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Protective Potential of Kersen Leaf Ethanol Extract (*Muntingia calabura* L.) Against Hepatic Histopathology in Diabetes Mellitus Model Rats

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Abstract: Kersen leaves (*Muntingia calabura* L.) are known as herbal plants used to lower blood glucose levels. This study evaluated the protective effect of ethanol extract of kersen leaves on the histopathology of the liver of white rats (*Rattus norvegicus*) model of diabetes mellitus. The experimental study with a Complete Randomized Design (RAL) involved five treatment groups and three replicates, using 55 streptozotocin (STZ)-induced mice. The results showed that the administration of 15% (K5) of kersen leaf ethanol extract improved the structure of hepatocytes, resembling normal tissue, compared to the positive control group (K2) who experienced severe necrosis and degeneration. In conclusion, 15% kersen leaf ethanol extract is effective in improving liver damage due to diabetes and potentially lowering blood glucose levels.

Keywords: Hepar; Histopathology; *Muntingia calabura* L.; Streptozocin

Introduction

An unhealthy lifestyle due to the improvement of people's welfare from year to year contributes to the increasing prevalence of degenerative diseases, one of which is diabetes mellitus. Diabetes mellitus is a metabolic disorder characterized by increased levels of glucose in the blood or hyperglycemia (Papachristoforou et al., 2020). This disease occurs due to resistance to insulin or absolute lack of insulin production caused by damage to pancreatic beta cells. Insulin itself is an important hormone that regulates glucose metabolism, both through glycolysis pathways and gluconeogenesis that takes place in hepatic cells (hepatocytes) (Petersmann et al., 2019). The process of gluconeogenesis that takes place continuously over the long term can lead to glucose auto-oxidation, protein glycation, as well as activation of polyol pathways, all of which contribute to increased free radical production and the formation of oxygen-reactive compounds (American Diabetes Association, 2014; CDC, 2020).

Diabetes mellitus (DM) is a metabolic disease that involves disturbances in insulin secretion and function, or a combination of both. This disease is characterized by chronic hyperglycemia which, if left untreated, can cause serious complications in large (macrovascular) and small (microvascular) blood vessels (Primal et al., 2022). One of the affected organs is the liver, where oxidative stress can alter the histological structure of the liver and significantly increase the amount of fat in hepatocytes (Wijayanti et al., 2023).

Currently, there are an estimated 422 million people worldwide suffering from diabetes, with the majority of cases occurring in developing or low- to middle-income countries. Diabetes is also the cause of death for about 1.5 million people every year. The

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prevalence of this disease has continued to show an increase over the past decade (WHO, 2023). Data from the Ministry of Health of the Republic of Indonesia (2020) shows that in 2018, the prevalence of diabetes mellitus in people aged 15 years and older increased by 2%. In Aceh Province, the number of diabetics in 2019 was recorded at 138,291 people (Supartiningsih et al., 2023). Based on a survey conducted by the Ministry of Health in Aceh Province in 2020, this area is included in the top nine regions in Indonesia with the highest prevalence of diabetes. In 2021, the number of DM cases in Aceh reached 318,527 sufferers (Aceh Health Office, 2021).

The current development of diabetes mellitus treatment is not only focused on conventional therapy, but also involves the use of traditional medicine as an alternative for the prevention of complications. One of the traditional treatments that is widely used is herbal plants, because they are considered to have milder side effects than commercial drugs. One potential plant is kersen (*Muntingia calabura* L.). Kersen leaf extract is known to contain various active compounds such as alkaloids, polyphenols, tannins, saponins, and flavonoids (Iswantini et al., 2021; Wahyusi et al., 2023; Widyaningrum et al., 2020). Research by Tunnur et al. (2023) also shows that the administration of kersen leaf ethanol extract at a dose of 15% is able to repair damage to the renal tubules and significantly lower blood glucose levels, with effects comparable to glibenchamide drugs.

Method

The Process of Making Kersen Leaf Extract

A total of 500 grams of kersen leaves (*Muntingia calabura* L.) were collected from a garden located in Atuk Palawan Village, Baiturrahman District, Banda Aceh City. The kersen leaves are then washed clean using running water, followed by rinsing with distilled water. After that, the leaves are cut into small pieces and dried by aeration, but not exposed to direct sunlight. The dried kersen leaves are then crushed using a blender until they become a fine powder. The extraction process is carried out by the maceration method, where kersen leaf powder is soaked for three days. After the maceration process, the solution is filtered with filter paper three times to obtain a clear extract. The liquid extract is then evaporated using a vacuum distillation device, and then concentrated until homogeneous with the help of a rotary evaporator (Orno, 2023).

Preparation of Test Animals

The study used thirty male white rats (*Rattus norvegicus*), three months old, weighing between 100 and 200 grams. The mice used were in good health and showed normal activity. Prior to the treatment, the test animals were acclimatized for seven days at room temperature of 25°C to stabilize their physiological and biochemical conditions. Next, the mice were divided into five treatment groups, each group consisting of three replicates.

K1 : (Negative control): only given aquades.
K2 : (Positive control): induced with streptozotocin at a dose of 30 mg/kg body weight once, then observed for 28 days.
K3 : given streptozotocin 30 mg/kg body weight once, followed by metformin administration ($C_4H_{11}N_5$) 2 ml.
K4 : induced streptozotocin 30 mg/kg body weight once, then given extract Kersen leaves concentration 10%.
K5 : induced streptozotocin 30 mg/kg body weight once, then given leaf extract Kersen concentration 15%.

Preparation of Hepatic Histology Preparations

One day after the treatment was completed, the rats were sacrificed and surgically performed to remove the liver organs. Immediately after removal, the liver is washed using a saline solution and fixed in 10% formalin buffer for 18–24 hours. Next, the liver tissue is inserted into a stratified alcohol solution (80%, 90%, 95%, to absolute alcohol) for the dehydration process. After that, the tissue is soaked in a solution of xylene for an hour and then continued with immersion in liquid paraffin for an hour for the formation of paraffin blocks. The paraffin blocks that have formed are then cut using microtomes with a slice thickness of about 5 micrometers.

The tissue pieces are placed on the glass of the object that has previously been coated with polylysine, then deparaphinized. The tissue that has been prepared to be stained with the hematoxylin and eosin (HE) staining method, is dried, and then dripped with Canadian balm. Observation of hepatocyte structure is carried out using Olympus brand optical microscopes, and micrographic images are taken for further analysis.

Result and Discussion

This study showed the effect of ethanol extract of kersen leaves in overcoming hyperglycemia on the histological picture of streptozotosin-induced rat liver histology (STZ). Data on hepatocyte cell damage rates are presented in Table 1.

Based on the results of the study, the control group (K1) showed normal liver condition, without any damage to hepatocyte tissue. In contrast, in the STZ-

induced K2 (positive control) group without treatment, severe liver damage occurred. It can be seen that about 50% of the liver tissue experiences swelling and turbidity, accompanied by hydropic/fat degeneration of 25%, and necrosis reaches 75%. In the K3 group, which received STZ and metformin treatment, liver damage was relatively mild. There is swelling and turbidity in about 50% of the tissues, while hydropic/fat degeneration reaches 10%, and necrosis is only 10%. The K4 group, which was STZ-induced and given 10% kersen leaf extract, showed a mild level of damage. The liver of the rats in this group experienced swelling and turbidity with a level of hepatocyte tissue damage of 50%, hydropic/fat degeneration of 10%, and necrosis of 10%. Meanwhile, the K5 group, which received STZ treatment and 15% kersen leaf extract, showed a very minimal damage rate, only 10%. The condition of the rat's liver still showed slight swelling and turbidity. The histopathological picture of each group can be observed in the figure below.

Table 1. Histological Damage Rate of White Rats (*Rattus norvegicus*)

Group	Hepatocyte Cell Damage Rate	Swelling & Turbidity/Fat	Degeneracy Hydro Shoes	Necrosis
K1	None	None	None	None (Normal)
K2 (Control- STZ)	Heavy Damage	50%	20%	75%
K3 (STZ + Metformin)	Minor Damage	50%	10%	10%
K4 (STZ + EDK 10%)	Minor Damage	50%	10%	10%
K5 (STZ + EDK 15%)	Very light damage	10%	None	None

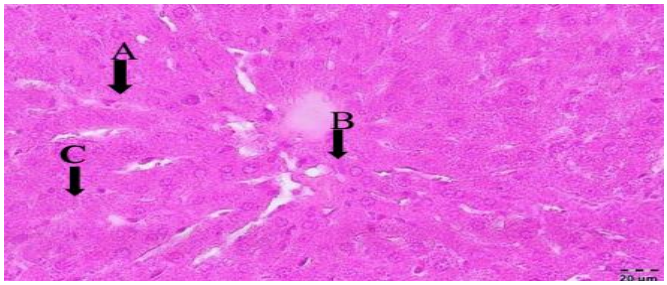

Figure 1. Histological description of the liver of white rats (*Rattus norvegicus*) of the Y0 group. Image caption: A) Vena, Sentralis, B) Sell Hepatosit, C) Sinosoid

Figure 1 shows the normal structure of liver tissue, where hepatocytes are arranged radially in the lobules of the liver. This is in line with the opinion of Gibson et al. (2006), who stated that hepatocytes are arranged like a layer of bricks 1-2 cells thick, forming a labyrinthine pattern from the edge of the lobules towards the center. Between the layers of hepatocytes are the sinusoids of the liver, which are sinuous and thin-walled capillaries, lined with discontinuous endothelial cells.

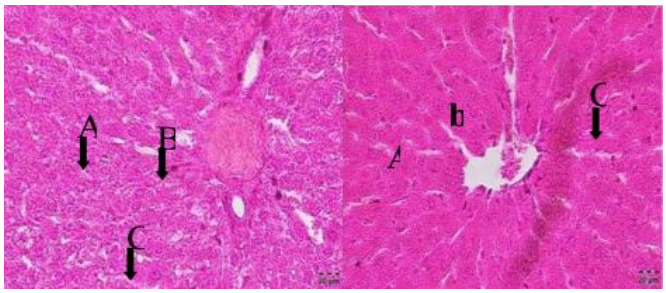

Figure 2. Histological description of rat liver; K2 (a) and K3 (b) groups. Image caption: A) Cloudy swelling, B) Necrosis (inti Piknotik), C) Fat degeneration

In the histopathological images of the K2 group, severe tissue damage appeared. Many hepatocyte cells undergo necrosis, as seen by the presence of opaque swelling and picnotic cell nuclei. Himawan et al. (2013) explained that this cloudy swelling is caused by a disorder of energy metabolism, which causes protein accumulation and the inability of cells to pump sodium out, resulting in changes in cell morphology.

Necrosis itself is the death of cells or tissues that are still part of the organism, characterized by changes in the shape of the nucleus. In the initial phase, the nucleus shrinks and darkens (picnosis), then disintegrates into chromatin fragments (karyostriction), and finally loses its ability to color (cariolisis), as explained by Castera et al. (2008).

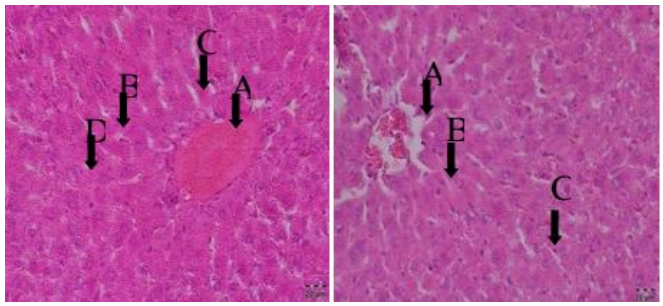

Figure 3. Mouse hepatic histological description; Group 4 (a) and Group 5 (b). Image caption: A) Vena Sentralis, B) Sel Hepatosit, C) Sinosoid, D) Fat degeneration (HE staining, 100X enlargement)

In the K3 group, only a few cells showed fat degeneration, with fat vacuolization in the cytoplasm, without necrosis being encountered. Fat degeneration in hepatocytes is generally reversible, caused by impaired triglyceride metabolism that increases synthesis or decreases fat secretion from within the cell. Normal hepatocyte cells show no vacuolization, the nucleus remains normochromatic, and there is no bleeding. If

vacuoles are found but the cell nucleus is still orthochromatic, then only degeneration occurs, while if the nucleus loses orthochromatic staining, this indicates necrosis (Darmawan, 2003).

In the K4 group, about 25% of liver tissue showed damage with cell degeneration, while the K5 group showed relatively normal liver conditions. Hepatocytes in this group appear to be arranged radially like the structure of a healthy liver.

Discussion

The study showed that ethanol extract of kersen leaves (*Muntingia calabura* L.) had a potential antihyperglycemic effect that affected the improvement of the histological structure of the liver (hepa) in white rats (*Rattus norvegicus*) induced by streptozotocin (STZ). The content of active compounds such as flavonoids and tannins acts as antioxidants that can reduce oxidative stress on liver tissue, thereby helping to repair hepatocyte damage due to hyperglycemia (Orno, 2023; Safna et al., 2021).

According to Jaya et al. (2018), the pharmacodynamic response of drugs is not always proportional to the increase in the dose given. This has to do with drug receptor saturation, where increasing doses beyond the maximum capacity of the receptors no longer enhances the therapeutic effect, and can even lead to toxicity or other side effects. Therefore, the administration of kersen leaf extract in optimal doses is the key to obtaining the maximum liver protection effect (Jaya et al., 2018).

The results of histopathological observations showed that the administration of kersen leaf ethanol extract to the STZ-induced rat group was able to improve the histological picture of the liver, including by reducing fat degeneration, necrosis, and swelling of hepatocyte cells (Andalia et al., 2017; Safna et al., 2021). Fat degeneration is reversible if treatment is given appropriately, while necrosis shows more severe damage and is often irreversible (Castera et al., 2008; Darmawan, 2003).

Conclusion

Based on the results of the research that has been conducted, it can be concluded that the administration of ethanol extract of kersen leaves (*Muntingia calabura* L.) shows a protective effect on the liver tissue of white rats (*Rattus norvegicus*) induced by streptozotocin (STZ). The degree of liver cell damage varies in each treatment group. The negative control group (K2) showed the most severe degree of damage, with necrosis and hepatocyte fat loss accounting for up to 75% of the histological field of view. Meanwhile, the K3 and K4 treatment groups showed a milder level of damage, with cell damage reaching about 25% of the field of view. The K5 treatment group showed the best results, with a near-normal hepatic histological picture and minimal damage level, only about 10% of the field of view. These findings indicate that kersen leaf ethanol extract has the potential to be a hepatoprotective agent, able to reduce the degree of liver cell damage due to STZ induction. This effect is most likely related to the content of bioactive compounds in kersen leaves, such as flavonoids and tannins, which act as antioxidants and anti-inflammatory agents.

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Author Contributions

For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, N.A. and M.R.; methodology, E.L.; software, J.A.; validation, A.R., N.A. and M.R.; formal analysis, E.L.; investigation, N.A.; resources, A.R.; data curation, J.A.; writing—original draft preparation, N.A.; writing—review and editing, M.R.; visualization, E.L.; supervision, A.R.; project administration, J.A.; funding acquisition, N.A. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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