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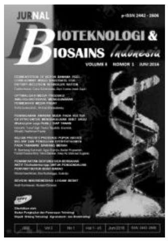

Short Communication

CHANGES IN BLOOD GLUCOSE LEVELS IN EXPERIMENTAL ANIMALS WITH HYPERGLYCEMIA DUE TO LIME (*Citrus aurantifolia* Swingle) PEEL EXTRACT

Perubahan Kadar Glukosa Darah pada Hewan Eksperimental dengan Hiperglikemia akibat Ekstrak Lime (*Citrus aurantifolia* Swingle)

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ABSTRACT
*Chronically elevated levels of glucose in the blood can lead to various complications. As a result, it can accelerate the damage to various organ tissues in the body. Several measures are needed to maintain the stability of normal blood glucose levels to prevent tissue damage, as well as providing additional intake such as lime peel extract which is believed to have high flavonoid content in lowering blood glucose levels. For this reason, this study aimed to analyse changes in blood glucose levels by giving lime extract to alloxan-induced experimental animals. This study uses an experimental post-test control group design. The results showed increased in blood glucose levels in the positive control group (p < 0.005). In addition, the lime (*Citrus aurantifolia *Swingle) peel extract treatment group showed changes in blood glucose levels (p < 0.005). It was concluded that increasing the intake of lime peel extract can reduce blood glucose levels.*

Keywords: *alloxan, blood glucose, hyperglycemia, lime,* Rattus novergicus

ABSTRAK
Peningkatan kadar glukosa dalam darah secara kronis dapat menyebabkan berbagai komplikasi. Akibatnya, dapat mempercepat kerusakan berbagai jaringan organ dalam tubuh. Beberapa tindakan diperlukan untuk menjaga stabilitas kadar glukosa darah normal untuk mencegah kerusakan jaringan. Serta memberikan asupan tambahan seperti ekstrak kulit jeruk nipis yang dianggap memiliki kandungan flavonoid yang tinggi dalam menurunkan kadar glukosa darah. Untuk itu, penelitian ini bertujuan untuk menganalisis perubahan kadar glukosa darah dengan pemberian ekstrak jeruk nipis pada hewan coba yang diinduksi aloksan. Penelitian ini menggunakan rancangan eksperimen post-test control group design. Hasil penelitian menunjukkan adanya peningkatan kadar glukosa darah pada kelompok kontrol positif (p < 0,005). Selain itu, kelompok perlakuan ekstrak kulit jeruk nipis (*Citrus aurantifolia* Swingle) menunjukkan perubahan kadar glukosa darah (p < 0,005). Oleh karena itu, dapat disimpulkan bahwa peningkatan asupan ekstrak kulit jeruk nipis dapat menurunkan kadar glukosa darah.

Kata Kunci: aloksan, gula darah, hiperglikemia, kapur, *Rattus novergicus*

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INTRODUCTION

Diabetes has become a severe public health problem as the number of diabetics increases yearly. In recent years, the number of adults with diabetes has increased twice compared to the previous years (Kharroubi and Darwish 2015). In 2000, the International Diabetes Federation estimated that the prevalence of diabetes globally had reached 3.2% and increased to 6.5% in 2013 (Ogurtsova et al. 2013). The number of diabetics in America was estimated to have reached 9.4% (30.3 million people) of the total population. In the adult age group, there were 415 million people with diabetes, and it is estimated that this will increase up to 642 million in 2040 (Xu et al. 2018).

Based on a survey conducted by the Global Burden of Disease (GBD), the prevalence of diabetes in adults in the world is estimated at 462 million or 6,28% of the world's population (Khan et al. 2020). In Indonesia, the number of diabetics was 172 million of the total population in 2020 (Tanoey and Becher 2021). This makes Indonesia one of the ten countries with the highest number of diabetics in the world. The prevalence of diabetes in urban areas reaches 5.7%, while impaired glucose tolerance reaches 10.2% (Mihardja et al. 2014).

The increase in the number of glucose levels can lead to serious health problems. Diabetes can be an underlying cause of various factors of macrovascular complications such as atherosclerosis, neuropathy, nephropathy, and retinopathy (Papatheodorou et al. 2016). These complications can reduce the quality of life and increase the risk of disabilities which can disrupt work productivity (Breton et al. 2013). A survey on economic losses due to diabetes conducted at one hospital in Indonesia showed that the estimated medical expenses each diabetic patient spent for medications was around $19.97/month (Soewondo et al. 2013).

Diabetes mellitus is usually associated with insulin resistance. An increase in insulin concentration (hyperinsulinemia) usually occurs in patients with diabetes mellitus in the early stage. In the later stage, the pancreatic beta cells become "tired" or damaged and are unable to produce enough insulin (Guyton and Hall 2018). In more severe cases, hyperglycemia may occur due to a decrease in insulin production. Low insulin levels fail to trigger the glucokinase enzyme, which affects intracellular free concentrations to remain high and blocks the entry of glucose into cells (Muhajirin et al. 2019, Barrett et al. 2020).

Patients with diabetes need to find appropriate glucose control. One of the ways is by using anti-diabetes drugs to achieve blood glucose stability within normal limits. However, anti-diabetes drugs have several adverse effects which can require hospital treatment. Sulfonylurea, for example, can lead to hypoglycemia that commonly occurs when people skip meals or after exercise. This adverse effect is mainly due to long-acting sulfonylureas such as chlorpropamide and glibenclamide (Sola et al. 2015).

Lime (*Citrus aurantifolia* Swingle) can be a solution to reduce glucose levels in the blood. Lime is very easy to get and is used daily by Indonesian people. Some people believe that herbs have lower side effects than chemical drugs. Therefore, it is expected that lime can comply with patients' needs in controlling blood glucose. In addition, lime contains various kinds of flavonoids which are found mainly in the flavedo (lime peel) (Narang and Jiraungkoorskul 2016, Suryadinata et al. 2021). Among various types of flavonoids, hesperidin has anti-diabetic activity. Study by Visnagri et al. (2014) showed that there was a decrease in blood glucose levels, an increase in insulin, and a decrease in HbA1c after hesperidin was given for 4 weeks. Another study suggested a decrease in glucose-6-phosphatase activity and an increase in the glucokinase enzyme (Akiyama et al. 2009). This study is a preliminary study on the use of lime peel extract in reducing glucose levels in the blood. Male Wistar rats (*Rattus novergicus*) were used as animals under investigation due to their similarity in physiology, anatomy, and immunity to humans (Barré-Sinoussi and Montagutelli 2015, Wirjatmadi and Suryadinata 2020). The purpose of this study was to determine the effectiveness of lime peel extract (peroral) in reducing blood glucose levels.

MATERIALS AND METHODS

This study was arranged with a randomized controlled trial (RCT) design. The sample used in this study was male Wistar rats (*R. novergicus*). Animals were divided into five groups (negative control group, positive control group, and groups that were treated with different doses). This research has obtained ethical approval from the Health Research Ethics Committee of the University of Surabaya (No: 137/KE/VI/2020).

Time and place

This research was accomplished in the Biomedical Laboratory, Faculty of Medicine, the University of Surabaya for 30 days. The research was conducted from July to August 2020.

Experimental animals

The male Wistar rats (*Rattus novergicus*) used were those that met the criteria which were having ± 200 g of weight and no macros abnormalities, as well as outside of objects in previous studies (Figure 1A). Meanwhile, experimental animals which were sick or died during the experiment were excluded. Moreover, this study refers to the 3R principles (Replacement, Reduction, and Refinement) for the maintenance and care procedure of the experimental animals during the research.

Extraction process

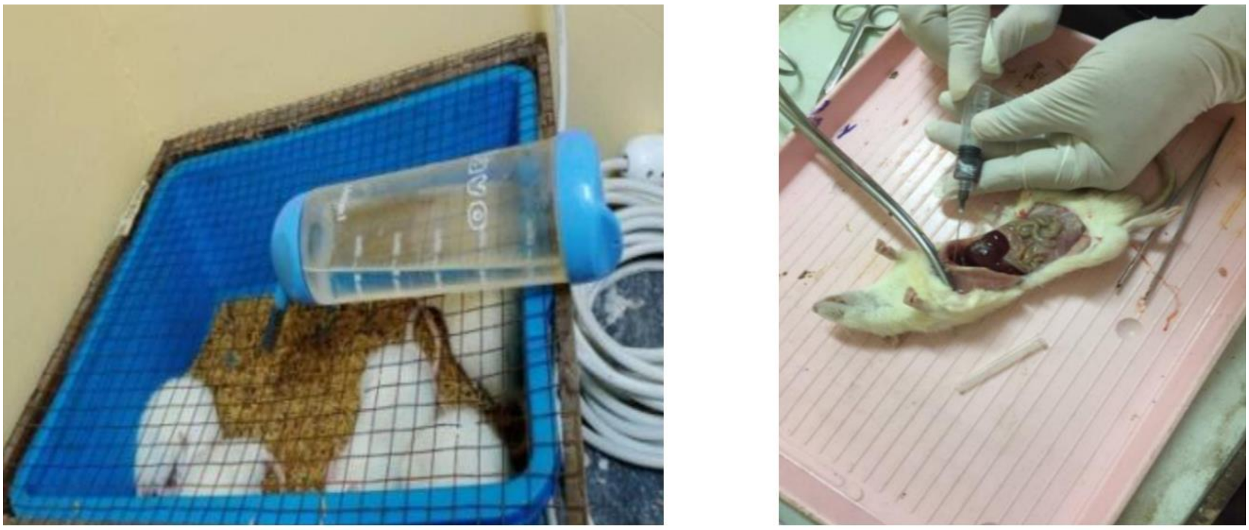
The lime peel (*Citrus aurantifolia* Swingle) was dried for several days. The dried lime peel would be crushed using a blender and sieved to obtain the extract. Furthermore, the extraction process would be carried out using a maceration method by adding 96% of ethanol solvent. By the end of the extraction process, a concentrated liquid of lime peel was obtained. Measurement of flavonoid levels in lime peel extract was then documented in a conversion table. After that, a calculation method based on Laurence and Bacharach was done between the organisms to obtain extract doses of 2.35 mg, 4.7 mg, and 9.4 mg.

Alloxan induction

The experimental animals underwent a fasting period for 6-8 hours before alloxan injection was given intraperitoneally at a dose of 140 mg/kg BW (diluted with 0.9% NaCl). Before the study began, the experimental animals were tested for blood glucose to ensure that the positive control group and experimental groups reached a hyperglycemic state.

Research procedures

This study was a 30-day experimental study involving the experimental animals. The experimental animals underwent an adaptation process in about 5-7 days. After that, the experimental animals were induced with alloxan, and their blood glucose levels



A B

Figure 1. Maintenance of *Rattus norvegicus* Wistar strain (A), Measurement of Intracardiac blood collection (B)

Table 1. Mean values of each group before dan after blood glucose levels test

	Groups	Mean ± SD	Maximum	Minimum
Pre-Test	I	75.40 ± 3.78	71.00	79.00
	II	86.80 ± 3.70	83.00	92.00
	III	87.00 ± 7.97	75.00	95.00
	IV	86.00 ± 5.75	79.00	94.00
	V	89.00 ± 4.00	84.00	94.00
Post-Test	I	74.60 ± 3.58	71.00	79.00
	II	84.00 ± 3.32	81.00	88.00
	III	94.80 ± 3.96	91.00	100.00
	IV	89.80 ± 5.63	83.00	98.00
	V	83.80 ± 2.77	81.00	87.00

Note:
Group I = Group with no alloxan, glimepiride, and lime peel extract
Group II = Group with alloxan, glimepiride, and lime peel extract at a dose of 0.036 mg/rat
Group III = Group with alloxan, glimepiride, and lime peel extract at a dose of 2.35 gr/rat
Group IV = Group with alloxan, glimepiride, and lime peel extract at a dose of 4.7 gr/rat
Group V = Group with alloxan, glimepiride, and lime peel extract at a dose of 9.4 gr/rat

Table 2. Results of ANOVA test on glucose levels in each group

	Group	Normality Test	Homogeneity Test	ANOVA Test
Pre-Test	I	0.222	0,353	0,005
	II	0.687		
	III	0.677		
	IV	0.971		
	V	0.833		
Post-Test	I	0.377	0,555	0,000
	II	0.182		
	III	0.305		
	IV	0.690		
	V	0.292		

were checked. After 30 days of treatment, the blood glucose levels were re-checked to determine changes after treatment (Figure 1B).

The experimental animals were divided into five groups. The first group was a negative control group in which the experimental animals were only given daily intake without any intervention. The second group was a positive control group where the experimental animals were only subjected to alloxan induction and daily intake. Meanwhile, the other three groups were groups that received treatments of alloxan induction, daily intake, and doses of lime peel extract. These groups were further divided based on the conversion of flavonoid requirements in humans to different amounts of lime peel extract (2.35 mg, 4.7 mg, and 9.4 mg).

Statistics

From this study, ratios of the glucose levels before and after the administration of lime peel extract were obtained. Data analysis was performed using a paired T-test to analyze changes in blood glucose levels before and after initiation. After that, the ANOVA test with SPSS version 22 was also performed to identify any differences between groups.

RESULTS AND DISCUSSION

From this research, it can be indicated that the mean values of each group before

Table 3. Results of least significant difference test on blood glucose levels in each group before treatment

Groups	I	II	III	IV	V
I	–	–	–	–	–
II	0.003	–	–	–	–
III	0.002	0.953	–	–	–
IV	0.005	0.814	0.769	–	–
V	0.001	0.519	0.558	0.382	–

Tabel 4. Results of least significant difference test on blood glucose levels in each group after treatment

Groups	**I**	**II**	**III**	**IV**	**V**
I	–	–	–	–	–
II	0.001	–	–	–	–
III	0.000	0.000	–	–	–
IV	0.000	0.032	0.060	–	–
V	0.002	0.937	0.000	0.27	–

Table 5. Results of paired samples T-test in each group

Groups	**Sig.**
I	0.793
II	0.002
III	0.022
IV	0.072
V	0.041

and after treatment (Table 1). The highest mean value of each group before the test is group V (89.00 ± 4.00), the lowest mean value is group I (75.40 ± 3.78). Meanwhile, the highest mean value of each group after the test is group III (94.80 ± 3.96), and the lowest mean value is the group I (74.60 ± 3.58).

This research also found a difference in the blood glucose levels between the Group I (negative control) and the Group II (positive control). The application of alloxan to the positive control group led to an increase in glucose levels. Alloxan works by partially degrading β cells in the Langerhans pancreas (Ighodaro et al. 2017, Putri et al. 2019). β cells are responsible for producing the insulin hormone in the body which can reduce blood glucose levels and increase carbohydrate storage. Therefore, a decrease in insulin levels due to damage to β cells will increase blood glucose levels (DiMeglio et al. 2018).

It was found that all of the groups were normally distributed. Meanwhile, the homogeneity test was p = 0.353 and it was found that the data is homogeneous. Therefore, the ANOVA test can be performed to compare the differences between groups (Table2). It was found that the p-value was 0.005 ($p < 0.05$). The normality test values ($p > 0.05$) in each group after treatment are 0.377 (Group I), 0.182 (Group II), 0.305 (Group III), 0.690 (Group IV), and 0.292 (Group V). It was found that all of the groups were normally distributed. Meanwhile, the homogeneity test shows a p-value of 0.555, meaning that the data were homogeneous. Therefore, the ANOVA test was performed to compare the differences between groups. It was found that the p-value was 0.000 ($p < 0.05$).

There was a difference between Group I and the other groups. Meanwhile, no differences were found between the groups with alloxan. This study also suggested a difference between Group II (injected with alloxan and glimepiride at the dose of 0.036 mg/rat) and the other groups except for Group V (treated with alloxan injection and lime peel extract at a dose of 9.4 g/rat). This indicated that giving glimepiride at the dose of 0.036 mg/rat and lime peel extract at a dose of 9.4 g/rat posed the same results. Glimepiride is an anti-diabetes drug classified as a second generation of sulfonylurea which stimulates β cells to produce insulin that can reduce blood glucose levels (Basit et al. 2012). Group III, which refers to the group that received an injection of alloxan and lime peel extract at a dose of 2.35 g/rat, showed insignificant results in reducing blood glucose levels as seen from the pre-treatment mean, which was lower compared to the post-treatment mean. In conclusion, lime peel extract at this dose still cannot accurately reduce the glucose levels in the blood. Group IV, which refers to the group injected with alloxan and lime peel extract at a dose of 4.7 g/rat, showed an insignificant decrease in the blood glucose levels. Group V, which refers to the group that received an injection of alloxan and lime peel extract at a dose of 9.4 g/rat, showed a significant decrease in the blood glucose levels after treatment. From this case, it can be seen that the more antioxidants, the more reduction of blood glucose level (Suryadinata et al. 2017, Suryadinata et al. 2019).

On the other side, there was a difference between Group I and the other groups. Meanwhile, no differences were found between Group II and Group III, Group V, but Group IV. Group III showed no difference from Group IV but Group V. Moreover, there was a difference between Group IV and Group V. Table 5 shows no difference in Group I before and after treatment, while in Group II, Group III, Group IV, and Group V, there were differences before and after treatment. The flavonoid in lime is found mostly in the flavedo (lime peel) (Narang and Jiraungkoorskul 2016). Among many other types of flavonoids, one that has an anti-diabetic activity is known as hesperidin. A study conducted on Sprague-Dawley rats showed an increase in insulin, a decrease in HbA1c, and a decrease in the blood glucose levels after treatment of hesperidin in four weeks (Visnagri et al. 2014).

In their study, Akiyama et al. (2009) found that streptozotocin hesperidin worked by decreasing the activity of glucose-6-phosphatase and enhancing the enzyme glucokinase. Glucose-6-phosphatase is regulated by glucose-6-phosphate concentration. Glucose-6-phosphatase is an enzyme that hydrolyzes glucose-6-phosphate, which then produces a phosphate group and free glucose in the blood (Varga et al. 2019). Meanwhile, Glucokinase is an enzyme in the liver triggered by the release of the hormone insulin. Glucokinase works by increasing glucose phosphorylation to ensure that intracellular free concentrations remain low and to facilitate the entry of glucose into cells. Thus, glucose levels in the blood can decrease (Barrett et al. 2020).

CONCLUSION

The application of alloxsan injection in experimental animals can increase blood glucose levels. The intake of lime peel extract reduced blood glucose levels. Increasing the dose of lime peel extract would be directly proportional to the decrease in glucose levels in the body.

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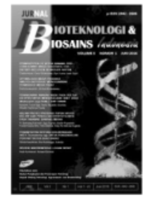

Short Communication

CHANGES IN BLOOD GLUCOSE LEVELS IN EXPERIMENTAL ANIMALS WITH HYPERGLYCEMIA DUE TO LIME (*Citrus aurantifolia* Swingle) PEEL EXTRACT

Perubahan Kadar Glukosa Darah pada Hewan Eksperimental dengan Hiperglikemia akibat Ekstrak Lime (*Citrus aurantifolia* Swingle)

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ABSTRACT
*Chronically elevated levels of glucose in the blood can lead to various complications. As a result, it can accelerate the damage to various organ tissues in the body. Several measures are needed to maintain the stability of normal blood glucose levels to prevent tissue damage, as well as providing additional intake such as lime peel extract which is believed to have high flavonoid content in lowering blood glucose levels. For this reason, this study aimed to analyse changes in blood glucose levels by giving lime extract to alloxan-induced experimental animals. This study uses an experimental post-test control group design. The results showed increased in blood glucose levels in the positive control group (p < 0.005). In addition, the lime (*Citrus aurantifolia *Swingle) peel extract treatment group showed changes in blood glucose levels (p < 0.005). It was concluded that increasing the intake of lime peel extract can reduce blood glucose levels.*

Keywords: *alloxan, blood glucose, hyperglycemia, lime,* Rattus novergicus

ABSTRAK
Peningkatan kadar glukosa dalam darah secara kronis dapat menyebabkan berbagai komplikasi. Akibatnya, dapat mempercepat kerusakan berbagai jaringan organ dalam tubuh. Beberapa tindakan diperlukan untuk menjaga stabilitas kadar glukosa darah normal untuk mencegah kerusakan jaringan. Serta memberikan asupan tambahan seperti ekstrak kulit jeruk nipis yang dianggap memiliki kandungan flavonoid yang tinggi dalam menurunkan kadar glukosa darah. Untuk itu, penelitian ini bertujuan untuk menganalisis perubahan kadar glukosa darah dengan pemberian ekstrak jeruk nipis pada hewan coba yang diinduksi aloksan. Penelitian ini menggunakan rancangan eksperimen post-test control group design. Hasil penelitian menunjukkan adanya peningkatan kadar glukosa darah pada kelompok kontrol positif (p < 0,005). Selain itu, kelompok perlakuan ekstrak kulit jeruk nipis (*Citrus aurantifolia* Swingle) menunjukkan perubahan kadar glukosa darah (p < 0,005). Oleh karena itu, dapat disimpulkan bahwa peningkatan asupan ekstrak kulit jeruk nipis dapat menurunkan kadar glukosa darah.

Kata Kunci: aloksan, gula darah, hiperglikemia, kapur, *Rattus novergicus*

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INTRODUCTION

Diabetes has become a severe public health problem as the number of diabetics increases yearly. In recent years, the number of adults with diabetes has increased twice compared to the previous years (Kharroubi and Darwish 2015). In 2000, the International Diabetes Federation estimated that the prevalence of diabetes globally had reached 3.2% and increased to 6.5% in 2013 (Ogurtsova et al. 2013). The number of diabetics in America was estimated to have reached 9.4% (30.3 million people) of the total population. In the adult age group, there were 415 million people with diabetes, and it is estimated that this will increase up to 642 million in 2040 (Xu et al. 2018).

Based on a survey conducted by the Global Burden of Disease (GBD), the prevalence of diabetes in adults in the world is estimated at 462 million or 6,28% of the world's population (Khan et al. 2020). In Indonesia, the number of diabetics was 172 million of the total population in 2020 (Tanoey and Becher 2021). This makes Indonesia one of the ten countries with the highest number of diabetics in the world. The prevalence of diabetes in urban areas reaches 5.7%, while impaired glucose tolerance reaches 10.2% (Mihardja et al. 2014).

The increase in the number of glucose levels can lead to serious health problems. Diabetes can be an underlying cause of various factors of macrovascular complications such as atherosclerosis, neuropathy, nephropathy, and retinopathy (Papatheodorou et al. 2016). These complications can reduce the quality of life and increase the risk of disabilities which can disrupt work productivity (Breton et al. 2013). A survey on economic losses due to diabetes conducted at one hospital in Indonesia showed that the estimated medical expenses each diabetic patient spent for medications was around $19.97/month (Soewondo et al. 2013).

Diabetes mellitus is usually associated with insulin resistance. An increase in insulin concentration (hyperinsulinemia) usually occurs in patients with diabetes mellitus in the early stage. In the later stage, the pancreatic beta cells become "tired" or damaged and are unable to produce enough insulin (Guyton and Hall 2018). In more severe cases, hyperglycemia may occur due to a decrease in insulin production. Low insulin levels fail to trigger the glucokinase enzyme, which affects intracellular free concentrations to remain high and blocks the entry of glucose into cells (Muhajirin et al. 2019, Barrett et al. 2020).

Patients with diabetes need to find appropriate glucose control. One of the ways is by using anti-diabetes drugs to achieve blood glucose stability within normal limits. However, anti-diabetes drugs have several adverse effects which can require hospital treatment. Sulfonylurea, for example, can lead to hypoglycemia that commonly occurs when people skip meals or after exercise. This adverse effect is mainly due to long-acting sulfonylureas such as chlorpropamide and glibenclamide (Sola et al. 2015).

Lime (*Citrus aurantifolia* Swingle) can be a solution to reduce glucose levels in the blood. Lime is very easy to get and is used daily by Indonesian people. Some people believe that herbs have lower side effects than chemical drugs. Therefore, it is expected that lime can comply with patients' needs in controlling blood glucose. In addition, lime contains various kinds of flavonoids which are found mainly in the flavedo (lime peel) (Narang and Jiraungkoorskul 2016, Suryadinata et al. 2021). Among various types of flavonoids, hesperidin has anti-diabetic activity. Study by Visnagri et al. (2014) showed that there was a decrease in blood glucose levels, an increase in insulin, and a decrease in HbA1c after hesperidin was given for 4 weeks. Another study suggested a decrease in glucose-6-phosphatase activity and an increase in the glucokinase enzyme (Akiyama et al. 2009). This study is a preliminary study on the use of lime peel extract in reducing glucose levels in the blood. Male Wistar rats (*Rattus novergicus*) were used as animals under investigation due to their similarity in physiology, anatomy, and immunity to humans (Barré-Sinoussi and Montagutelli 2015, Wirjatmadi and Suryadinata 2020). The purpose of this study was to determine the effectiveness of lime peel extract (peroral) in reducing blood glucose levels.

MATERIALS AND METHODS

This study was arranged with a randomized controlled trial (RCT) design. The sample used in this study was male Wistar rats (*R. novergicus*). Animals were divided into five groups (negative control group, positive control group, and groups that were treated with different doses). This research has obtained ethical approval from the Health Research Ethics Committee of the University of Surabaya (No: 137/KE/VI/2020).

Time and place

This research was accomplished in the Biomedical Laboratory, Faculty of Medicine, the University of Surabaya for 30 days. The research was conducted from July to August 2020.

Experimental animals

The male Wistar rats (*Rattus novergicus*) used were those that met the criteria which were having ± 200 g of weight and no macros abnormalities, as well as outside of objects in previous studies (Figure 1A). Meanwhile, experimental animals which were sick or died during the experiment were excluded. Moreover, this study refers to the 3R principles (Replacement, Reduction, and Refinement) for the maintenance and care procedure of the experimental animals during the research.

Extraction process

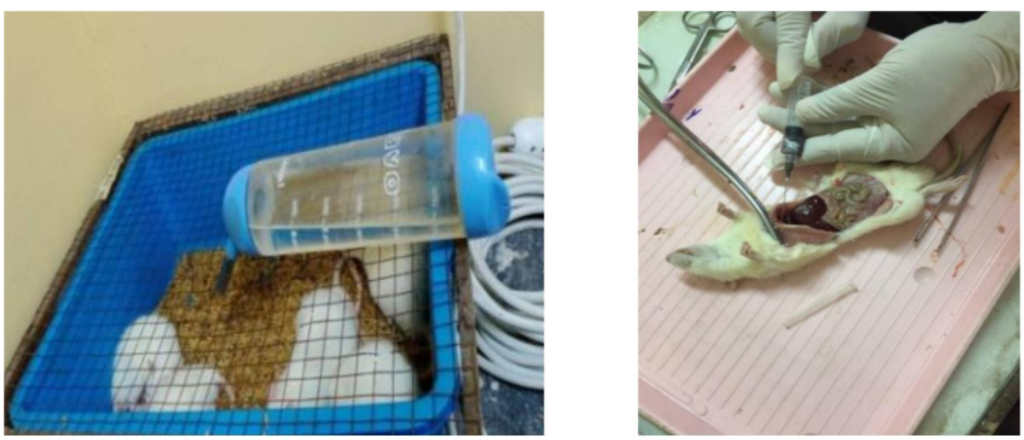
The lime peel (*Citrus aurantifolia* Swingle) was dried for several days. The dried lime peel would be crushed using a blender and sieved to obtain the extract. Furthermore, the extraction process would be carried out using a maceration method by adding 96% of ethanol solvent. By the end of the extraction process, a concentrated liquid of lime peel was obtained. Measurement of flavonoid levels in lime peel extract was then documented in a conversion table. After that, a calculation method based on Laurence and Bacharach was done between the organisms to obtain extract doses of 2.35 mg, 4.7 mg, and 9.4 mg.

Alloxan induction

The experimental animals underwent a fasting period for 6-8 hours before alloxan injection was given intraperitoneally at a dose of 140 mg/kg BW (diluted with 0.9% NaCl). Before the study began, the experimental animals were tested for blood glucose to ensure that the positive control group and experimental groups reached a hyperglycemic state.

Research procedures

This study was a 30-day experimental study involving the experimental animals. The experimental animals underwent an adaptation process in about 5-7 days. After that, the experimental animals were induced with alloxan, and their blood glucose levels



A B

Figure 1. Maintenance of *Rattus norvegicus* Wistar strain (A), Measurement of Intracardiac blood collection (B)

Table 1. Mean values of each group before dan after blood glucose levels test

	Groups	Mean ± SD	Maximum	Minimum
Pre-Test	I	75.40 ± 3.78	71.00	79.00
	II	86.80 ± 3.70	83.00	92.00
	III	87.00 ± 7.97	75.00	95.00
	IV	86.00 ± 5.75	79.00	94.00
	V	89.00 ± 4.00	84.00	94.00
Post-Test	I	74.60 ± 3.58	71.00	79.00
	II	84.00 ± 3.32	81.00	88.00
	III	94.80 ± 3.96	91.00	100.00
	IV	89.80 ± 5.63	83.00	98.00
	V	83.80 ± 2.77	81.00	87.00

Note:
Group I = Group with no alloxan, glimepiride, and lime peel extract
Group II = Group with alloxan, glimepiride, and lime peel extract at a dose of 0.036 mg/rat
Group III = Group with alloxan, glimepiride, and lime peel extract at a dose of 2.35 gr/rat
Group IV = Group with alloxan, glimepiride, and lime peel extract at a dose of 4.7 gr/rat
Group V = Group with alloxan, glimepiride, and lime peel extract at a dose of 9.4 gr/rat

Table 2. Results of ANOVA test on glucose levels in each group

	Group	Normality Test	Homogeneity Test	ANOVA Test
Pre-Test	I	0.222	0,353	0,005
	II	0.687		
	III	0.677		
	IV	0.971		
	V	0.833		
Post-Test	I	0.377	0,555	0,000
	II	0.182		
	III	0.305		
	IV	0.690		
	V	0.292		

were checked. After 30 days of treatment, the blood glucose levels were re-checked to determine changes after treatment (Figure 1B).

The experimental animals were divided into five groups. The first group was a negative control group in which the experimental animals were only given daily intake without any intervention. The second group was a positive control group where the experimental animals were only subjected to alloxan induction and daily intake. Meanwhile, the other three groups were groups that received treatments of alloxan induction, daily intake, and doses of lime peel extract. These groups were further divided based on the conversion of flavonoid requirements in humans to different amounts of lime peel extract (2.35 mg, 4.7 mg, and 9.4 mg).

Statistics

From this study, ratios of the glucose levels before and after the administration of lime peel extract were obtained. Data analysis was performed using a paired T-test to analyze changes in blood glucose levels before and after initiation. After that, the ANOVA test with SPSS version 22 was also performed to identify any differences between groups.

RESULTS AND DISCUSSION

From this research, it can be indicated that the mean values of each group before

Table 3. Results of least significant difference test on blood glucose levels in each group before treatment

Groups	I	II	III	IV	V
I	–	–	–	–	–
II	0.003	–	–	–	–
III	0.002	0.953	–	–	–
IV	0.005	0.814	0.769	–	–
V	0.001	0.519	0.558	0.382	–

Tabel 4. Results of least significant difference test on blood glucose levels in each group after treatment

Groups	**I**	**II**	**III**	**IV**	**V**
I	–	–	–	–	–
II	0.001	–	–	–	–
III	0.000	0.000	–	–	–
IV	0.000	0.032	0.060	–	–
V	0.002	0.937	0.000	0.27	–

Table 5. Results of paired samples T-test in each group

Groups	**Sig.**
I	0.793
II	0.002
III	0.022
IV	0.072
V	0.041

and after treatment (Table 1). The highest mean value of each group before the test is group V (89.00 ± 4.00), the lowest mean value is group I (75.40 ± 3.78). Meanwhile, the highest mean value of each group after the test is group III (94.80 ± 3.96), and the lowest mean value is the group I (74.60 ± 3.58).

This research also found a difference in the blood glucose levels between the Group I (negative control) and the Group II (positive control). The application of alloxan to the positive control group led to an increase in glucose levels. Alloxan works by partially degrading β cells in the Langerhans pancreas (Ighodaro et al. 2017, Putri et al. 2019). β cells are responsible for producing the insulin hormone in the body which can reduce blood glucose levels and increase carbohydrate storage. Therefore, a decrease in insulin levels due to damage to β cells will increase blood glucose levels (DiMeglio et al. 2018).

It was found that all of the groups were normally distributed. Meanwhile, the homogeneity test was p = 0.353 and it was found that the data is homogeneous. Therefore, the ANOVA test can be performed to compare the differences between groups (Table2). It was found that the p-value was 0.005 ($p < 0.05$). The normality test values ($p > 0.05$) in each group after treatment are 0.377 (Group I), 0.182 (Group II), 0.305 (Group III), 0.690 (Group IV), and 0.292 (Group V). It was found that all of the groups were normally distributed. Meanwhile, the homogeneity test shows a p-value of 0.555, meaning that the data were homogeneous. Therefore, the ANOVA test was performed to compare the differences between groups. It was found that the p-value was 0.000 ($p < 0.05$).

There was a difference between Group I and the other groups. Meanwhile, no differences were found between the groups with alloxan. This study also suggested a difference between Group II (injected with alloxan and glimepiride at the dose of 0.036 mg/rat) and the other groups except for Group V (treated with alloxan injection and lime peel extract at a dose of 9.4 g/rat). This indicated that giving glimepiride at the dose of 0.036 mg/rat and lime peel extract at a dose of 9.4 g/rat posed the same results. Glimepiride is an anti-diabetes drug classified as a second generation of sulfonylurea which stimulates β cells to produce insulin that can reduce blood glucose levels (Basit et al. 2012). Group III, which refers to the group that received an injection of alloxan and lime peel extract at a dose of 2.35 g/rat, showed insignificant results in reducing blood glucose levels as seen from the pre-treatment mean, which was lower compared to the post-treatment mean. In conclusion, lime peel extract at this dose still cannot accurately reduce the glucose levels in the blood. Group IV, which refers to the group injected with alloxan and lime peel extract at a dose of 4.7 g/rat, showed an insignificant decrease in the blood glucose levels. Group V, which refers to the group that received an injection of alloxan and lime peel extract at a dose of 9.4 g/rat, showed a significant decrease in the blood glucose levels after treatment. From this case, it can be seen that the more antioxidants, the more reduction of blood glucose level (Suryadinata et al. 2017, Suryadinata et al. 2019).

On the other side, there was a difference between Group I and the other groups. Meanwhile, no differences were found between Group II and Group III, Group V, but Group IV. Group III showed no difference from Group IV but Group V. Moreover, there was a difference between Group IV and Group V. Table 5 shows no difference in Group I before and after treatment, while in Group II, Group III, Group IV, and Group V, there were differences before and after treatment. The flavonoid in lime is found mostly in the flavedo (lime peel) (Narang and Jiraungkoorskul 2016). Among many other types of flavonoids, one that has an anti-diabetic activity is known as hesperidin. A study conducted on Sprague-Dawley rats showed an increase in insulin, a decrease in HbA1c, and a decrease in the blood glucose levels after treatment of hesperidin in four weeks (Visnagri et al. 2014).

In their study, Akiyama et al. (2009) found that streptozotocin hesperidin worked by decreasing the activity of glucose-6-phosphatase and enhancing the enzyme glucokinase. Glucose-6-phosphatase is regulated by glucose-6-phosphate concentration. Glucose-6-phosphatase is an enzyme that hydrolyzes glucose-6-phosphate, which then produces a phosphate group and free glucose in the blood (Varga et al. 2019). Meanwhile, Glucokinase is an enzyme in the liver triggered by the release of the hormone insulin. Glucokinase works by increasing glucose phosphorylation to ensure that intracellular free concentrations remain low and to facilitate the entry of glucose into cells. Thus, glucose levels in the blood can decrease (Barrett et al. 2020).

CONCLUSION

The application of alloxsan injection in experimental animals can increase blood glucose levels. The intake of lime peel extract reduced blood glucose levels. Increasing the dose of lime peel extract would be directly proportional to the decrease in glucose levels in the body.

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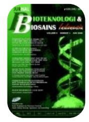

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