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Tectona grandis Linn. : ANTIDIABETIC ACTIVITY OF THE FRACTIONS USING AN IN VIVO APPROACH

Nurramadhani A. Sida[1], Rifa'atul Mahmudah[1], Nita Trinovitasari[1], Nada Shofa[2], Parawansah[3], Nuralifah[1*], Abd Rafid[4], Risma[5]
[1]*Faculty of Pharmacy, Universitas Halu Oleo, Indonesia*
[2]*Faculty of Teacher Training and Education, Universitas Halu Oleo, Indonesia*
[3]*Faculty of Medicine, Universitas Halu Oleo, Indonesia*
[4]*Faculty of Public Health, Universitas Halu Oleo, Indonesia*
[5]*Konawe District Health Service, Indonesia*
**Email Corresponding: nuralifah@uho.ac.id*

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ABSTRACT

The exploration of *Tectona grandis* Linn. from Indonesia, especially its use as an anti-diabetes agent is still quite limited. This study aims to determine the antidiabetic activity of the fractions from *Tectona grandis* Linn. leaves in male *Rattus norvegicus*. The animal blood glucose level was measured first as T0, then the animals were injected with streptozotocin (STZ) 40 mg/Kg BW to induce diabetes mellitus (DM), and then the blood was collected to determine the blood glucose level (T1). The animal was divided into six groups, namely normal group (NC) without treatment, positive control (K+) (DM+glibenclamide 5 mg), negative control (K-) (DM+NaCMC 0.5%), fractions group (DM+nHexane fraction (P1), DM+chloroform fraction (P2), and DM+ethyl acetate fraction (P3), each dose 300 mg/kg BW). The duration of treatment was 7 days, and at the end of treatment, the blood glucose levels were determined. The T0, T1, and T2 are analyzed using One-Way ANOVA and post-hoc LSD. The results obtained that the K+, P3, P2, and P1 groups were able to reduce the animals' blood glucose levels significantly ($p<0.05$), with the blood glucose levels are 97.01; 110.96; 129.38; and 111.46 mg/dL, respectively. The percentage of reduction in blood glucose level shows that the K+ group has the highest percentage at 66.8%, followed by the P3 group at 64.0%. The n-hexane, chloroform, and ethyl acetate fractions showed similar effectiveness to glibenclamide in reducing blood glucose levels statistically ($p>0.05$). Consequently, *Tectona grandis* Linn. has the potential to anti-diabetes mellitus, and the ethyl acetate fraction can reduce blood glucose levels more effectively than the n-hexane and chloroform fraction groups.

Keywords: Diabetes, Streptozotocin, Ethyl Acetate Fraction

INTRODUCTION

Currently, diabetes mellitus (DM) is a real threat to public health. This disease is the main cause of death in developed countries and is expected to become an epidemic in newly industrialized countries. Uncontrolled diabetes is a major factor in several serious disorders including macrovascular disease, vision impairment, kidney failure, neuropathy, and amputation (Russell *et al.*, 2016). Indeed, prolonged hyperglycemia has been associated with cardiovascular complications, although such complications are not criteria for the diagnosis of diabetes mellitus (Wu *et al.*, 2016). Due to the high risk of complications associated with DM, this condition poses an urgent threat. (Al-Lawati, 2017). Moreover, every year a progression in the prevalence of this disease is observed. The prevalence of DM continues to rise, according to data from the International Diabetes Federation (IDF). Diabetes mellitus (DM) is projected to affect 10.2% (578 million people) of the global population in 2045, up from 9.3% (463 million people) in 2019. With the most individuals affected by DM

worldwide, Indonesia was positioned seventh in 2015. By 2040, that ranking is projected to have risen to sixth (Soelistijo, 2021). The Riskesdas report from 2018 revealed that the prevalence of diabetes mellitus (DM) patients increased from 2.0% in 2013 to 3.4% in 2018. Among the total number of DM patients, 1.68% (8,060 individuals) dwell in the Riau Islands (Kemenkes RI, 2018). In Southeast Sulawesi Province, the incidence of DM has risen steadily in recent years, from ninth place in 2014 with 2,768 cases to third place in 2016 with 3,983 cases. Data from Bahteramas General Hospital in Southeast Sulawesi Province From 2015 to 2017, treated 670 outpatient visits and 649 inpatient visits for DM patients (Indrasari, 2018).

The essential to preventing complications associated with diabetes mellitus is through altering consumption patterns through the restriction of glucose and compliance with the administration of DM medication (American Diabetes Association, 2019). DM may be managed through the administration of antihyperglycemic medications and herbal remedies derived from traditional plants. Currently, the public prefers the use of traditional plants due to their lowered adverse effects, particularly when DM medication is taken for an extended period (Verma *et al.*, 2018). Hence, to improve public knowledge, it is important to explore the potential of plants for medicinal use as treatments for diabetes.

One of the herbs with the potential to be developed into an antidiabetic mellitus medicine is *Tectona grandis* Linn. The empirical use of *Tectona grandis* Linn leaves as antidiabetic by the people of Southeast Sulawesi and Padang (Ikhwan *et al*., 2021). Antidiabetic pharmacological assay of the extract, fractions of butanol, ethyl acetate, and methanol of *Tectona grandis* Linn. leaves have been carried out in vitro and it was found that *Tectona grandis* Linn. may decreased the blood glucose levels (Han *et al*., 2023). In various studies, in vivo, the antidiabetic assay has been carried out using extracts and showed the potential for the development of the extract as the treatment of DM (Kushwah, 2018; Nuralifah *et al*., 2021). Currently, there is a lack of research exploring the antidiabetic effects of *Tectona grandis* Linn. Through in vivo assays, existing studies have only used extract samples. The effects of reducing blood glucose levels using fractions in vivo have not been determined in any reports. In our previous study, the antidiabetes activity in vivo assay from methanol extract of *Tectona grandis* Linn. was reported and the concentration of 300 mg/kg BW showed a significant reduction in blood glucose level (Nuralifah *et al*., 2021). Hence, this research conducted additional in vivo antidiabetic assay utilizing the fractions from *Tectona grandis* Linn., employing animal models with induced diabetes mellitus.

RESEARCH METHODS

Equipment and Materials

Oven (B-One®), *rotary evaporator* (Buchi®), the solvents are ethanol 96%, n-heksan, aquades, and choloroform. HCl solution (Merck®), magnesium powder (Merck®), H_2SO_4 (Merck®), separotory funnel (pyrex®), test tube (pyrex®), NH_3 (Merck®), $FeCl_3$ (Merck®), dragendroff reagent, potassium acetate (Merck®), acetic acid, NaCMC, streptozotocin (bioworld®), hematocrit microcapillary tube (Nesco®), UV-Vis spectrophotometry (DLab®), centrifuge, tube centrifugation (Eppendorf®), incubator (Nesco®), vaculab EDTA K3 (Onemed®), reagent of GOD-PAP (Dumolab®), glass container, brown vial, glibenclamide tablets (Indofarma®), electric chopper (Philips®), syringe (Onemed®). The experimental animal used was a male white rat (*Rattus norvegicus*) Wistar strain, 3 months old, weighing 200–300 grams, obtained from the E-mentik farm, Kendari, Southeast Sulawesi. The ethical clearance for animal subject use was approved by the Committee on Health Research Ethics of the Institution of Research and Community Service, Universitas Halu Oleo, Kendari (ethical clearance certificate number: 1006a/UN29.20.1.2/PG/2023). *Tectona grandis* Linn. leaves were collected from Lapulu Village, Abeli subdistrict, Kendari City, Southeast Sulawesi.

Research Procedure

1. Preparation, Maceration, and Samples Fractionation

   The leaves was harvested, collected, and determinated in Faculty of Teaching and Educational Sciences Universitas Halu Oleo. Then the *Tectona grandis* Linn. leaves was sorted, washed, ground, and dried in an oven preheated to 60°C to obtain dry simplicia powder. Then, the simplicial powder (800 g) was subsequently macerated for three to twenty-four hours in ethanol solvent to obtain the macerate. Next, the macerate was collected and concentrated using a rotary evaporator to obtain the crude extract, and the yield of the extract was calculated. The extract (30 g) was then fractionated using the liquid-liquid partition method. The extract was dissolved in a solvent mixture of n-hexane: aquades (1:1) with a volume of 200 mL in a separating funnel, shaken, and allowed to stand for 5 minutes until two layers of n-hexane-water solution were formed. The n-hexane layer was separated, collected, and concentrated until a crude n-hexane fraction was obtained. The distilled water layer is to be partitioned again using chloroform solvent (1:1) in 200 mL, shaken, left to stand, then separated, collected, and concentrated to obtain the crude chloroform fraction. The same process is used for partitioning with ethyl acetate solvent to obtain a crude ethyl acetate fraction. The yield of n-hexane, chloroform, and ethyl acetate fraction respectively was calculated (Mistriyani *et al*., 2018).

2. Phytochemical Screening

   Analytical phytochemical screening was carried out on the n-hexane, chloroform, and ethyl acetate fractions using a method with slight modifications (Yamin *et al.*, 2020) :

   a. Flavonoids

      Each sample was taken in 1 mL and placed in a tube, then 2 drops of HCl solution were added and shaken. Next, magnesium powder was added to the tube. A positive result is indicated by a color change in the sample to orange, pink or dark red, and yellow.

   b. Alkaloids

      Chloroform and NH_3 were added to each 1 mL sample and then heated using hot water. One drop of H_2SO_4 is added to the tube then Dragendorff's reagent is added. The result is positive for alkaloids if the sample changes color to an orange or red or brownish red precipitate.

   c. Tannin

      The sample was added with potassium acetate, and 1 mL $FeCl_3$. The sample is positive if there is a color change to bright green, purple, red, blue, or black.

   d. Saponins

      Each sample (1 mL) was placed in a tube, 5 mL of hot water was added, and shaken. After that, leave it for 10 minutes. The result is positive if foam forms and does not disappear with shaking.

   e. Terpenoids

      The sample was added with 0.5 mL of acetic acid solution, then 2 mL of H_2SO_4 was added. Positive results for steroids are indicated by the formation of blue and green colors. The formation of orange, purple, and golden yellow colors indicates a positive test for triterpenoids.

3. Antidiabetic Activity Assay

   a. Preparation of The Animal Models

      The animals were adapted to familiarize the animals with a new environmental condition, they are provided with standard food and drinks. The temperature in the animal cave is always controlled, ranging from 18–26°C, with room humidity maintained between 40–70%, in a light/dark cycle of 12 hours. Then, the animals were divided into 6 groups, normal control (KN), positive control group given glibenclamide 5 mg (0.04 mg) (K+), negative control group given Na-CMC 0.5% (K-), treatment group given n-hexane fraction (P1), chloroform fraction (P2), ethyl acetate fraction (P3).

b. Preparation of the samples

The samples used in this study were the n-hexane, chloroform, and ethyl acetate fractions. The sample was weighed according to the dose (300 mg/kgBB) calculation results and the average body weight of the animals. Furthermore, each sample was dissolved in Na-CMC 0.5% to produce a stock solution of 20 mL. The administration volume is adjusted to the body weight of each animal with a percentage of administration volume of 5 mL/200 gBW.

c. Animal modeling

The animals were fasted for 12 hours, and the fasting blood glucose levels of the were measured as the blood glucose level at time 0 (T0) before being given induction of streptozotocin (STZ). The animals with blood glucose levels more than 135 mg/dL were classified as diabetic animals and used for further antidiabetic assay. Then, the animal groups of K+, K-, P1, P2, and P3 were induced with streptozotocin (STZ) intraperitoneally (dose of 40 mg/KgBW). Then, the blood samples were collected from the orbital sinuses of animal eyes, after the animals were fasted for 12 hours, and expressed as T1. Further, each treatment group was given therapy once a day. After a week of therapy, the fasting blood glucose samples were taken from the animals again as T2.

The fasting blood glucose levels of T0, T1, and T2 were analyzed using the GOD–PAP (Glucose Oxidase – Aminoantipyrine Peroxidase) method. Briefly, the blood samples of T0, T1, and T2 were centrifuged (3000 rpm, 15 minutes) to separate the serum. Then, 10 mL of serum was taken and mixed with 1 mL of GOD-PAP reagent solution. This sample was mixture and vortex for 5 seconds and after that the sample was incubated for 10 minutes (37°C). The absorbance of the sample was measured using spectrophotometry at a wavelength of 546 nanometers (Nuralifah *et al*., 2021). The animal blood glucose levels were calculated using the following formula (Putri *et al*., 2022) :

$$\text{Plasma glucose levels} = \frac{\text{sample absorbance}}{\text{standard absorbance}} \text{ x standard concentration(mg/mL)}$$

Data Analysis

Data from measurements of fasting blood glucose levels for each group are expressed in the form of mean ± SD. The blood glucose levels of each group before and after STZ induction were statistically analyzed by paired sample t-test ($\alpha = 5\%$). Data of blood glucose levels after treatment were analyzed using the ANOVA (Analysis of Variance) method and continued with the LSD post-hoc test using the IBM SPSS version 24 application.

RESULT AND DISCUSSION

Tectona grandis Linn., commonly known as teak, exhibits promising characteristics that render it a viable candidate for pharmaceutical development. This botanical specimen has a longstanding history of traditional usage for therapeutic purposes. The leaves of the plant have been extensively documented to possess various pharmacological effects, including antioxidant (Suryanti *et al.*, 2020), antibacterial (Danlami & Simon, 2017), anti-inflammatory, anthelmintic (Javalgikar *et al*., 2019), anticancer (Younis *et al*., 2023), hepatoprotective (Deswal *et al*., 2019), and antidiabetic properties (Kushwah, 2018; Nuralifah *et al*., 2021; Han *et al*., 2023). Extensive research has been conducted on the utilization of *Tectona grandis* Linn. to reduce blood glucose levels. However, the current research primarily focuses on the utilization of the plant's bark (Rajaram, 2013; Mishra *et al.*, 2021), root (Sharma & Samanta, 2011; Daswad & Wadher, 2022), and flower (Ramachandran *et al*., 2011), with a limited investigation into the potential antidiabetic properties of its leaves. Although various studies reported the presence of antidiabetic compounds, such as phenolics, in numerous types of leaves (Atawodi *et al*., 2010; Jin *et al*.,

2020). Hence, the present study was undertaken to investigate the potential antidiabetic properties of *Tectona grandis* Linn leaves.

The *Tectona grandis* Linn. leaves (4 kg) were harvested and collected. The results of the determination confirmed that the plant utilized was *Tectona grandis* Linn F., belonging to the *Verbenaceae* family. The determination key was 1a-2a-3b-4b-5a-6a-7b-9a-10b-11a. The samples were dried and ground and obtained 800 grams of dry simplicia powder. Next, the simplicial powder was macerated using 96% ethanol solvent, then filtered to obtain the macerate, and concentrated to be a crude extract (178.6 grams) with extract yield was 22.32% (w/w). The crude extract was fractionated by liquid-liquid partition. In the first stage of partition, the extract was fractionated using n-hexane solvent to separate non-polar compounds from the sample. The second stage of partition uses chloroform solvent to separate semipolar compounds and is followed by fractionation using ethyl acetate to filter more polar compounds. Each fraction was collected and concentrated until a crude fraction was obtained and the fractions yield was calculated (Table I).

Table I. Percentage of N-Hexane, Chloroform, Ethyl Acetate Fraction of *Tectona grandis* Linn. Leaves

No.	Sample	Weight (g)	Yield (%) (b/b)
1.	*n*Hexane fraction	1.72	5.73
2.	Chloroform fraction	3.69	13.20
3.	Ethyl acetate fraction	12.2	40.66

The chemical compound screening was carried out using the tube method with tests for alkaloids, flavonoids, saponins, tannins, and terpenoids. The result of chemical compound screening is seen in Table II.

Table II. Results of Phytochemical Screening of N-Hexane, Chloroform, and Ethyl Acetate Fraction Samples Using Tube Methods

Compounds	Reagents	Samples		
		N-Hexane Fraction	Chloroform Fraction	Ethyl acetate Fraction
Alkaloids	Dragendorff + HCl	+	+	+
Flavonoids	Magnesium powder + HCl	+	+	+
Tannin	$FeCl_3$ 1%	-	-	-
Saponins	Aquades + HCl	-	-	-
Terpenoids	Anhydrous acetic acid + H_2SO_4	+	+	+

Note: (+) Positive result containing compound. (-) Negative results contain compounds

The animal modeling carried out in this study aims to obtain type II diabetes mellitus animals with blood glucose levels of more than 135 mg/kgBW. The diabetogenic substance used is streptozotocin (STZ) 40 mg/kgBB. Streptozotocin may increase blood glucose levels and is predicted cause by the same structure of STZ with glucose, which facilitated the STZ to enter the β cells via the GLUT2 transporter and accumulate intracellularly. STZ in cells forms an alkylating agent, diazomethane (DAM), which causes DNA methylation and gives rise to diabetogenic conditions (Goyal *et al.*, 2016).

The results of measuring the fasting blood glucose levels of animals before and after STZ induction can be seen in Figure 1. The measurement results show that there is a significant difference ($p<0.05$) in the fasting blood glucose levels of mice after being given STZ induction. Fasting blood glucose levels before STZ induction in the KN, K-, K+, P1, P2, and P3 groups were 98.13; 102.14; 98.28; 98.77; 100.33; 105.59 mg/dL, respectively. Meanwhile, the blood glucose levels of each group after STZ induction were 96.59; 291.95;

327.49; 273.29; 291.24; and 315.12 mg/dL, respectively. This indicates that the diabetes induction method was successful in increasing the blood glucose levels of the animals.

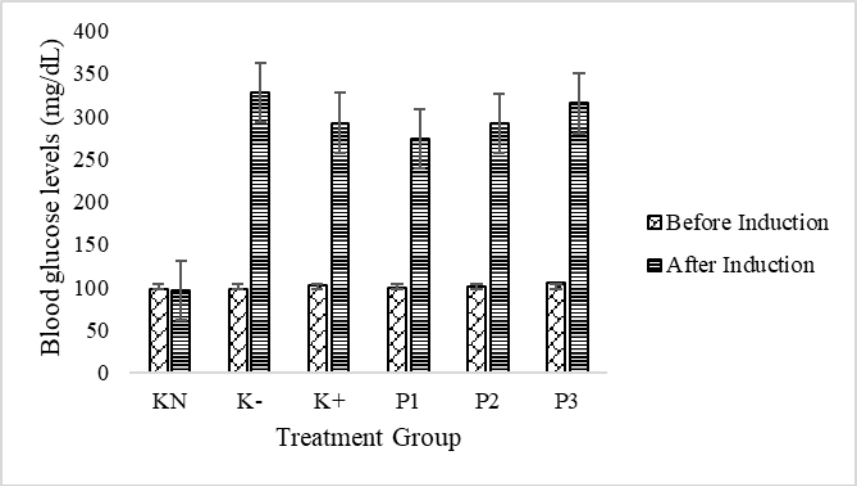

Figure 1. The graph of fasting blood glucose levels in animal models before and after streptozotocin induction.

Normal control (KN), negative control (Na-CMC 0.5%) (K-), positive control (DM + glibenclamide) (K+), treatment (DM + n-hexane fraction 300 mg/kgBB) (P1), treatment (DM + chloroform fraction 300 mg/kgBW) (P2), treatment (DM + ethyl acetate fraction 300 mg/kgBW) (P3).

The n-hexane, chloroform, and ethyl acetate fractions have antidiabetic potential. The results of the antidiabetic assay show that administering fractions for seven days may reduce the fasting blood glucose levels of the animal models significantly ($p<0.05$) compared to the K- group. The blood glucose levels for groups K+, P3, P2, and P1 were 97.01; 110.96; 129.38; and 111.46 mg/dL, respectively (Figure 2). After seven days of therapy, the blood glucose levels of the K+, P1, P2, and P3 groups showed significant differences ($p<0.05$) to KN. This indicates that administration of glibenclamide, the n-hexane, chloroform, and ethyl acetate fractions in 7 days of treatment, may only reduce the blood glucose level but could not normalize it. Additional calculations in the form of percentage reduction in blood glucose level were carried out to see the pattern of reduction in blood glucose level for each group. The results obtained were that the largest percentage reduction was in the K+ group (66.8%), followed by the P3 group (64.8%), P1 (59.2%), and P2 (55.6%) (Figure 3). The ethyl acetate fraction showed a decrease in blood glucose level same as in the K+ group.

The effectiveness of the fractions in reducing blood glucose levels was assessed based on the results of comparing the blood glucose level of each fraction to the K+ group. The results of the LSD posthoc analysis showed that all fractions had no significant differences in blood glucose level ($p>0.05$) to K+. These results indicated that the fractions have the same effectiveness in reducing blood glucose levels as the K+ group statistically.

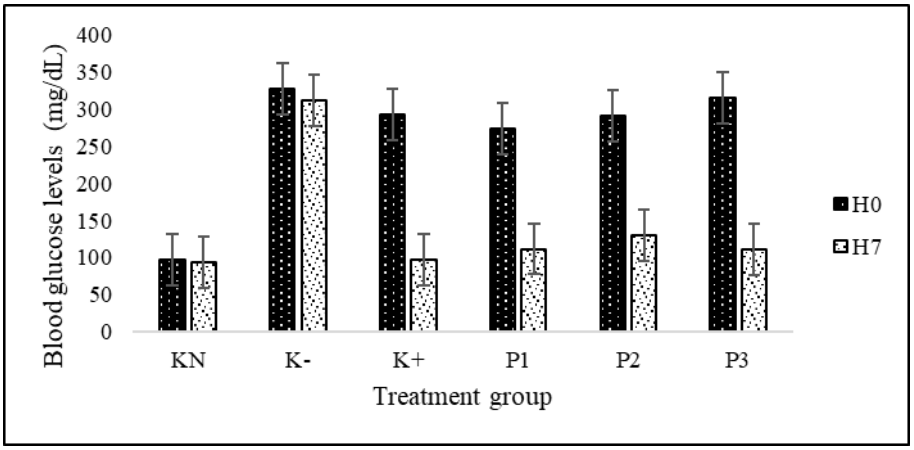

Figure 2. The graph of fasting blood glucose levels of the animal model after therapy.

Data in the form of animal blood glucose levels before therapy (H0) and after therapy for seven days (H7). Normal control (KN), negative control (Na-CMC 0.5%) (K-), positive control (DM + glibenclamide) (K+), treatment (DM + n-hexane fraction 300 mg/kgBB) (P1), treatment (DM + chloroform fraction 300 mg/kgBW) (P2), treatment (DM + ethyl acetate fraction 300 mg/kgBW) (P3).

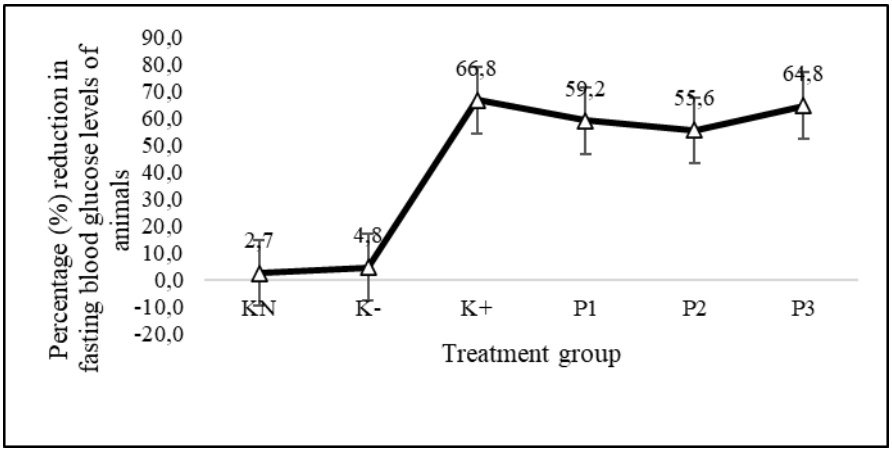

Figure 3. The graph of the percentage (%) reduction in fasting blood glucose levels of animals after being given therapy for 7 days.

In the blood glucose level measurement results, the interesting thing was that the ethyl acetate fraction showed better potential in reducing blood glucose levels than the chloroform and n-hexane fractions. This may be caused by the chemical compounds extracted by each solvent. The polarity index of each solvent influences the ability of a solvent to extract compounds. The polarity of the solutions, nHexane, chloroform, and ethyl acetate, is 0.0; 4.1; and 4.3, respectively (Pernak *et al.*, 2016). This polarity shows how polar the solvent is and affects the compounds that can be extracted. Ethyl acetate is semi-polar, and the greatest amount of the compound is extracted using this solvent. Chloroform is considered a more non-polar solvent than ethyl acetate, so it can extract more non-polar compounds. While n-hexane is a nonpolar organic compound that is commonly used to remove fat from samples, many substances that dissolve in n-hexane during extraction are nonpolar, including octacosane and fatty acid derivatives (Jafarian *et al.*, 2012).

The chemical compound of the ethyl acetate fraction of *Tectona grandis* Linn. has been isolated in different studies, and it is known that there are flavonoid compounds dihydroquercetin or taxifolin, and hesperidin (Ghareeb *et al.*, 2013). In different studies, it has been reported that taxifolin has antidiabetic activity through an activation mechanism by

phosphorylating Akt and AMPK, and promoting translocation of glucose transporter 4 (GLUT4) to the plasma membrane from the cytosol of L6 myotubes via the PI3K/Akt and AMPK signaling pathways (Kondo *et al*., 2021). The publication of antidiabetic activity from hesperidin has been reported, and it is known that this compound can regulate glycolysis and gluconeogenesis by increasing glucokinase activity, inducing phosphorylation of the insulin receptor (IR) and phosphoinositide-dependent kinase 1 (PDK1), while reducing the activity of glucose six phosphatase and phosphoenolpyruvate carboxykinase. in the liver. In cell-based assays, hesperidin increased adipocyte glucose uptake (Peng *et al*., 2020). The presence of these compounds is thought to be the cause of the potential and effectiveness of *Tectona grandis* in reducing blood glucose levels in animal models.

CONCLUSION

Tectona grandis Linn. is a plant that has the potential to be developed into an antidiabetic drug, and the ethyl acetate fraction can reduce blood glucose levels more effectively than the n-hexane and chloroform fraction groups.

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REFERENCES

Al-Lawati, J. A. (2017). Diabetes Mellitus: A Local and Global Public Health Emergency! *Oman Medical Journal*, 177–179. doi: 10.5001/omj.2017.34.

American Diabetes Association. (2019). 5. Facilitating Behavior Change and Well-being to Improve Health Outcomes: Standards of Medical Care in Diabetes—2020. *Diabetes Care*, *43*(Supplement_1), S48–S65. doi: 10.2337/dc20-S005.

Atawodi, S. E., Atawodi, J. C., Idakwo, G. A., Pfundstein, B., Haubner, R., Wurtele, G., Bartsch, H., & Owen, R. W. (2010). Evaluation of the Polyphenol Content and Antioxidant Properties of Methanol Extracts of the Leaves, Stem, and Root Barks of *Moringa oleifera* Lam. *Journal of Medicinal Food*, *13*(3), 710–716. doi: 10.1089/jmf.2009.0057.

Danlami, U., & Simon, O. (2017). A Comparative Study on the Phytochemicals and Antimicrobial Activities of the Hexane Extracts of the Leaves of *Tectona grandis* and Its Mistletoe. *American Journal of Heterocyclic Chemistry*, *3*(2), 19–22.

Daswad, A. K., & Wadher, S. J. (2022). Anti-Diabetic Traditional Medicinal Plants: A Comprehensive Review. *World Journal of Pharmaceutical Research*, *11*(10), 110–119.

Deswal, G., Guarve, K., Kriplani, P., Dhingra, A. K., Chopra, B., Sidana, J. (2019). Hepatoprotective Activity of *Tectona grandis* against CCl4-Induced Hepatic Damage in Rats. *The Open Pharmacology Journal*, *9*(1).

Ghareeb, M. A., Shoeb, H. A., & Madkour, H. M. F. (2013). Radical Scavenging Potential and Cytotoxic Activity of Phenolic Compounds From *Tectona grandis* Linn. *Global Journal of Pharmacology*, *7*(4), 486–497.

Goyal, S. N., Reddy, N. M., Patil, K R., Nakhate, K. T., Ojha, S., Patil, C. R., & Agrawal, Y. O. (2016). Challenges and Issues with Streptozotocin-Induced Diabetes – A Clinically Relevant Animal Model to Understand the Diabetes Pathogenesis and Evaluate Therapeutics. *Chemico-Biological Interactions*, *244*, 49–63.

Han, M., Yang, F., Zhang, K., Ni, J., Zhao, X., Chen, X., Zhang, Z., Wang, H., Lu, J., & Zhang, Y. (2023). Antioxidant, Anti-Inflammatory, and Anti-Diabetic Activities of *Tectona grandis* Methanolic Extracts, Fractions, and Isolated Compounds. *Antioxidants*. doi: 10.3390/antiox12030664.

Ikhwan, M., Des, M., & Chatri, M. (2021). Inventory of Medicinal Plants that have the Potential to Treat Diabetes Mellitus in Sijunjung District. *Jurnal Serambi Biologi*,

6(2), 1–8.

Indrasari, H. N. (2018). *Penerapan Manajemen Nutrisi untuk Mengontrol Glukosa Darah Pada Pasien Diabetes Melitus Tipe 2 di RSU Bahteramas Provinsi Sulawesi Tenggara*. *Karya Tulis Ilmiah*. Poltekkes Kemenkes Kendari.

Jafarian, A., Zolfaghari, B., & Parnianifard, M. (2012). The Effects of Methanolic, Chloroform, and Ethylacetate Extracts of the *Cucurbita pepo* L. on the Delay Type Hypersensitivity and Antibody Production. *Research in Pharmaceutical Sciences*, *7*(4), 217.

Javalgikar, A., Shaikh, H., Sargar, M., Survanshi, H., & Rathod, M. (2019). In Vitro Anti-Inflammatory and Anthelmintic Activity of *Tectona grandis* Leaves Extract," *Internationa Journal of Herbal Medicine*, *7*(2), 26–40.

Jin, D., Dai, K., Xie, Z., & Chen, J. (2020). Secondary Metabolites Profiled in Cannabis Inflorescences, Leaves, Stem Barks, and Roots for Medicinal Purposes. *Scientific Reports*, *10*(1), 3309. doi: 10.1038/s41598-020-60172-6.

Kemenkes RI. (2018). *Hasil Riset Kesehatan Dasar Tahun 2018*. *Kementrian Kesehatan RI*, *53*(9), 1689–1699.

Kondo, S., Adachi, S., Yoshizawa, F., & Yagasaki, K. (2021). Antidiabetic Effect of Taxifolin in Cultured l6 Myotubes and Type 2 Diabetic Model kk-ay/ta Mice with Hyperglycemia and Hyperuricemia. *Current Issues in Molecular Biology*, *43*(3), 1293–1306. doi: 10.3390/cimb43030092.

Kushwah, A. S. (2018). Effect of Methanolic Extracts of *Tectona grandis* Linn Leaves on Diabetic Neuropathy in Streptozotocin–Induced Diabetic Rats. *MOJ Drug Design Development & Therapy*, *2*(4), 203–209. doi: 10.15406/MOJDDT.2018.02.00048.

Mishra, B., Kar, D. M., Maharana, L., dash, S., Mishra, G. P. (2021). Hypoglycemic Activity of Methanol Fraction of *Tectona grandis* (Linn) Bark in Experimental Rat Models. *Research Journal of Pharmacy and Technology*, *14*(8), 4247–4252.

Mistriyani, Riyanto, S., & Rohman, A. (2018). Antioxidant Activities of Rambutan (*Nephelium lappaceum* L) Peel In Vitro. *Food Research*, *2*(1), 119–123. doi: 10.26656/fr.2017.2(1).150.

Nuralifah, N., Parawansah, P., & Rahmawati, N. F. (2021). Antihyperglycemic Activity Test of Teak Leaves (*Tectona grandis* L.) Ethanol Extract in Streptozotocin-Induced Rats. Jurnal Farmasi Sains dan Praktis, *7*(3), 412–419.

Peng, P., Jin, J., Zou, G., Sui, Y., Han, Y., Zhao, D., & Liu, L. (2020). Hesperidin Prevents Hyperglycemia in Diabetic Rats by Activating The Insulin Receptor Pathway. Experimental and Therapeutic Medicine, *21*(1), 1–7. doi: 10.3892/etm.2020.9485.

Pernak, J., Niemczak, M., Materna, K., Zelechowski, K., Marcinkowska, K., & Praczyk, T. (2016). Synthesis, Properties, and Evaluation of Biological Activity of Herbicidal Ionic Liquids with 4-(4-chloro-2-methylphenoxy)butanoate Anion. *RSC Advances*, *6*(9), 7330–7338. doi: 10.1039/C5RA23997D

Putri, M. F. D., Kleden, M. M., & Amalo, D. (2022). *Pengaruh Penggantian Tepung Ikan dengan Tepung Daun Kelor dalam Konsentrat Terhadap Metabolit Darah Ternak Kambing yang diberi Pakan Silase Rumput Kume dan Daun Gamal*. Jurnal Nukleus Peternakan Juni 2022, *9*(1), 48–56.

Rajaram, K. (2013). Antioxidant and Anti-Diabetic Activity of *Tectona grandis* Linn. in Alloxan-Induced Albino Rats. *drugs*, *4*, 5.

Ramachandran, S., Rajasekaran, A., & Kumar, K. T. M. (2011). Antidiabetic, Antihyperlipidemic, and Antioxidant Potential of Methanol Extract of *Tectona grandis* Flowers in Streptozotocin Induced Diabetic Rats. Asian Pacific Journal of Tropical Medicine, *4*(8), 624–631. doi: 10.1016/S1995-7645(11)60160-0

Russell, W. R., Baka, A., Björck, I., Delzenne, N., Gao, D., Griffiths, H. R., Hadjilucas, E., Juvonen, K., Lahtinen, S., Lansink, M., Loon, L. V., Mykkänen, H., östman, E., Riccardi, G., Vinoy, S., & Weickert, M. O. (2016). Impact of Diet Composition on Blood Glucose Regulation. Critical Reviews in Food Science and Nutrition, *56*(4), 541–590. doi: 10.1080/10408398.2013.792772.

Sharma, V. & Samanta, K. C. (2011). Hypoglycemic Activity of Methanolic Extract of *Tectona grandis* Linn. Root in Alloxan Induced Diabetic Rats. Journal of Applied Pharmaceutical Science, *1*(4), 106–109.

Soelistijo, S. (2021). *Pedoman Pengelolaan dan Pencegahan Diabetes Melitus Tipe 2 Dewasa di Indonesia 2021*, Global Initiative for Asthma. PB. PERKENI. Tersedia pada: https://ginasthma.org/.

Suryanti, V., Kusumaningsih, T., Marliyana, S. D., Setyono, H. A., & Trisnawati, E. W. (2020). Identification of Active Compounds and Antioxidant Activity of Teak (*Tectona grandis*) Leaves. Biodiversitas Journal of Biological Diversity, *21*(3). doi: 10.13057/biodiv/d210313.

Verma, S., Gupta, M., Popli, H., & Aggarwal, G. (2018). Diabetes Mellitus Treatment using Herbal Drugs. International Journal of Phytomedicine, *10*(1), 1–10. doi: 10.5138/09750185.2181.

Wu, N., Shen, H., Liu, H., Wang, Y., Bai, Y., & Han, P. (2016). Acute Blood Glucose Fluctuation Enhances Rat Aorta Endothelial Cell Apoptosis, Oxidative Stress and Pro-Inflammatory Cytokine Expression In Vivo. Cardiovascular Diabetology, *15*(1), 109. doi: 10.1186/s12933-016-0427-0.

Yamin, Y., Ruslin, R., Sabarudin, S., Sida, N. A., Kasmawati, H., & Diman, L. O. M. (2020). Determination of Antiradical Activity, Total Phenolic, and Total Flavonoid Contents of Extracts and Fractions of Langsat (*Lansium domesticum* Coor.) Seeds. *Borneo Journal of Pharmacy*, *3*(4), 249–256. doi: 10.33084/bjop.v3i4.1500.

Younis, H. M. Hussein, H. A., Khaphi, F. L., & Saeed, Z. K. (2023). Green Biosynthesis of Silver and Gold Nanoparticles using Teak (*Tectona grandis*) Leaf Extract and its Anticancer and Antimicrobial Activity. *Heliyon*, 9(11). doi: 10.1016/j.heliyon.2023.e21698.