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# THE EFFECT OF *Muntingia calabura* L. LEAF EXTRACT ADMINISTRATION ON BLOOD GLUCOSE LEVELS AND SPERM MOTILITY AND VIABILITY IN STREPTOZOTOCIN-INDUCED MICE

## PENGARUH PEMBERIAN EKSTRAK DAUN *Muntingia calabura* L. TERHADAP KADAR GULA DARAH SERTA MOTILITAS DAN VIABILITAS SPERMA MENCIT DIABETIK YANG DIINDUKSI STREPTOZOTOCIN

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**Abstract**

Increased reactive oxygen species levels, a result of antioxidant imbalance in diabetic, can affect metabolism and cellular respiration, especially spermatogenesis that affects sperm quality. *Muntingia calabura* has proven to be effective as an antidiabetic and rich antioxidant through several studies. This study aims to analyse the effectiveness of *Muntingia* leaf extract on blood sugar levels, sperm motility, and viability in mice induced by streptozotocin. A diabetic animal model was developed with repeated low doses of streptozotocin. The group was divided into 5 groups, which are the negative control, positive control, and three extract groups (100, 150, 200 mg/kg). Blood sugar tests showed that the positive control group, mice induced with streptozotocin without *Muntingia* leaf extract, had the highest blood sugar levels. Treatment groups with *Muntingia* leaf extract had different results, those groups successfully reduced blood sugar levels to normal levels. The highest dose, 200 mg/kg, of *Muntingia* leaf extract reached 85.9% normal sperm motility and 82.9% sperm viability. The ANOVA test result showed a significant relationship between blood sugar levels with sperm motility and viability in streptozotocin-induced mice after *Muntingia* leaf extract administration. *Muntingia* leaf extract has the potential to reduce blood sugar levels in hypergly-cemic conditions and to improve sperm motility and viability.

**Keywords:** Antioxidant; Blood sugar; Diabetic; *Muntingia calabura*; Sperm motility; Sperm viability

***Abstrak***

*Peningkatan kadar reaktif oksigen spesies akibat ketidakseimbangan antioksidan pada penderita diabetes dapat memengaruhi metabolisme dan respirasi sel, terutama spermatogenesis dalam memengaruhi kualitas sperma. Muntingia calabura telah terbukti efektif sebagai antidiabetes dan kaya akan antioksidan melalui beberapa penelitian. Penelitian ini bertujuan untuk menganalisis efektivitas ekstrak daun Muntingia terhadap kadar gula darah, motilitas, dan viabilitas sperma pada mencit yang diinduksi streptozotocin. Model hewan coba diabetes dikembangkan dengan pemberian streptozotocin dosis rendah secara berulang. Kelompok dibagi menjadi 5 kelompok, yaitu kelompok kontrol negatif, kelompok kontrol positif, dan tiga kelompok ekstrak dengan konsentrasi 100, 150, 200 mg/kg. Hasil pemeriksaan gula darah menunjukkan bahwa kelompok kontrol positif, yaitu mencit yang diinduksi dengan streptozotocin tanpa ekstrak daun Muntingia, memiliki kadar gula darah tertinggi. Kelompok perlakuan dengan ekstrak daun Muntingia memiliki hasil yang berbeda, kelompok tersebut berhasil menurunkan kadar gula darah mencapai kadar normal. Dosis tertinggi, 200 mg/kgBB ekstrak daun Muntingia mencapai 85,9% motilitas sperma normal dan 82,9% viabilitas sperma. Hasil uji ANOVA menunjukkan adanya hubungan yang signifikan antara kadar gula darah dengan motilitas dan viabilitas sperma pada mencit yang diinduksi streptozotocin setelah pemberian ekstrak daun Muntingia. Ekstrak daun Muntingia memiliki potensi untuk menurunkan kadar gula darah pada kondisi hiperglikemik dan meningkatkan motilitas dan viabilitas sperma.*

***Kata Kunci**: Antioksidan; Diabetes; Gula darah; Motilitas sperma; Muntingia calabura; Viabilitas sperma*

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## INTRODUCTION

Diabetes is a global health emergency and one of the fastest-growing diseases. The International Diabetes Federation states that 537 million people worldwide have diabetes, and it is predicted that the prevalence will increase to 46% by 2030 and 2045. In developing countries, including Indonesia, four out of five people suffer from diabetes. In Indonesia, people with diabetes in the age group of 20–79 years amounted to 19,465,100 people, or the prevalence reached 10.6%. This indicates that one in nine people in Indonesia has diabetes (International Diabetes Federation, 2021).

There are about 17.5% of the world's adult population experiencing infertility in 2023. This means that one in six people experience infertility (World Health Organization, 2023). The prevalence of infertility increases as the prevalence of diabetes increases (Huang et al., 2024). Oxidative stress due to reactive oxygen species that increase in diabetic conditions will interfere with the process of spermatogenesis. This disrupts cellular metabolism and respiration, triggering DNA mutations and leading to apoptosis of spermatozoa cells (Awuy et al., 2021). These disorders can reduce sperm motility and viability, as well as sperm count and quality, sperm abnormality, and even disruption of sperm DNA integrity (Huang et al., 2024). Another study mentioned that in type 1 diabetes, there can be changes in epididymis function and damage to sperm cell mitochondria that affect motility (Wulandari et al., 2024), while in type 2 diabetes there is inflammation that affects sperm quality (Condorelli et al., 2018).

Antioxidant imbalance in diabetic conditions will increase reactive oxygen species in the body. Increasing antioxidants in the body can correct this because electrons from antioxidants can stabilize free radicals so that oxidative stress will not be formed (Mutammimah et al., 2022). Antioxidants are found in *Muntingia* leaves and are classified as strong antioxidants (Sumarni et al., 2022). *Muntingia* plants, usually called *kersen*, are easily found in Indonesia, but are usually only used as shade, even though the leaves have secondary metabolite compounds that have potential as traditional medicines. Research related to *Muntingia* leaf herbal tea as a traditional medicine has effects as an antioxidant, anti-inflammatory, analgesic, antipyretic, and antibacterial (Nawir et al., 2021). *Muntingia* leaves can be used as anti-hyperlipidemia, antidiabetic, and anthelmintic (Sumarni et al., 2022), as well as headache and anti-inflammatory drugs (Mutammimah et al., 2022). Previous studies have shown that *Muntingia* leaves can be used as an antidiabetic, but research related to the effect of *Muntingia calabura* leaf administration on sperm quality in diabetic conditions is still limited. This study aims to provide a new alternative to improve blood sugar levels and sperm quality, especially sperm motility and viability, in diabetic conditions through the mechanism of action of antioxidants in *Muntingia* leaves using an animal model of streptozotocin-induced diabetic mice.

## MATERIALS AND METHODS

This study used *Muntingia calabura* leaf extract, male mice (*Mus musculus* L.) Swiss Webster strain, aged 8–12 weeks, and an average body weight of 32 g, streptozotocin injection, distilled water (NaCl 0.9%), blood glucose test strips, HCL, 70% ethanol, alcohol, Mg powder, and 0.5% eosin solution. This study uses several important tools, namely analytical balance to measure the body weight of mice and extraction results, glass containers for storing extraction samples, filter paper to help the separation of extracts, rotatory vacuum evaporator for thickening extracts, breaker glass, measuring cups, and test tubes as semen sample containers, gloves as safety tools, animal cages, animal feeding and drinking places, pipettes, 10 cc syringes for injecting streptozotocin, sonde for administering *Muntingia* leaf extract, glucometer to check blood sugar levels, surgical boards, and minor sets for dissecting mice, staining racks, object and cover glass, and microscopes for spermatozoa observation.

The research was conducted from June to November 2024. The location of *Muntingia* leaf collection is around the outside of the Cijantung urban forest area. Preparation of *Muntingia* leaf extract and phytochemicals, maintenance and treatment of experimental animals, surgical procedure, as well as reading the results of observations of spermatozoa motility and viability were carried out at the Pharmacology and Therapy Laboratory, Faculty of Medicine, Padjajaran University. This

research has obtained ethical approval with letter number 348/VII/2024/KEP from the authorized institution.

**Methods**

This study was conducted through a true experimental design with a post-test-only control group design, which is the observation of results after treatment. This study focuses on the effect of *Muntingia calabura* leaf extract on blood sugar levels, as well as the motility and viability of streptozotoxin-induced mice after being given *Muntingia* leaf extract. Treatment results will be compared with the control group.

**Research Variable**

The independent variable in this study is *Muntingia calabura* L. leaf extract with doses of 100, 150, and 200 mg/kg body weight. The dependent variables are blood glucose levels, sperm motility, and viability of diabetic mice (*Mus musculus* L.) induced by repeated low doses of streptozotocin (40 mg/kg body weight, intraperitoneally).

**Sampling Technique and Intervention**

Sample collection is carried out using a probability sampling in a homogeneous population without considering strata (purposive random sampling). The mice used met the inclusion criteria, namely male *Mus musculus* L. mice in good health (active, not disabled, able to move as usual), aged 8–12 weeks, with a body weight of 20–40 g. The exclusion criteria for this study were changes in mice behaviour (inactive behaviour, unwilling to eat) and/or illness, and mice that died during the study. Grouping was carried out after the mice met the inclusion criteria and after 7 days of acclimatization. The experimental animals will be grouped into five groups, namely the negative control group, the positive control group, and three different dosing groups, namely doses of 100, 150, and 200 mg/kg body weight. The negative group is a group that is not given treatment, while the positive group is a diabetic group that is induced by streptozotocin.

***Muntingia* Leaf Extraction**

Preparation of *Muntingia calabura* leaf extract was carried out using the maceration method. The *Muntingia* leaves used were old leaves. *Muntingia* leaves that have been washed clean are then dried. A total of 2,000 g of dried *Muntingia* leaves was then pulverized into powder, and 1,500 g of powder was produced. The powder was then soaked with 70% ethanol solvent in a ratio of 1:4 for 4 days. Storage was carried out using a closed container protected from light and occasionally stirred. The macerate was then filtered using filter paper, resulting in the first filtrate and residue. The residue was macerated again with 70% ethanol in a ratio of 1:3 and left again like the previous maceration for 2 days. Then filtered again to form the residue and second filtrate. The first and the second filtrates were mixed and then evaporated using a rotatory vacuum evaporator at 40 °C for 2 days to obtain a thick extract. The extract formed as much as 215 g of dark green-black color with a strong, distinctive odor. *Muntingia* leaf extract in this study has a yield value of 14.3% in the good category because the value is more than 10% (Wardaningrum et al., 2019).

**Mice Procedure**

A total of 29 mice, which met the inclusion and exclusion criteria, were acclimatized for one week in the research environment with the aim of acclimatization and reducing stress in an unfamiliar environment. Acclimatization was carried out with standard individually ventilated cages, temperature 20–25 °C, humidity 45–55%, and lighting 12 hours light-12 hours dark according to the activity of mice. Food and water were given as desired by the mice (ad libitum) with standardized composition. The total research treatment was carried out for 36 days, corresponding to 1 cycle of mouse spermatogenesis, starting from acclimatization to the administration of extracts. In the negative control group (K-), mice were only given normal feed and drink. In the positive control group (K+), treatment group 1 (K1), treatment group 2 (K2), and treatment group 3 (K3), streptozotocin was induced with repeated low doses of streptozotocin (40 mg/kg body weight,

intraperitoneally) to mice on 5 consecutive days starting on the 9th day of the study. On day 15, mice in treatment group K1 were given *Muntingia* leaf extract at a dose of 100 mg/kg body weight, group K2 was given 150 mg/kg body weight, and group K3 was given 200 mg/kg body weight. The administration of the extract was carried out for 22 days. The treatment was stopped, and termination was carried out on the 37th day.

**Blood Sugar Levels Examination**

The fasting sugar levels were checked after acclimatization, on day 8, with the aim of ensuring that all mice used were in healthy inclusion criteria, not in a congenital diabetic condition. Fasting blood sugar levels were then measured again after streptozotocin induction, on day 14, to ensure that mice in the positive control group (K+), treatment group 1 (K1), treatment group 2 (K2), and treatment group 3 (K3) were in diabetic conditions. Mice are considered hyperglycemic if their blood sugar levels are more than 150 mg/dL (Furman, 2021). Blood sugar levels were measured again on day 37 to see the effect of *Muntingia calabura* leaf extract on blood sugar levels in streptozotocin-induced mice.

**Collecting Sperm Samples**

Furthermore, the mice were dissected by surgical procedures to collect experimental samples. Dissection is done by taking the epididymis organ to get the spermatozoan suspension. The organ was taken with tweezers and chopped, then the chopping was mixed with 1 mL of 0.9% NaCl solution and homogenized until a spermatozoa suspension was obtained (Nugroho, 2018).

**Sperm Samples Observation**

After preparing the sample, drop one drop of the sperm sample on the object glass then cover with a cover glass, then observe the motility under a microscope at 400× magnification and calculate the percentage. Another object glass is prepared for viability observation. Mix the sperm suspension and 0.5% eosin dye in a ratio of 1:1 and stir until homogeneous. Then the mixture is dripped into the object glass that has been prepared and covered with cover glass. Observe the viability with a 400× magnification microscope and calculate the percentage (Nugroho, 2018; World Health Organization, 2021).

## RESULTS

**Analysis of Mice's Blood Sugar Levels**

The assessment of fasting blood sugar levels before intervention showed that the experimental subjects met the inclusion criteria because the fasting blood sugar levels of all mice used in the normal category were not hyperglycemia. Then, the positive control group (K+) and treatment groups K1, K2, and K3, which were induced by streptozotocin, showed that the subjects were in a diabetic condition with fasting blood sugar levels of more than 150 mg/dL. Measurement of blood sugar levels after intervention (on the 37th day), aims to see changes and the effect of *Muntingia* leaf extract given to mice subjects in diabetic conditions. The results of fasting blood sugar measurements before intervention and after streptozotocin induction, as well as blood sugar levels after administration of *Muntingia calabura* leaf extract, can be seen in Table 1.

**Table 1.** Fasting blood sugar levels of mice before and after induced streptozotocin, and blood sugar levels after *Muntingia* leaf extract treatment

| Mice group | Before intervention (mean ± sd) | After stz administration (mean ± sd) | After administration of *Muntingia* leaf extract (mean ± sd) |
|---|---|---|---|
| Negative control group (K-) | 91.80 mg/dL ± 5.40 | 95.80 mg/dL ± 4.14 | 95.80 mg/dL ± 3.56 |
| Positive control group (K+) | 89.17 mg/dL ± 5.70 | 258.00 mg/dL ± 21.67 | 377.83 mg/dL ± 25.73 |
| K1 (extract 100 mg/kg) | 92.17 mg/dL ± 4.49 | 299.67 mg/dL ± 34.62 | 131.83 mg/dL ± 22.26 |
| K2 (extract 150 mg/kg) | 83.67 mg/dL ± 11.41 | 244.67 mg/dL ± 30.97 | 120.33 mg/dL ± 11.14 |
| K3 (extract 200 mg/kg) | 92.33 mg/dL ± 4.8 | 267.67 mg/dL ± 19.47 | 109.33 mg/dL ± 9.24 |

Descriptively, there are changes in fasting blood sugar levels before and after streptozotocin induction, which indicates that repeated administration of low doses of streptozotocin in this study succeeded in making mice in a state of hyperglycemic. The negative control group is a normal control and does not show any changes in blood sugar levels due to normal feeding and drinking. The positive group showed an increase in blood sugar levels due to the administration of streptozotocin, which identified the mice as diabetic. On the other hand, the treatment group given the extract showed a significant decrease in blood sugar levels and approached normal after the intervention. Group K1, the treatment group with a dose of 100 mg/kg body weight, had the lowest blood sugar level, which was 131.83 mg/dL. Group K3, the treatment group with a dose of 200 mg/kg body weight, had the highest blood sugar level reduction, which was 109.33 mg/kg body weight.

**Analysis of Mice Sperm Motility**

The average value of the percentage of sperm motility of mice (*Mus musculus* L.) in each group is presented in Table 2. The positive control group that only received streptozotocin had a lower mean percentage of motility, which was 72.5%, compared to the negative control group that was not given treatment, which was 92.4%. The K3 treatment group that received *Muntingia* leaf extract at a dose of 200 mg/kg body weight showed the highest mean motility percentage, which was 85.9%.

**Table 2.** Mean result of sperm motility percentage in mice (*Mus musculus* L.)

| Mice group | Mean result of sperm motility percentage (mean ± sd) |
|---|---|
| Negative control group (K-) | 92.4% ± 4.73 |
| Positive control group (K+) | 72.5% ± 4.51 |
| K1 (extract 100 mg/kg body weight) | 84.5% ± 4.18 |
| K2 (extract 150 mg/kg body weight) | 85.4% ± 3.25 |
| K3 (extract 200 mg/kg body weight) | 85.9% ± 2.59 |

The percentage of motility was measured by simplifying the categories of sperm cells per field of view. Progressive motility if the sperm move actively, either linearly or rotating in a large circle. Non-progressive motility if the sperm movement pattern is other than the progressive category. Immotility : there is no movement of sperm. The percentage of motile sperm is obtained by summing the progressive and non-progressive motility values.

**Analysis of Mice Sperm Viability**

The data in Table 3 descriptively illustrate the average value of the percentage of sperm motility of mice (*Mus musculus* L.) at 200 cells. The positive control group that only received streptozotocin had a lower mean percentage of viability, which was 71.2%, compared to the negative control group that was not given treatment, which was 92.4%. The K3 treatment group that received *Muntingia* leaf extract at a dose of 200 mg/kg body weight showed the highest mean viability percentage, which was 82.9%.

**Table 3.** Mean result of sperm viability percentage in mice (*Mus musculus* L.)

| Mice group | Mean result of sperm viability percentage (mean ± sd) |
|---|---|
| Negative control group (K-) | 92.4% ± 4.73 |
| Positive control group (K+) | 71.2% ± 5.36 |
| K1 (extract 100 mg/kg body weight) | 81.0% ± 5.05 |
| K2 (extract 150 mg/kg body weight) | 82.6% ± 3.15 |
| K3 (extract 200 mg/kg body weight) | 82.9% ± 4.33 |

The sperm viability description was obtained using a light microscope with a 400× magnification (Figure 1–5). Calculate the percentage of viable sperm that are not stained and viable sperm that are stained.

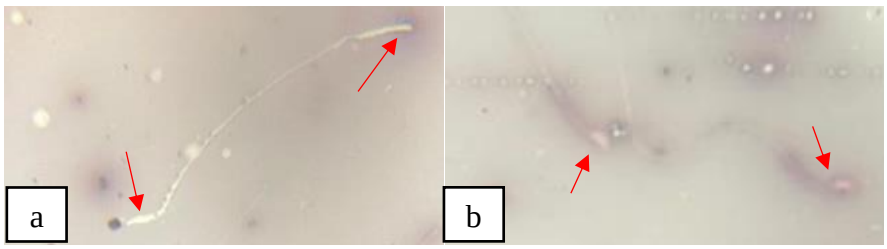


**Figure 1.** Sperm viability of the negative control group at 400× magnification light microscope; viable sperm that are not stained (a) and viable sperm that are stained (b)

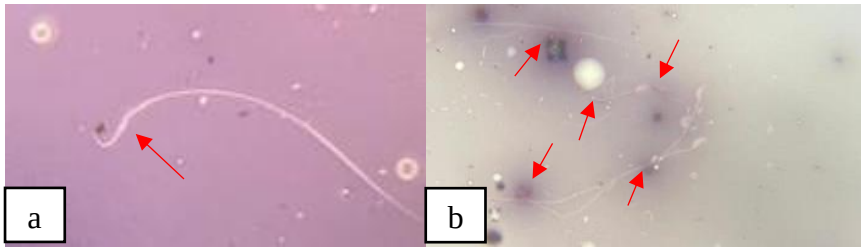


**Figure 2.** Sperm viability of the positive control group at 400× magnification light microscope; viable sperm that are not stained (a), and viable sperm that are stained

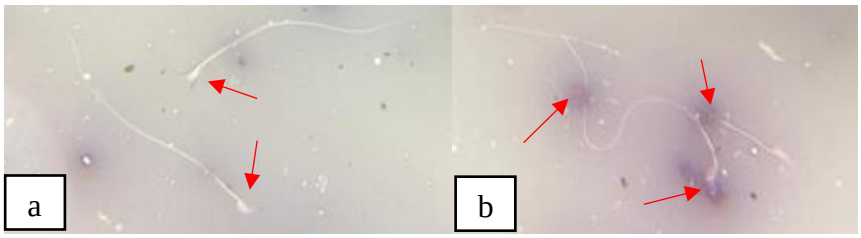


**Figure 3.** Sperm viability of treatment group K1 at 400× magnification light microscope; viable sperm that are not stained (a) and viable sperm that are stained (b)

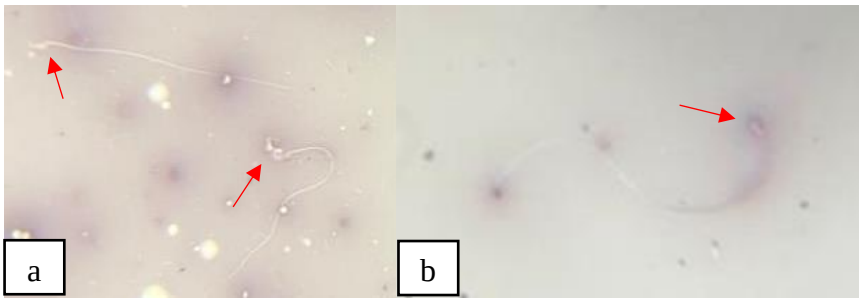


**Figure 4.** Sperm viability of treatment group K2 at 400× magnification light microscope; viable sperm that are not stained (a) and viable sperm that are stained (b)

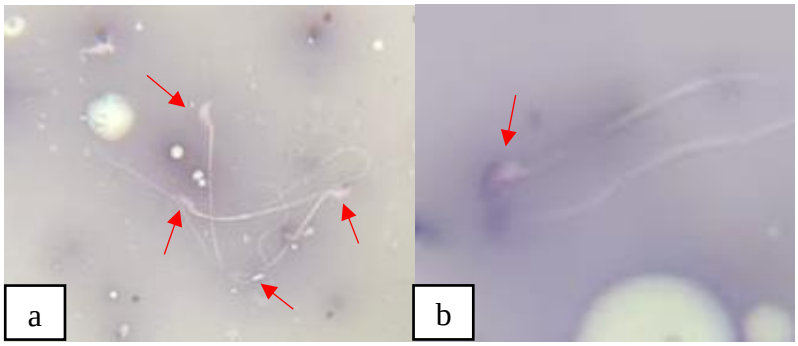


**Figure 5.** Sperm viability of treatment group K3 at 400× magnification light microscope; viable sperm that are not stained (a) and viable sperm that are stained (b)

## DISCUSSION

This study shows the results that the administration of various doses of *Muntingia* leaf extract (*Muntingia calabura* L.) has a significant impact on blood sugar levels and sperm quality of mice (*Mus musculus* L.). This was evidenced by a decrease in blood sugar levels and an increase in the average motility and viability of mice in the K1, K2, and K3 treatment groups against the positive control group. The difference occurs due to secondary metabolite compounds contained in the *Muntingia* leaf extract itself. The *Muntingia* leaf extract used has a value of 14.3% and indicates that the leaves used have good levels of bioactive compounds. Phytochemical analysis conducted on *Muntingia* leaves identified the presence of flavonoids, alkaloids, saponins, tannins, phenolics, glycosides, steroids, and triterpenoid compounds that function as antioxidants, anti-inflammatories, and antidiabetics.

Flavonoids as antioxidants can increase glucose uptake per cell, insulin production, and pancreatic β-cell sensitivity and help reduce blood sugar levels (Nuraini et al., 2025). Alkaloids reduce the speed of absorption and synthesis of glucose, and encourage increased blood glucose transport (Maisarah et al., 2023). Tannins increase glycogenesis and play a role in cytoprotection (Salsabila et al., 2021). Antioxidants in *Muntingia* leaf extract work by breaking the oxidative chain of free radicals due to the effect caused by streptozotocin induction. Diabetogenic effects that occur in the form of toxic effects on pancreatic β-cells. This triggers impaired insulin production, resistance to GLUT 1 expression, and triggers DNA damage and DNA fragmentation. The fragmentation will later lead to a decrease in cellular ATP, characterized by the formation of peroxide and hydroxyl radicals that cause oxidative stress (Nahdi et al., 2017). Disruption of glucose metabolism due to this affects the process of spermatogenesis. Glucose plays an important role as fuel to maintain cellular activity and specific functions, so that if there is a disturbance in GLUT 1, it will affect sperm motility and viability (Huang et al., 2024).

The administration of *Muntingia* leaf extract to the treatment group previously induced by streptozotocin is considered to correct the imbalance of free radicals and help improve glucose metabolism caused by streptozotocin induction. This was shown by the improvement in blood sugar levels and sperm quality, namely motility and viability. The average blood sugar levels in groups K1, K2, and K3 after administration of *Muntingia* leaves extract showed a decrease in blood sugar levels to normal levels. This shows that *Muntingia* leaves are useful as antidiabetics. This is in line with the increase in the average percentage of motility and viability of sperm. The increase in the average motility and viability of spermatozoa can be seen in the K1, K2, and K3 treatment groups against the positive control group, which is only induced by streptozotocin, namely, motility and viability of the K1 group 84.5% and 81%, the K2 group 85.4% and 82.6%, and the K3 group 85.9% and 82.9%. The K3 treatment group with a dose of 200 mg/kg body weight *Muntingia* leaf extract had the mean blood sugar levels to normal levels, as well as the highest mean percentage of motility and viability.

## CONCLUSION

Administration of *Muntingia* leaf extract at doses of 100, 150, and 200 mg/kg body weight can reduce blood sugar levels to normal levels in mice (*Mus musculus* L.) induced by streptozotocin. The administration of *Muntingia* leaf extract can also improve sperm quality by increasing the average percentage of sperm motility and viability of mice based on the dose of administration of each group. For further research suggestions, researchers can conduct further research related to the impact of giving *Muntingia* leaf extract at higher doses or the same dose in the long term.

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