg/head/Day and 500 mg/head/day. In the positive control group and the group of mice that will be given extract streptozotocin injected dose of 0.2 ml and observed blood sugar levels if sugar levels have increased then given methanol extract bark *Cinnamomum burmannii* with a dose that has been determined and blood sugar levels were measured. On the last day, surgery is performed to remove the liver, after which histological preparations are made. The results showed that the administration of bark extract *Cinnamomum burmanii* can regenerate damaged liver cells of mice due to diabetes mellitus. This is due to the content of secondary metabolite compounds contained in the bark of *Cinnamomum burmannii*.

**Keywords:** *Cinnamomum burmannii*, cell regereneasi, liver

### Abstrak

Diabetes melitus merupakan salah satu penyakit kronis yang dapat meningkatkan dengan cepat prevalensi komplikasi pada penderitanya, seperti kerusakan hati. Penelitian ini bertujuan untuk mengkaji pengaruh pemberian ekstrak metanol kulit batang kayu manis (*Cinnamomum burmanii* Bl) dalam meregenerasi kerusakan sel hati mencit (*Mus musculus*) Diabetes Mellitus melalui gambaran histologis. Mencit sebanyak 20 ekor dibagi menjadi 5 kelompok dimana terdiri dari kelompok kontrol negatif, kontrol positif dan kelompok mencit yang diberi ekstrak metanol kulit batang *Cinnamomum burmannii* dosis 125 mg/ekor/hari, 250 mg/ekor/hari dan 500 mg/ekor/hari. Pada kelompok kontrol positif dan kelompok mencit yang akan diberi ekstrak diinjeksi streptozotocin dosis 0,2 ml dan diamati kadar gula darah, apabila kadar gula sudah mengalami peningkatan maka diberi ekstrak metanol kulit batang *Cinnamomum burmannii* dengan dosis yang sudah ditentukan dan dilakukan pengukuran kadar gula darah. Pada hari terakhir dilakukan pembedahan untuk mengambil organ hati, yang selanjutnya dilakukan pembuatan preparat histologi. Hasil penelitian menunjukkan bahwa pemberian ekstrak kulit batang *Cinnamomum burmanii* dapat meregenerasi kerusakan sel hati mencit akibat diabetes mellitus. Hal ini disebabkan karena adanya kandungan senyawa metabolit sekunder yang terdapat dalam kulit batang *Cinnamomum burmannii*.

**Kata kunci:** *Cinnamomum burmannii*, regereneasi sel, hati,

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## INTRODUCTION

Diabetes mellitus (DM) is a chronic, heterogeneous life-threatening disease in the form of metabolic disorders usually characterized by hyperglycemia, glycosuria, negative nitrogen balance, and sometimes ketonemia. A diabetic syndrome is characterized by a reduced amount of insulin or decreased insulin sensitivity or a combination of both.<sup>1,2</sup> DM is a non-communicable disease but is predicted to increase in number in the future.<sup>3</sup> World Health Organization (WHO) predicts that longer will be an increase in people, in the year 2000 the number of patients amounted to 171,230,000 people.<sup>4</sup>

Patients with diabetes have a high prevalence of liver abnormalities.<sup>5</sup> the liver is an important organ in maintaining blood glucose levels within normal limits. Hepatic tissue performs the process of homeostasis of glucose levels in the body, especially fasting glucose levels where the amount of endogenous glucose derived from the results of gluconeogenesis and glycogenolysis increases. In this situation, insulin plays a role in the inhibitory effect of the work of the metabolism. When insulin resistance occurs, the ability to inhibit gluconeogenesis and glycogenolysis will decrease so that there is an increase

in the production of blood glucose levels from the liver.<sup>6</sup> elevated glucose levels can cause other metabolic disorders and produce free radicals.<sup>7</sup>

Hyperglycemic conditions can lead to oxidative stress because excess reactive oxygen species (ROS) interfere with the work of antioxidants, and high glucose conditions can worsen the damaging effects on cells and organs.<sup>8</sup> oxidative stress can result in changes in the structure of the histological picture of the liver and can significantly increase the number of fatty hepatocytes.<sup>9</sup> liver damage occurs degenerative changes in cells can return to normal if the cause of the damage is stopped. In such damage, there are changes up to cell death called necrosis.<sup>10,11</sup>

The treatment of DM that is usually done conventionally is by taking drugs from chemicals. However, such treatment can result in hypoglycemia, especially for patients who are accompanied by vascular disease, and kidney failure, in pregnant women and children suffering from DM type 1.<sup>12</sup> treatment of DM using chemical drugs shows many side effects and can worsen the symptoms of DM.<sup>13</sup> Research Qi et al. state that the treatment of DM can also be done using natural ingredients, including natural ingredients derived from plants.<sup>14</sup>



*Cinnamomum burmanii* B1 is a plant that can be found in the plains of Indonesia, especially in the province of North Sulawesi. This plant is used empirically by the public to overcome diabetes mellitus (DM).<sup>15</sup> the chemical content of cinnamon includes astir oil, safrole, cinnamaldehyde, tannin, dammar, calcium oxalate, flavonoids, triterpenoids, and saponins.<sup>16</sup> secondary metabolite compounds from bark *Cinnamomum burmanii* B1 proved to be antidiabetic and regenerate pancreatic cells,<sup>17</sup> increase creatinine levels and improve kidney damage in mice with diabetes mellitus model.<sup>18</sup> this research aims to assess the effect of methanol extract cinnamon bark (*Cinnamomum burmanii* B1) in regenerating liver cell damage mice (*Mus musculus*) Diabetes Mellitus through a histological picture.

## METHODOLOGY

### *Types of Research*

This research is a laboratory experiment.

### *Research Design*

The research was a complete randomized study with five treatments and three replications. The division of groups can be seen as follows:

1. Group I: negative control mice
2. Group II: positive control mice.

3. Group III: mice DM + bark extract *Cinnamomum burmanii* dose 125 mg
4. Group IV: mice DM + bark extract *Cinnamomum burmanii* dose 250 mg
5. Group V: mice DM + bark extract *Cinnamomum burmanii* dose 500 mg

### *Tools and Materials*

The tools used are cages for mice, digital Ohaus scales, Erlenmeyer, sonde tools, experimental animal surgical tools (scalpel), tweezers, dissecting sets, glass objects, incubators, microtomes, film Roll holders, microscopes, and digital cameras.

While the material is bark *Cinnamomum burmanii*, STZ (streptozotocin), mice, aluminum foil, methanol, filter paper, cotton, tissue, formalin, mouse feed, and water PAM, Giemsa solution, alcohol level 50%, 70%, 80%, 90%, and 100%, formalin 4%, xylol I, xylol II, paraffin, NaCl 0.9 molal, equates, immersion oil, and rice husk.

### *Research Implementation*

#### *Try Animal Setup*

A total of 20 male mice were divided into five groups and acclimatized for 1 Week in a laboratory room.



### *Streptozotocin Injection in Mice*

A total of 0.2 ml of STZ was injected into mice in groups II, III, IV, and V.<sup>19</sup>

### *Preparation of Test Material*

Samples of bark *Cinnamomum burmanii* were taken then cut into small pieces and dried in the laboratory. After drying it is mashed with a blender to get the powder from the bark of *Cinnamomum burmanii* which is then extracted with metabolic solvent using the maceration method. After that, it is evaporated with a rotary evaporator to obtain a concentrated extract.<sup>18</sup>

### *Testing Procedure*

Before being barked extract *Cinnamomum burmanii* first measured blood sugar levels in groups II, III, IV, and V. Measurement of blood sugar levels using a glucose tool and blood sugar strips. If blood sugar levels increased, then groups III, IV, and V were given bark extract *Cinnamomum burmanii* by the dose that has been determined.

The administration of the drug is carried out for 14 days and on the last day the final blood sugar level measurement and also surgery to remove the liver.<sup>20</sup>

### *Preparation Of Liver Histology Preparations*

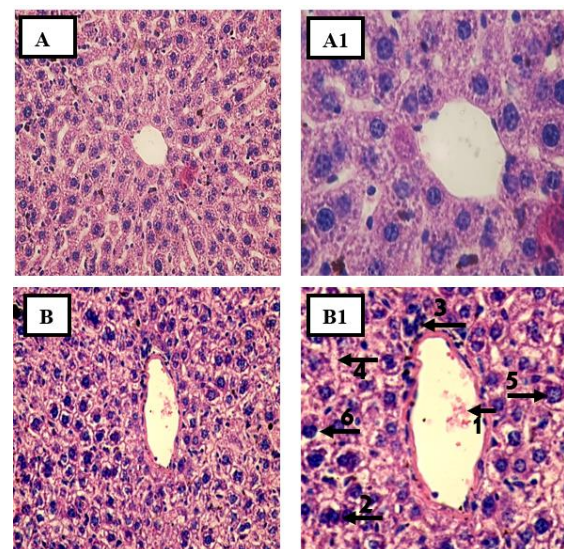
Preparation of liver tissue is carried out using Hematoxylin Eosin (HE) Processing.<sup>18</sup>

### *Data Analysis*

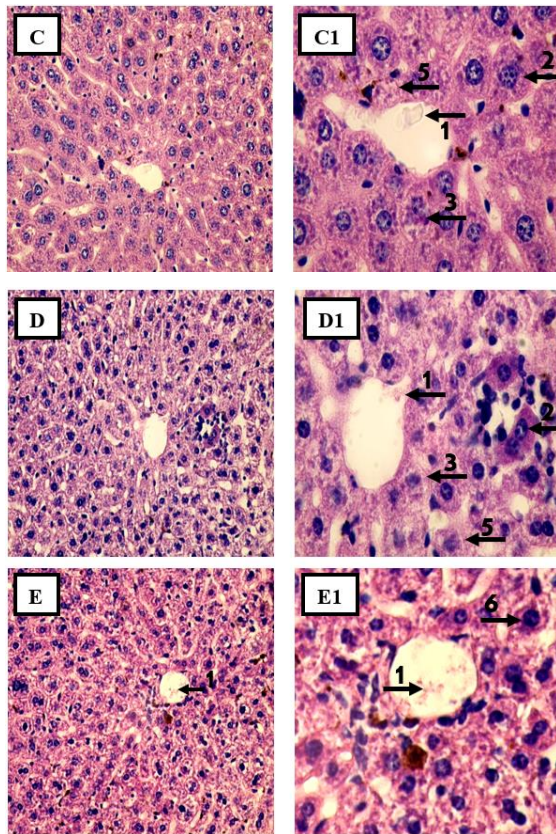
Histological pictures of mouse liver will be analyzed descriptively by displaying images.

## RESULT AND DISCUSSION

Histological picture of liver cells of mice of a negative control group (K(-)), positive control group (K(+)), DM model mice given bark extract of *Cinnamomum burmanii* dose 125 mg/g BB (P1), 250 mg/g BB (P2) and 500 mg/g BB (P3) can be seen in Figure 1.







**Figure 1.** Histology of mouse liver cells: 400x magnification A: negative control K(-), B: Positive control K (+), C: P1, D: P2 and E: P3.

1000X magnification A1: negative control K(-), B1: positive control K (+), C1: P1, D1: P2 and E1: P3.

Description :

1. Central venous congestion
2. Hydrophilic degeneration
3. Fatty degeneration
4. Sinusoid Congestion
5. Necrosis
6. Pycnotic Nucleus

The histological picture of mouse liver cells in Figure 1 shows that in the negative control group (Figure 1a) it is

seen that the central vein, endothelial cells, and hepatocytes are in a normal state. In the positive control group (Figure 1B), it was seen that liver cells suffered damage in the form of congestion in the central vein, hydrophobic degeneration of hepatocytes, fatty degeneration, necrosis, and hepatocyte nuclei experienced pycnotic. In the group of mice DM model treated with bark extract *Cinnamomum burmanii* doses of 125 mg / g BB (Figure 1C) and 250 mg / g BB (figure 1D) seen the central vein has begun to experience improvements but there is still damage in the form of congestion at the edges of the central vein, hydrophilic degeneration, fatty degeneration, and necrosis, While in the group of mice DM model treated with bark extract *Cinnamomum burmanii* dose of 500 mg/g BW (figure 1E) liver cells are already in a normal state but there is still damage in the form of central venous congestion and hepatocyte nuclei experience pycnotic.

Furthermore, the number of central venous congestion, hydrophilic degeneration, fatty degeneration, sinusoid congestion, necrosis, and pycnotic nuclei in the three visual fields was calculated as shown in Table 1.



Table 1. Average type and amount of liver cell damage

Treatment	Types of liver cell damage					
	Ventral venous congestion	Hydrophysical Degeneration	Fat Degeneration	Sinusoidal congestion	Necrosis	Picnotic Core
Control -	0,00 ± 0,00 <sup>a</sup>	1,67 ± 1,53 <sup>a</sup>	1,00 ± 1,00 <sup>a</sup>	2,00 ± 1,00 <sup>a</sup>	0,33 ± 0,58 <sup>a</sup>	3,00 ± 2,00 <sup>a</sup>
Control +	11,67 ± 4,04 <sup>b</sup>	52,00 ± 6,56 <sup>b</sup>	30,00 ± 1,73 <sup>b</sup>	20,00 ± 2,00 <sup>b</sup>	33,00 ± 6,56 <sup>b</sup>	43,00 ± 4,00 <sup>b</sup>
P1	8,00 ± 1,73 <sup>c</sup>	38,67 ± 2,52 <sup>c</sup>	23,00 ± 1,73 <sup>c</sup>	17,67 ± 2,89 <sup>b</sup>	22,67 ± 8,51 <sup>c</sup>	34,00 ± 2,65 <sup>c</sup>
P2	6,33 ± 1,53 <sup>d</sup>	22,00 ± 2,65 <sup>d</sup>	14,00 ± 2,00 <sup>d</sup>	10,67 ± 1,16 <sup>c</sup>	15,00 ± 4,58 <sup>d</sup>	14,00 ± 3,00 <sup>d</sup>
P3	1,00 ± 1,00 <sup>e</sup>	9,67 ± 1,53 <sup>e</sup>	3,33 ± 1,16 <sup>a</sup>	1,67 ± 1,53 <sup>d</sup>	4,33 ± 1,53 <sup>e</sup>	3,00 ± 1,00 <sup>a</sup>
Mean	5,40 ± 4,87	24,80 ± 19,34	14,27 ± 11,16	10,40 ± 8,06	15,07 ± 13,13	19,40 ± 17,08

Note: superscripts with the same letter do not differ significantly ( $P > 0.05$ )

Based on the results in Table 1 show that ventral venous congestion in the negative control group of mice was as much as 0.00, in the positive control group of mice as much as 11.67, the DM model of mice treated with bark extract *Cinnamomum burmanii* dose of 125 mg/g BB as much as 8.00, a dose of 250 mg/g BB as much as 6.33 and at a dose of 500 mg/g BB as much as 1.00. Congestion is a term that indicates excess blood volume in a section of blood vessels. This can occur due to too much blood entering the arteries or too little blood going to the veins, congestion that occurs in this study can be seen in Figures 1B, 1C, 1D, and 1E). Microscopically, congestion is characterized by the presence of dilatation in the walls of arteries or capillaries caused by the large volume of blood in these parts.<sup>21</sup> the presence of

damage to the central vein can be caused due to too much blood being collected, this is what can cause the concentration of substances of a toxic nature to be much greater, thus clarifying the damage that occurs in the central vein.<sup>21</sup>

The average hepatocyte cells that undergo hydrophysical degeneration in the negative control group of mice were as much as 1.67, in the positive control group of mice as much as 52.00, in the DM model mice treated bark extract *Cinnamomum burmanii* dose of 125 mg/g BB as much as 38.67, dose of 250 mg/g BB as much as 22.00 and at a dose of 500 mg/g BB as much as 9.67. Hydrophilic degeneration can occur due to disruption of the sodium-potassium pump in the regulation of the entry and exit of ions. Hydrophilic degeneration is caused due to



metabolic disorders in the liver. Hydropis degeneration is a temporary change if observed microscopically visible vacuoles in the cytoplasm of the cell so that the liver cells look swollen, and liver cells look paler in color (Figure 1B, 1C, and 1D).

Hydrophilic degeneration is a state that most often arises as a result of cell damage. Damage to the cell membrane causes membrane leakage, disrupting the activity of K<sup>+</sup> transport out of the cell and the entry of a certain amount of Ca<sup>2+</sup>, Na<sup>+</sup>, and water into the cell. As a result of the large amount of extracellular fluid entering the cytoplasm, it causes swelling of the cytoplasm, mitochondria, and rough endoplasmic reticulum<sup>22</sup> hydro pis degeneration includes minor damage because it can heal and liver cells become normal again (reversible). The increase in the number of hydrophilic degenerated hepatocytes in this study is suspected to be due to compounds from STZ that are toxic and inhibit the work of enzymes involved in intracellular lipid metabolism.

If the damage of hydrophilic degeneration does not return to normal, then the liver cells will experience fatty degeneration before irreversible damage occurs (fixed), microscopically, in the cytoplasm of cells there is a lot of fat, fat grains that look white (Figure 1B, 1C and 1D). The average number of cells that experience

fatty degeneration in the negative control mice group of 1.00, the positive control mice group of 30.00, in the DM model mice treated with bark extract *Cinnamomum burmanii* dose of 125 mg/g BB of 23.00, a dose of 250 mg/g BB of 14.00 and dose of 500 mg / g BB of 3.33. Fatty degeneration was present in both control mice and treated animals, but in line with the duration of treatment, the number of liver cells damaged by fatty degeneration increased in the percentage of the positive control group (Table 1).

In addition, there was liver sinusoid congestion in the treatment group compared to the control group (Figure 1B). The average number of sinusoid cells that experienced congestion in the negative control mice group of 2.00, the positive control mice group of 20.00, DM model mice treated with bark extract *Cinnamomum burmanii* dose of 125 mg/g BB of 17.67, a dose of 250 mg/g BB of 10.67 and dose of 500 mg/g BB of 1.67. The average number of cells that experience necrosis in endothelial cells for the negative control group of mice as much as 0.33, the positive control group of mice as much as 33.0, DM model group of mice treated with bark extract *Cinnamomum burmanii* dose of 125 mg/g BB as much as 22.67, a dose of 250 mg/g BB as much as 15.00 and at a dose of 500 mg/g BB as much as 4.33. Sinusoid congestion is the presence of clumping of red blood cells



in the sinusoid. High levels of white vitamin C in acidic blood can damage the sinusoid endothelium membrane which causes red blood cells to clot easily.<sup>23</sup>

Liver cells if continuously exposed to toxic substances will cause cell necrosis. Before the cell undergoes necrosis, the cell nucleus will undergo pycnotic where the histological preparation shows a dark core color compared to the normal hepatocyte nucleus (Figure 1B and 1E). This occurs because the chromosomes in the pycnotic nucleus are homogenized and absorb a lot of dye. The average number of hepatocyte cells experiencing pycnotic nuclei in the negative control group of mice was 3.00, the positive control group of mice was 43.00, DM model group treated bark extract *Cinnamomum burmanii* dose of 125 mg/g BB of 34.00, a dose of 250 mg/g BB of 14.00 and dose of 500 mg/g BB of 3.00.

Necrosis is the death of cells or tissues in living organisms. Microscopically, there is a change in the core, which is the loss of chromatin image, the core becomes wrinkled, no longer vascular, the core appears denser, the color is dark black (pyknosis), the core is divided into fragments, torn (karyorrhexis), the core no longer takes on much color because it is pale not real (karyolysis).<sup>24</sup> this can

be seen in Figures 1B, 1C, and 1D. According to Ressang, necrosis of the liver can also be caused by the direct influence of toxic agents such as chemicals or germ toxins (sociopathic necrosis).<sup>25</sup> chemicals that are too much in the liver will cause cell damage, such as inflammatory cell infiltration, fatty degeneration, pycnosis, and congestion.<sup>26</sup>

The body needs antioxidants that can help protect the body from free radical attacks by reducing the negative impact of these compounds. Synthetic antioxidants such as BHA (butyl hydroxy Anisole), BHT (Butyl hydroxytoluene), PG (propyl gallate), and TBHQ (Tert-butyl hydroquinone) can cause carcinogenesis. This antioxidant can transform body cells into a safety net to fight free radicals that cause various diseases. Uncontrolled free radicals can cause damage to cells.

Administration of bark extract *Cinnamomum burmanii* doses of 125 mg / g BB, 250 mg/g BB and 500 mg / g BB in this study led to liver cell repair. This is due to antioxidant compounds in the form of flavonoids, saponins, tannins, and triterpenoids contained in the bark of cinnamon. Flavonoids are known to have hepatoprotective activity. Compound-polyphenol compounds such as flavonoids can inhibit oxidation reactions through radical scavenging mechanisms by donating one electron





to an unpaired electron in a free radical so that the number of free radicals is reduced.<sup>27</sup> the antioxidant mechanism of flavonoids is to capture ROS directly, prevent ROS regeneration and can indirectly enhance the antioxidant activity of cellular antioxidant enzymes.<sup>28</sup> flavonoids are thought to have an effect in inhibiting liver damage by binding free radicals so that their impact on the liver is reduced. In addition, according to Sharma and Shukla, the antioxidant effect of flavonoids enhances the regeneration process by destroying free radicals, providing a competitive substrate for unsaturated lipids in membranes and or accelerating the repair mechanisms of damaged cell membranes.<sup>29</sup>

Based on the analysis of variance (ANOVA) of one pathway using the SPSS 16.0 program also showed that  $f$  count >  $F$  table, which means that the bark of *Cinnamomum burmanii* effect on reducing the amount of damage to the liver cells of mice.

## CONCLUSION

Based on the results and discussion, it can be concluded that the administration of bark extract *Cinnamomum burmanii* can regenerate damaged liver cells of mice due to diabetes mellitus.

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