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JURNAL TEKNOSAINS

The effect of administering ethanolic extract of red lotus stem (*nymphaea rubra*) on blood sugar levels of mice (*mus musculus*)

Indonesian title: Pengaruh pemberian ekstrak etanol batang teratai merah (nymphaea rubra) terhadap kadar gula darah mencit (mus musculus)

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ABSTRAK

Metformin, obat yang umum digunakan oleh penderita diabetes, diketahui memiliki efek samping utama berupa intoleransi gastrointestinal seperti begah, rasa tidak nyaman, diare, dan asidosis laktat. Penggunaan metformin dalam jangka panjang (>2 tahun) juga dapat meningkatkan risiko terjadinya diabetic neuropathy hingga empat kali lebih tinggi. Adanya efek samping tersebut mendorong perlunya alternatif berbahan alami dengan risiko yang lebih rendah, salah satunya adalah ekstrak batang teratai merah (Nymphaea rubra). Kandungan dalam ekstrak batang teratai merah, seperti vitamin C, mineral, senyawa fenol, dan flavonoid, diketahui berpotensi sebagai antidiabetes. Penelitian ini bertujuan untuk mengetahui pengaruh ekstrak etanol batang teratai merah (Nymphaea rubra) terhadap kadar gula darah mencit (Mus musculus). Objek penelitian menggunakan 25 ekor mencit putih jantan (Mus musculus) dengan berat badan ±35 g dan umur 16 minggu, yang dibagi ke dalam 5 kelompok penelitian dengan 5 ulangan. Mencit diinduksi menggunakan aloksan dosis 90 mg/kgBB sebanyak satu kali secara intraperitoneal (i.p.), kemudian diberikan terapi ekstrak etanol batang teratai merah dengan dosis 200 mg/kgBB dan 400 mg/kgBB secara oral selama 14 hari. Pengukuran kadar gula darah dilakukan sebelum induksi aloksan, setelah induksi, dan 14 hari setelah perlakuan menggunakan spektrofotometer dengan metode GOD-PAP (Glucose Oxidase-Peroxidase Aminoantipyrine). Hasil penelitian menunjukkan bahwa rerata kadar gula darah pada kelompok P1 (200 mg/dL) dan P2 (400 mg/dL) secara berturut-turut sebesar 171,00 mg/dL (hiperglikemia) dan 105,00 mg/dL (normal). Berdasarkan persentase penurunan kadar gula darah, kelompok T1 menunjukkan penurunan yang lebih besar, yaitu 37,64%, dibandingkan kelompok T2 sebesar 26,31%. Simpulan penelitian menunjukkan bahwa pemberian ekstrak etanol batang teratai merah dapat berpengaruh terhadap penurunan kadar gula darah mencit..

Kata kunci: *Antidiabetes; Kadar Gula Darah; Diabetes; Metformin; Ekstrak Batang Teratai Merah.*

ABSTRACT

Metformin, a drug commonly used by patients with diabetes, is known to have major side effects in the form of gastrointestinal intolerance, including bloating, discomfort, diarrhea, and lactic acidosis. Long-term use of metformin (>2 years) may also increase the risk of developing diabetic neuropathy by up to four times. The presence of these side effects calls for natural alternatives with lower risk, one of which is red lotus stem extract (Nymphaea rubra). The compounds contained in red lotus stem extract, such as vitamin C, minerals, phenolic compounds, and flavonoids, are known to have antidiabetic potential. This study aimed to determine the effect of

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Ethanolic extract of red lotus stem (Nymphaea rubra) on the blood sugar levels of mice (Mus musculus). The research subjects consisted of 25 male white mice (Mus musculus) weighing approximately ±35 g and aged 16 weeks, divided into 5 treatment groups with 5 replications. The mice were induced with alloxan at a dose of 90 mg/kgBW through a single intraperitoneal (i.p.) injection, followed by oral administration of Ethanolic extract of red lotus stem at doses of 200 mg/kgBW and 400 mg/kgBW for 14 days. Blood sugar levels were measured before alloxan induction, after induction, and 14 days after treatment using a spectrophotometer with the GOD-PAP (Glucose Oxidase-Peroxidase Aminoantipyrine) method. The results showed that the average blood sugar levels in groups P1 (200 mg/dL) and P2 (400 mg/dL) were 171.00 mg/dL (hyperglycemia) and 105.00 mg/dL (normal), respectively. Based on the percentage reduction in blood sugar levels, group T1 showed a greater reduction of 37.64% compared with group T2 at 26.31%. In conclusion, the administration of Ethanolic extract of red lotus stem was shown to affect the reduction of blood sugar levels in mice.

Keywords**:** *Antidiabetic; Blood Sugar Level; Diabetes; Metformin; Ethanolic extract of N. rubra stem.*

INTRODUCTION

Diabetes mellitus is a chronic metabolic disease in which the pancreas does not produce enough insulin or the body does not use it properly, leading to elevated blood sugar levels (IDF, 2019). International data from 2021 show that 537 million adults aged 20-79 have diabetes, 90% of whom have type 2 diabetes, and if this trend continues, by 2045, it is estimated that there will be 700 million adults with diabetes (IDF, 2021). Indonesia ranks 7th among the top 10 countries worldwide, with 20.4 million people living with diabetes (Kemenkes RI, 2020).

One step in diabetes management is pharmacological intervention, namely the administration of oral hypoglycemic drugs (Purwandari et al., 2022). The drugs commonly used by people with diabetes aged >10 years are biguanides, namely metformin, at a dose of 500 mg (Primadi, 2017; Kemenkes, 2019). Metformin is known to have major side effects in the form of gastrointestinal intolerance, such as bloating, discomfort, diarrhea, and lactic acidosis (Soelistijo, 2021). People with diabetes aged <60 years with comorbidities without antihypertension or antihyperlipidemic are at 4.31 times the risk of developing diabetic neuropathy at a daily dose of metformin >2 g with a treatment time of >2 years (Yang et al., 2023).

Meanwhile, in elderly patients, consumption of metformin for at least 18 months has 2–3 times the risk of developing diabetic neuropathy compared to those who consume <18 months (Serra et al., 2021). This case is the basis for the need for alternatives to reduce blood sugar levels and avoid complications such as diabetic neuropathy with *Nymphaea rubra* stem extract, which contains vitamin C, minerals, phenol compounds, and flavonoids as antidiabetics (Nishan, 2020) by stimulating glucose uptake, reducing oxidative stress, and increasing insulin sensitivity (Jang et al., 2020).

Nymphaea rubra plants as shown in Figure 1 are commonly consumed in Bangladesh and India as vegetables (Khan et al., 2022). *Nymphaea rubra* is an aquatic plant that grows on the surface of lakes and rivers, with benefits as an antitumor and antioxidant (Abelti et al., 2023). *Nymphaea rubra* plants in traditional ayurvedic medicine are known to treat diarrhea, act as anthelmintics, antidyslipidemic, antihyperglycemic, anti-inflammatory, antipyretic, hepatoprotective, and free radical scavengers (Kumar et al., 2017). Phytochemicals in *N. rubra,* such as quinine, can reduce plasma glucose levels by inhibiting intestinal glucose absorption, increasing tissue and organ glucose levels, and increasing insulin secretion by beta cells (Tang et al., 2020). Quercetin doses of 10 mg/kg and 50 mg/kg can prevent oxidative stress in myocardial mitochondria of mice with type 2 DM (Gorbenko et al., 2021). Scopoline, a phenolic compound, has antidiabetic potential because it can stimulate glucose uptake and increase insulin sensitivity (Jang et al., 2020).

The results of studies on rutin content are beneficial in reducing blood sugar levels, lipid profiles, and microvascular and macrovascular complications of diabetes due to the mechanism of rutin, which will inhibit car-

bohydrate absorption in the intestine, reduce gluconeogenesis, increase sugar uptake in tissues, stimulate insulin secretion, and protect the degeneration of islets of Langerhans (Ghorbani, 2017).

Figure 1.
Nymphaea rubra
Source: Author's documentation (2024)

Phytochemical results of the ethanolic extract of *N. rubra* rhizome by the RP-HPLC method showed the presence of rutin content of 3.2 µg/mg, caffeine acid 4.9 µg/mg, and quinine 3.2 µg/mg (Kumar et al., 2017). Ethanolic extract of *N. rubra* flowers with chloroform fraction showed the effect of sugar uptake from insulin receptors in L6 myotubes and adipogenesis in 3T3-L1 preadipocytes of mice (Rahuja et al., 2013). In vitro antioxidant examination of the ethanolic extract of *N. rubra* rhizome resulted in a total phenol content of 0.36 g/100g and a flavonoid content of 0.67 g/100g. Flavonoids have potential as antioxidants to prevent oxidation and cell damage (Daffodil & Mohan, 2014). *Nymphaea rubra* roots contain a high potassium content, with 846 milligrams/100 g of minerals, which is very appropriate for hyperglycemia patients because it can help the body maintain fluid balance by regulating muscle and nerve cells (Abelti et al., 2023).

The content in the stem of *N. rubra* includes total phenols 15.48 ± 0.2 mg/gGAE and flavonoids 7.864 ± 0.1 mg/gQE; the results are similar to the stem of *Nymphaea nouchali*, total phenols of 16.51 ± 0.05 milligrams / gGAE and flavonoids 7.476 ± 0.1 mg / gQE (Khan et al., 2022). *Nymphaea nouchali* and *N. rubra* stem parts showed antidiabetic α-amylase IC50 values of 59.71 µg/mL and 50.89 µg/mL, respectively, compared to roots at 22.52 µg/mL (Nishan, 2020). The stem of *N. rubra* had an antioxidant IC50 of 5.189 µg/mL, and the tuber had an antioxidant IC50 of 2.091 µg/mL, whereas ascorbic acid had an IC50 of 22.23 µg/mL (Metasari et al., 2020). The stem part extracted by methanol solvent was tested for OGTT which was compared between doses of 50, 100, 200 and 400 mg/kgBW with glibenclamide dose of 10 mg/kgBW against mice, obtained a 40.1% decrease in blood sugar levels at a dose of 400 mg/kgBW extract as an effective result close to the decrease in blood sugar levels in glibenclamide by 45.3% (Saha et al., 2015). The extraction of *N. rubra* stem in this study was carried out by maceration 3x24 hours using 70% ethanol solvent because of the lower toxicity of organic solvents such as chloroform and methanol (Andrian et al., 2018), and 70% ethanol concentration on antioxidant activity is better than boiling (Chandra et al., 2022). The dose of Extract used in this study is based on research on previous results, respectively 200 and 400 mg/kgBW, which are known to be effective in reducing blood sugar by around 40.1%, at a dose of 400 mg/kgBW, because there are alkaloid, flavonoid, saponin, and tannin contents as antidiabetics (Saha et al., 2015).

The experimental animal model of hyperglycemia in the study was conducted on white mice (*Mus musculus*) injected intraperitoneally with alloxan 90 mg/kgBB, resulting in hyperglycemia within 3 days. This is due to the inhibition of glucokinase, which reduces sugar oxidation and ATP formation and suppresses insulin secretion (Rompas et al., 2021). Based on the content and benefits possessed by *N. rubra stem*s, it is necessary to research the effect of giving Ethanolic extract

of *N. rubra* stems on blood sugar levels in mice (*Mus musculus*).

Research on the phytochemical content contained in the stems of *N. nouchali* and *N. rubra* has been conducted previously. The phytochemical content of the stems of *N. nouchali* and *N. rubra*, including vitamin C, minerals, phenolic compounds, and flavonoids, can function as antidiabetics. Research on the phytochemical content of N. rubra stems, roots, and bulbs indicates that it is higher in the stems, with levels close to those in the flower part.

Research using *N. rubra* flowers and ethanolic extracts of *N. Nouchali* stems has been conducted in vivo, and the results show that the extracts can reduce blood glucose levels in hyperglycemia model rats. The novelty of this study is the use of *N. rubra* stem Extract in vivo to modulate glucose levels in hyperglycemic model mice. The purpose of the study was to determine the effect of the Ethanolic extract of *N. rubra* stem on the blood sugar levels of mice (*Mus musculus*).

METHOD

The tools used in this research include *a* spectrophotometer (*Microla 300 & 30000 LX*), a dosing syringe, a lancet, an oven, a water bath, a tube mic, a hematocrit, *and* oral gavage. The materials used in the study were 70% ethanol, Ethanolic extract of *N. rubra* stem, 25 white mice, alloxan monohydrate, 0.9% NaCl, ether, and glucose test reagent (*Dyasis*).

The object of research in the study was male white mice (*Mus musculus*) weighing about ± 35 g, aged 16 weeks, with 25 heads, obtained from Farma Farm Semarang. The research design used a completely randomized design (CRD) with 5 research groups, each with 5 repetitions, determined using the Federer formula. The design of the research groups conducted is listed in Table 1 below.

Table 1.
Treatment Group Design

Treatment	Description	Number
NC	Normal Control, test animals without alloxan induction	5
NC	Negative Control, test animals with alloxan induction without special treatment	5
PC	PC Positive Control, test animals with alloxan induction and then treated with Metformin 1.3 mg/20gBW	5
T1	T1 Treatment group 1, test animals with alloxan induction and then treated with Ethanolic extract of *N. rubra* stem 200 mg/kgBW	5
T2	T2 Treatment group 2, test animals with alloxan induction and then treated with Ethanolic extract of *N. rubra* stem 400 mg/kgBW	5

Source: Author's analysis (2024)

Preparation of N. rubra Stem Extract

The water lily used has been tested at the Ecology & Biosystematics Laboratory, Department of Biology, Faculty of Science and Mathematics, Diponegoro University, Semarang. The determination results indicate that the water lily is the genus Nymphaea, specifically *Nymphaea rubra* Roxb, Ex Andrews, or known as red water lily. The clean *N. rubra* stems were dried and pulverized in a blender, and the resulting powder was filtered.

The simplicial powder was then macerated with 70% ethanol for 24 hours, with 2 repetitions. The Extract is filtered through filter paper to separate the filtrate into a liquid extract, and the evaporation process is carried out in a water bath at 45-50 ^{0}C to obtain a concentrated extract (Chandra et al., 2022). The yield of the Ethanolic extract from *N. rubra* stems was 22.28%. Preparation of 200 mg/kgBB and 400 mg/kgBB extract suspension doses was carried out by dissolving the thick Extract with distilled water.

Experimentation of N. rubra Stem Extract on Hyperglycemic Mice

The research was approved by the Health Research Ethics Commission of the Faculty of Nursing and Health Sciences, Universitas Muhammadiyah Semarang, Number 041/KE/01/2024, and the Ethics Commission for Health Research, Faculty of Medicine, Universitas Muhammadiyah Semarang, Number 008/EC/KEPK-FK/UNIMUS/2024. Twenty-five mice were acclimated for 1 week before the experiment, with food and drink given ad libitum. After acclimation, mice were injected intraperitoneally with alloxan (90 mg/kg BW) after 24 hours of feeding, while still given water.

Blood sugar levels in mice were measured before alloxan induction and 3 days after. After obtaining hyperglycemic mice, N. rubra stems were administered orally at the indicated kgBW concentrations once daily for 14 days. The mice's blood sugar was then measured again. Measurement of mice blood sugar levels using a semi-automatic photometer (Micro lab 300 & 300 LX), the GOD-PAP *(Glucose Oxidase-Peroxidase Aminoantipyrine)* method, and using serum samples. Blood is sampled from mice after they have been fed for 24 hours. How to take blood using a microhematocrit through the orbital sinus, then collect the blood using a micro cup. The blood is then centrifuged to obtain serum. Measurement of blood sugar levels was carried out in accordance with the procedures listed in the procedure kit (Diasys). The blood sugar levels measured were fasting blood sugar levels before and after alloxan induction, and after treatment with the Ethanolic extract of *N. rubra* stems.

Data Analysis and Processing

Data from the measurement of blood sugar levels of mice are presented in the mean and percentage reduction in blood sugar levels in tabular form. Data were analyzed using SPSS version 26, namely the Shapiro-Wilk, Levene, One-Way ANOVA, and LSD Post Hoc Test.

RESULTS AND DISCUSSION

The results of measuring blood sugar levels in each treatment group are presented in Table 2, showing the mean and percentage reductions in blood sugar levels in mice before and after alloxan induction, and 14 days after the administration of *N. rubra* stem Extract.

Table 2.
Mean and Percentage of Blood Sugar Level Reduction

Treatment Group	Mean Blood Sugar Level ±SD (mg/dL)			Decrease in Blood Sugar Level (%)
	Before Alloxan Induction	After Alloxan Induction	14 days after extract administration	
NC	84.20±17.60[a]	108.80±5.77[a]	120.00±7.07[a]	-
NC	80.00±21.06[a]	131.67±4.16[a]	227.00±15.00[b,d]	-
PC	119.60±3.58[b]	233.60±39.53[b]	109.25±32.13[a,c]	53.23
T1	113.67±14.74[b]	274.67±41.10[c]	171.00±53.86[a,b,d]	37.64
T2	105.40±15.27[b]	142.50±13.77[a]	105.00±26.22[a,c]	26.31
P value	0.023	0.002	0.002	

Source: Author's analysis (2024)
Hyperglycemia: blood sugar level ≥126 mg/dL.
p results of the One-Way Anova analysis between groups in the same column
a, b, c, and d. Different notations in the same column indicate significant differences in the LSD test (<0.05)

Blood sugar levels are measured before induction in alloxan-treated 90 mg/kgBB mice to ensure that the mice are in the normal category. The measurement results showed that mice in all treatment groups were still in the normal category. Blood sugar levels were

measured 3 days after alloxan induction to confirm that the increase in blood sugar levels in mice was stable and that the mice had entered a hyperglycemic state. Mice are considered hyperglycemic if their fasting blood glucose levels are≥126 mg/dL (Liputo et al., 2022). The measurement results show that mice in the NC, PC, T1, and T2 groups are already in hyperglycemia. Measurement of blood sugar levels was again performed 14 days after administration of the Ethanolic extract of *N. rubra* stems.

The results indicated that the average blood sugar level in group T2 (105.00 mg/dL) was within the normal range, the same as in the NC and PC groups. The blood sugar level in the T1 group was 171.00 mg/dL, still in the hyperglycemic range, similar to that in the NC group. However, the table shows that the percentage reduction in blood sugar levels in group T1 (37.64%) is greater than in group T2 (26.31%). From the results table, it is evident that blood sugar levels 3 days after alloxan induction are higher in group T1 (274.67 mg/dL) than in group T2 (142.50 mg/dL).

Blood sugar measurement data have been statistically analyzed using SPSS. The results of the Shapiro-Wilk and Levene tests indicate that all groups have normally distributed homogeneous data ($p>0.05$), so the data are continued with the one-way ANOVA. The results of the one-way ANOVA test showed that all data significantly reduced blood sugar levels. The test continued with Post Hoc LSD, which showed a significant effect between groups T1 and T2 in reducing blood sugar levels.

Diabetes Mellitus (DM) is a metabolic disorder characterized by hyperglycemia caused by defects in insulin secretion, insulin action, or both, and by metabolic disorders of carbohydrates, fats, and proteins (WHO, 2019). The results indicated that blood sugar levels in the NC, PC, T1, and T2 groups entered the hyperglycemic range after alloxan induction. Alloxan is known to have a relatively rapid and persistent effect, producing hyperglycemia by increasing blood sugar levels within 2 to 3 days. The hyperglycemic condition induced by alloxan is identical to that observed in type 1 DM in humans (Dachi et al., 2022; Prambudi et al., 2022). Alloxan can cause hyperglycemia by inhibiting insulin secretion through 2 mechanisms: blocking glucokinase activity and generating reactive oxygen species (ROS). Alloxan induction causes the binding of thiol groups, inhibiting insulin formation in the glucokinase mechanism. Furthermore, inhibition of glucokinase can reduce glucose oxidase activity, thereby reducing ATP and insulin production.

The process that increases ROS can lead to pancreatic beta cell necrosis, which can destroy DNA structures and prevent the cell from producing insulin (Hasim et al., 2020; Sindi et al., 2022; Luh et al., 2024). Disruption of insulin production can decrease blood insulin levels, leading to reduced blood sugar uptake by target cells and ultimately insulin resistance (Fajriana, 2022).

Insulin resistance is associated with impaired insulin signaling, intrinsic impairment, and decreased stimulation of glucose transport in muscle and fat tissue. Disruption of the system for transporting blood sugar can occur due to failure of the GLUT-4 transporter translocation into the plasma membrane (Steck & Rewers, 2015). This condition will further trigger a decrease in blood sugar utilization in peripheral tissues (muscle and fat), causing an increase in blood sugar levels (hyperglycemia) (Banday et al., 2020). Based on the results of the study, it can be seen that although blood sugar levels after alloxan induction in all NC, PC, T1, and T2 groups fall into the hyperglycemia category, the groups differ in their levels. This can be caused by differences in the endurance of test animals across groups (Rompas et al., 2021).

Giving Ethanolic extracts of *N. rubra* stems at doses of 200mg/kg BW and 400mg/kg BW to mice for 14 days, based on the results obtained, can reduce blood sugar levels in hyperglycemic mice. This effect can be caused by the presence of phytochemicals in water lily red stems, such as vitamin C, minerals, phenolic compounds, and flavonoids, which can function as antidiabetics (Nishan,

2020). In general, the mechanism by which phytochemicals in the Ethanolic extract of *N. rubra* stems act as antidiabetics is by stimulating glucose uptake, reducing oxidative stress, and increasing insulin sensitivity (Jang et al., 2020). Vitamin C and phenolic compounds act as antioxidants, reducing oxidative stress.

Antioxidants will neutralize free radicals or support antioxidant defense mechanisms (Daffodil & Mohan, 2014). If free radicals are reduced, necrosis in pancreatic beta cells, which can affect insulin production, will also be reduced. In addition, scopoline, one of the phenolic compounds found in *N. rubra* stems, acts as an antidiabetic by stimulating blood sugar uptake in tissues and increasing insulin sensitivity.

The mechanism of scopoline to increase sugar uptake in tissues is to stimulate the translocation of Glucose Transporter Type 4 (GLUT4) at the plasma membrane by activating the Phosphatidyl Inositol-3-Kinase (PI3K) and adenosine monophosphate (AMP)-activated protein kinase (AMPK) pathways in 3-Phosphoinositide Dependent Kinase-1 (3T3-L1) adipocyte cells (Jang et al., 2020). Meanwhile, increasing insulin sensitivity can prevent the onset of insulin resistance, which can trigger hyperglycemia.

Flavonoid compounds found in red stems include quinine and rutin. Quercetin will inhibit the absorption of blood sugar by the small intestine by increasing blood sugar levels in tissues and organs and by increasing insulin secretion by pancreatic beta cells (Tang et al., 2020). Quercetin is also known to activate insulin-independent glucose uptake, increasing the ability of protein kinase to stimulate GLUT4 translocation to the plasma membrane in skeletal muscle and reducing the activity of gluconeogenic enzymes in the liver (Gorbenko et al., 2021). Meanwhile, rutin compounds can reduce blood sugar levels by inhibiting intestinal carbohydrate absorption, reducing gluconeogenesis, increasing tissue sugar uptake, stimulating insulin secretion, and protecting against islet degeneration (Ghorbani, 2017).

Based on the results of the study, it can also be seen that the use of *N. rubra* stem Extract at a dose of 200 mg/kgBW decreased blood sugar levels more than the 400 mg/kgBW dose. These results differ from those of Saha et al. (2015), which reported a greater decrease at a dose of 400 mg/kgBB. However, the Ethanolic extract of *N. rubra* stems has antidiabetic effects, mediated by flavonoids, phenols, and antioxidants, as shown in the study by Saha et al. (2015), who used *Nymphaea nouchali* Burm stem extract. The decrease in sugar levels in the treatment group has not fully matched that in the positive control group, which had the largest decrease in this study. These results imply that the ability of *N. rubra* stem extract, at the same time, has not been able to reduce blood sugar levels like drugs commonly consumed by people with DM.

The greater decrease in blood sugar levels with small doses is similar to the research of Maliangkay et al. (2018), which found that the administration of mangosteen peel extract at 150 mg/BW resulted in a greater decrease than at 300 mg/BW. This effect can be caused by antagonistic active compounds at higher doses, resulting in decreased antidiabetic activity. A greater decrease was observed with the 200 mg/ mg kg BW dose of Ethanolic extract due to inhibition of α-amylase activity in the small intestine by rutin, a natural flavonoid (Ghorbani, 2017). *Nymphaea rubra* stem Extract at a concentration of 40 µg/mL was 46.93%, which was greater than the inhibition by *N. nouchali* extract, which was 37.42% (Nishan, 2020). In addition, the potassium content in N. rubra, a mineral beneficial for people with hyperglycemia, is known to be higher at 980.73 mg/100g than *in N. nouchali* at 871.24 mg/100g (Khan et al., 2022).

The study results were supported by statistical tests, which showed that administering *N. rubra* stem Extract significantly decreased blood sugar levels in both treatment groups.

CONCLUSION

Based on the results of the study, it can be concluded that the administration of Ethanolic extract of *N. rubra* stems at doses of 200 and 400 mg/kgBB can decrease blood sugar levels in mice. Based on the percentage of blood sugar reduction, the administration of the Ethanolic extract of *N. rubra* stem at 200 mg/kgBB showed a greater reduction (37.64%) than at 400 mg/kgBB (26.31%). Further researchers are advised to increase the dose and duration of alloxan induction to ensure homogeneous blood sugar levels, thereby making the difference between before and after treatment more visible.

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