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Combination of *Gmelina arborea* and *Falcataria moluccana* Extracts in Reducing Glucose and Improving Histology in Hyperglycemic Mice Model

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Abstract

The White Teak plant (*G. arborea*) and Sengon (*F. moluccana*) contain flavonoids that act as antioxidants and have the potential to lower blood sugar levels. This study aims to examine the effects of *G. arborea* and *F. moluccana* extracts with polar and non-polar (methanol and n-hexane) solvents on blood glucose levels as well as the histological condition of the pancreas and liver in mice. The extract was obtained through maceration, and its effectiveness was tested by measuring blood glucose levels and conducting histological analysis of the organs. Data were analyzed using SPSS. The research results show that extracts of *G. arborea* and *F. moluccana* lower blood glucose levels and improve the histology of the pancreas and liver in mice. Polar solvents (methanol) are more effective in lowering blood glucose levels, while non-polar solvents (n-hexane) have a greater impact on improving organ histology. In conclusion, the extracts of these two plants have a positive effect on the liver condition of hyperglycemic mice.

Keywords: Antidiabetic, Blood Glucose, *Falcataria moluccana, Gmelina arborea*, Histology

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Kombinasi Ekstrak *Gmelina arborea* dan *Falcataria moluccana* dalam Menurunkan Glukosa dan Memperbaiki Histologi Mencit Hiperglikemia

Abstrak

Tanaman Jati Putih (*G. arborea*) dan Sengon (*F. moluccana*) mengandung flavonoid yang berperan sebagai antioksidan dan berpotensi menurunkan kadar gula darah. Penelitian ini bertujuan untuk mengetahui pengaruh ekstrak *G. arborea* dan *F. moluccana* dengan pelarut polar dan non-polar (metanol dan n-heksana) terhadap kadar glukosa darah serta kondisi histologis pankreas dan hati mencit. Ekstrak diperoleh melalui maserasi dan diuji efektivitasnya dengan mengukur kadar glukosa darah serta analisis histologi organ. Data dianalisis menggunakan SPSS. Hasil penelitian menunjukkan bahwa ekstrak *G. arborea* dan *F. moluccana* menurunkan kadar glukosa darah dan memperbaiki histologi pankreas serta hati mencit. Pelarut polar (metanol) lebih efektif dalam menurunkan kadar glukosa darah, sedangkan pelarut non-polar (n-heksana) lebih berpengaruh dalam memperbaiki histologi organ. Kesimpulannya, ekstrak kedua tanaman ini memiliki efek positif terhadap kondisi hati mencit hiperglikemia.

Kata Kunci: Antidiabetes, *Falcataria moluccana,* Glukosa darah, *Gmelina arborea*, Histologi.

1. Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by high blood glucose levels that, if not controlled effectively, can cause major consequences in the body. This condition develops when the body becomes insulin resistant or does not produce enough insulin to appropriately control blood sugar levels.[1] According to data from the International Diabetes Federation (IDF) in the 2021 Atlas edition, there are approximately 537 million people worldwide suffering from diabetes between the ages of 20 and 79, with a global prevalence of 10.5%. The majority of patients are from low- and middle-income nations, including Indonesia, which ranks fifth with 19.5 million patients, a figure that grows year after year.[2]

Insulin resistance and pancreatic beta-cell failure are the primary pathophysiological processes underlying type 2 diabetes.[3] Insulin resistance hinders insulin from acting on target organs, while pancreatic beta cell malfunction and apoptosis are caused by ROS damage, further disrupting insulin production and secretion. Oxidative stress reduces insulin's ability to absorb glucose into cells.[4] Excessive oxidative stress can be reduced by taking antioxidants that suppress free radicals or strengthen the body's antioxidant defenses. Antioxidants can contribute electrons when reacting with free radicals before the primary molecule is destroyed.[5]

Antioxidants produced by the human body cannot absorb free radicals, hence, exogenous antioxidants are required to supplement the body's natural antioxidants. Synthetic antioxidants, on the other hand, cannot be used as a first line of defense because they are hazardous to health. The use of natural materials becomes an essential alternative for developing novel natural antioxidants. Flavonoid chemicals found in plants that are often utilized in traditional medicine have been shown to be bioactive.[6] Secondary metabolites found in plants, such as flavonoids, have been linked to antioxidant, antibacterial, and antihelminthic activity.[7] White teak (*Gmelina arborea*) and sengon (*Falcataria moluccana*) are two plants that are thought to be effective as antidiabetics.

The extraction technique is required to acquire active chemicals from plants. The adequacy of the extraction method and the choice of solvent must be examined, as the extraction procedure has a significant impact on the extraction results and subsequent testing. The chemical properties of the substance to be extracted are used to select solvents, which are commonly classed as polar or non-polar.[8]

Several studies have demonstrated the antidiabetic potential of *G. arborea*. Warrier et al.[9] found that *G. arborea* extract can reduce blood glucose levels in alloxan-induced rats.[10] *G. arborea* also includes flavonoid, terpenoid, and phenol components, which act as antioxidants9 and have antihyperglycemic and antioxidant properties.[11] *G. arborea* extract can effectively lower blood sugar levels in the same way that standard antidiabetic drugs do,[12] whereas the sengon plant (*F. moluccana*) contains natural antioxidants as well as active compounds such as flavonoids, steroids, terpenoids, saponins, and tannins, all of which have the potential to be antidiabetic.[13–15] The use of *Gmelina* is generally more focused on construction products,16 whereas the optimization of wood waste as a source of raw materials for medicine is still limited. On the other hand, sengon plant waste has the potential to be used as an alternative medication for diabetes. Based on the preceding description, further research is needed to investigate the effects of G. arborea and *F. moluccana* extracts in both polar (methanol) and non-polar (n-hexane) solvents on blood glucose levels and pancreatic histology in mice (*Mus musculus*).

2. Methods

This research procedure has been approved by the Health Research Ethics Committee (REC) of Institute of Health Rajawali Bandung with ethical clearance 014/IKR/KEPK/VII/2024 on August 23, 2024.

2.1. Tools

Maceration chamber, stirring rod, histology cassette, erlenmeyer, measuring cup, beaker, glucometer (Easytouch GCU), histology stainer (Lieca ST5020), mice cage, microtome (HistoCore Multicut), tweezers, 1 cc syringe, embedding work station (Thermo Histostar), scalpel, surgical scissors, needles, waterbath (Lieca HI1210), microscope (Olympus CX-23), digital scales (ACS-A), object glass, rotary evaporator (IKA RV 3V).

2.2. Materials

Mice, distilled water, alloxan, entellan, alcohol cotton, 0.5% acid-alcohol solution, 70%, 80%, 90%, 100% alcohol, 0.5% lithium carbonate, 10% NBF solution, xylol, white teak wood waste, sengon wood waste, methanol, 0.9% NaCl, paraffin, hematoxylin-eosin stain.

2.3. Procedures

2.3.1. Extract Preparation

The parts of *G. arborea* and *F. moluccana* were cleaned and chopped into little pieces. For one week,

the fragments were dried at room temperature before being ground into powder for extraction. 50 grams of dried powder from *G. arborea* and *F. moluccana* were placed in separate glass cups, and 1 liter of methanol and 1 liter of N-hexane were added to each glass. The maceration process was used for a three-stage extraction that lasted 24 hours in a dark environment at room temperature. After the extraction procedure, filtering is used to separate the filtrate from the powder residue. *G. arborea* and *F. moluccana* powder extracts were obtained by concentrating the methanol and N-hexane filtrate with a rotary evaporator.[7]

2.3.2. Preparation for Animal Test

This study utilized male mice (*Mus musculus*) aged 2 to 3 months, weighing between 20 and 30 grams, from the Swiss Webster strain, and in good health, with no injuries or disabilities. A total of 24 mice (*Mus musculus*) were divided into six groups: negative control, positive control, Methanol *Gmelina* (GM), N-hexane *Gmelina* (GN), methanol *Falcataria* (SM), and N-hexane *Falcataria* (SN). After three days of adaptation, all groups except the negative control groups were administered alloxan to increase the blood glucose levels of mice (*Mus musculus*), and the glucose levels were measured three days later.

The treatment with Methanol *Gmelina* (GM), N-hexane *Gmelina* (GN), methanol *Falcataria* (SM), and N-hexane *Falcataria* (SN) extracts at a dose of 400 mg/kg BB was carried out for 7 days, after which the blood glucose levels were checked and the liver and pancreas of the mice (*Mus musculus*) were dissected and placed in a 10% NBF solution. The details of treatment given are as follows:

a. Negative control : The control group was not given any diabetes drugs (alloxan) and was only given normal food.
b. Positive control: The control group was given a diabetic drug (alloxan) with a dose 125 mg/kg BB and without the injection of the extract
c. Treatment group of *Gmelina* and *Falcataria* extracts with methanol and N-hexane solvents: Treatment group with the intraperitoneally injection of diabetic drugs (alloxan) at a dose of 125 mg/kg BB and the treatments with *Gmelina* and *Falcataria* extracts with methanol and N-hexane solvents at a dose 400 mg/kg BB was injected orally given for 7 days.

2.3.3. Histology Preparation

Liver and pancreas organs of the mice that have been fixation with 10% NBF solution then carried out a whole series of the process until it became a histology preparation starting from the process of tissue processing, paraffin block cutting, mounting until the staining process using Hematoxyllin-Eosin (HE).[17] The histology preparation has been colorized and observation using microscope at 40x magnification.

3. Results

3.1. Analysis of Blood Glucose Levels

Table 1. shows the result of measurement blood glucose levels in 6 groups of subjects are negative control (K-), positive control (K+), Methanol *Gmelina* (GM), N-hexane *Gmelina* (GN), Methanol *Falcataria* (SM) and N-hexane *Falcataria* (SN). The measurements were taken at three times, before injection alloxan (T0), after the injection alloxan (T1) and after after the injection alloxan (T1) and after treatment with *Gmelina arborea* extract and *Falcataria* extract (T2). Based on results of the research that has been done, the blood glucose levels of the mice, the negative control group are at normal values while the result of blood glucose levels in the positive control group with all four treatment groups have been increased. This shows that alloxan injection has been successful in inducing hyperglycemia in mice.

The results of the Post-Hoc LSD further test analysis showed that there was a significant differencing the

Table 1. Measurement Result of The Glucose Levels (mg/dL)

Group	T0 mean ±SEM	T1 mean ±SEM	T2 mean ±SEM
Negative Control (K-)	82.5 ± 9.54	83.3 ± 4.23	79.8 ± 4.66
Positive Control (K+)	83.3 ± 8.47	212.5 ± 66.76	361.5 ± 126.52
Methanol *Gmelina* (GM)	94 ± 14.11	612 ± 51.59	284.3 ± 90.76
N-hexane *Gmelina* (GN)	109.8 ± 22.11	405 ± 133.10	264.3 ± 94.44
Methanol *Falcataria* (SM)	107 ± 7.80	225 ± 63.68	112 ± 18.58
N-hexane *Falcataria* (SN)	89.5 ± 6.18	294 ± 135.86	216 ± 67.08

Description:
T0: before given alloxan and *Gmelina arborea* extract treatment
T1: after the injection alloxan
T2: after treatment with *Gmelina arborea* extract and *Falcataria moluccana* extract

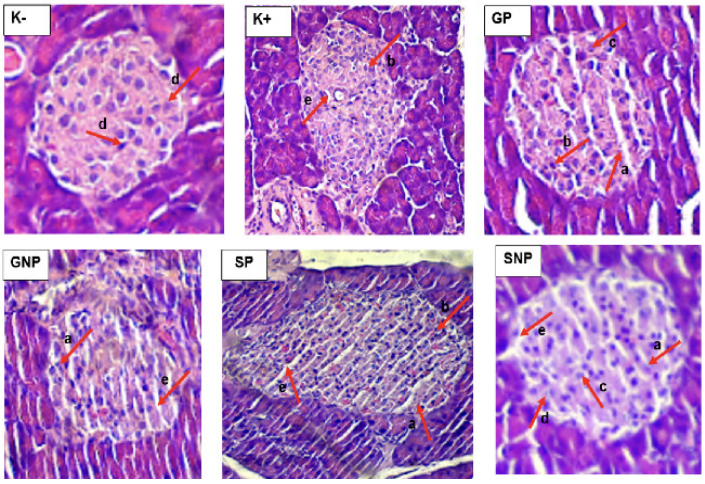

Figure 1. Histological image of mice pancreas stained with Hematoxylin-Eosin (HE) at 400× magnification. (a) Abnormal Cell Shape, (b) Pyknotic Nucleus, (c) Karyorrhexis Nucleus, (d) Karyolysis Nucleus, (e) Intercellular Empty Space.

percentage of decreased blood glucose levels of mice (< 0,05) in the positive groups (K+) against the Methanol *Gmelina* (GM), positive group (K+) against the N-hexane *Gmelina* (GN), positive group (K+) against the Methanol *Falcataria* (SM) and positive group (K+) against the N-hexane *Falcataria* (SN).

3.2. Pancreatic Histology Result

The results of the histological observations were then scored for the degree of damage and analyzed descriptively by comparing the histological observations of the pancreatic organs between the treatment groups and the control group, as shown in Table 2.

Table 2. Results of Damage Assessment of Pancreatic Islets of Langerhans

Group	Mice	Abnormal Cell Shape	Pyknotic Nucleus	Karyorrhexis Nucleus	Intercellular Empty Space	Total Score	Percentage of Damage	Average
Negative	1	0	0	0	0	0	0.0%	7.1%
	2	0	0	0	0	0	0.0%	
	3	1	0	0	1	2	28.6%	
	4	0	0	0	0	0	0.0%	
Positive	1	1	1	0	2	4	57.1%	60.7%
	2	1	1	1	2	5	71.4%	
	3	1	1	0	2	4	57.1%	
	4	1	1	1	1	4	57.1%	
Gmelina arborea Methanol	1	1	0	1	1	3	42.9%	46.4%
	2	1	1	0	1	3	42.9%	
	3	1	0	1	1	3	42.9%	
	4	1	1	1	1	4	57.1%	
Gmelina arborea N-Hexane	1	0	0	1	1	2	28.6%	35.7%
	2	1	0	1	1	3	42.9%	
	3	0	1	1	1	3	42.9%	
	4	0	0	1	1	2	28.6%	
Falcataria moluccana Methanol	1	0	0	1	1	2	28.6%	39.3%
	2	1	1	1	1	4	57.1%	
	3	0	1	1	1	3	42.9%	
	4	0	0	1	1	2	28.6%	
Falcataria moluccana N-hexane	1	0	0	1	1	2	28.6%	28,6%
	2	0	0	0	1	1	14.3%	
	3	1	0	1	1	3	42.9%	
	4	0	0	1	1	2	28.6%	

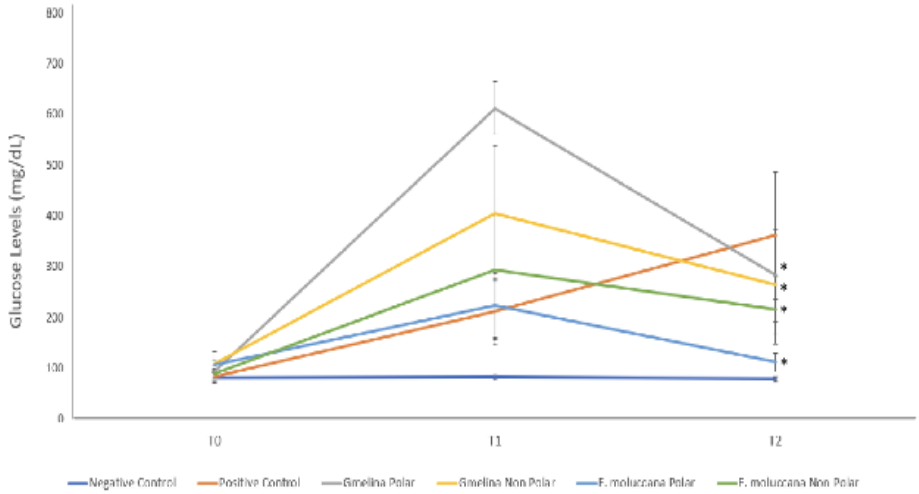

Figure 2. Graph of blood glucose change over treatment time. The significant difference was indicated by * p<0.05

The normality test using the Shapiro-Wilk test showed that the data were not normally distributed. Subsequently, the non-parametric Kruskal-Wallis test was performed, yielding significant results (<0.05) at 0.005. therefore, the analysis was continued with the Mann-Whitey test, as shown with graph in Figure 2

The Mann-Whitney test results showed a significant difference (0.05) in the degree of damage to the pancreatic islets of Langerhans between the positive group (K+) and the Methanol *Gmelina* (GM), N-Hexane *Gmelina* (GN), Methanol *Falcataria* (SM), and n-Hexane *Falcataria* groups.

3.3. Liver Histology Result

The degree of liver histological damage in this study was assessed using the Mitchel Method, with the following criteria: 0 = no liver cell damage; 1 = liver cell damage of 0-0,15%; 2 = liver cell damage of 6-20% ; 3 = liver cell damage of 26-50%; 4 = liver cell damage reaching 50%. The degree of liver damage is evident in Table 3. The average degree of liver damage was analyzed using the Shapiro-Wilk normality test, which indicated that the data were not normally distributed (<0.05). Consequently, the Kruskal-Wallis test was performed, yielding significant results (<0.05) with a value of 0.002. Therefore, a follow-up Mann-Whitney test was conducted. The Mann-Whitney test results showed a significant difference (<0.05) in the degree of damage to the liver between the positive group (K+) and each treatment group, including the Methanol *Gmelina* (GM), N-Hexane *Gmelina* (GN), Methanol *Falcataria* (SM), and n-Hexane *Falcataria*.

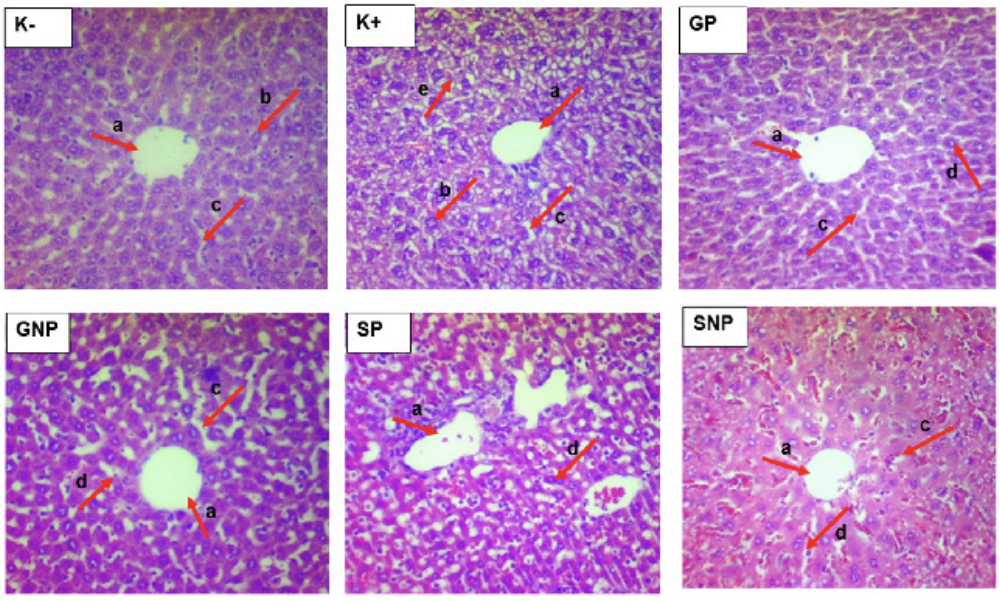

Figure 3. Histological image of mice liver stained with Hematoxylin-Eosin (HE) at 400× magnification. (a) Central Vein, (b) Normal Hepatocytes, (c) Sinusoid, (d) Pyknotic Nucleus, (e) Fatty Degeneration.

Table 3. Liver Damage Degree

Group	Mice	Total degree of damage	Average	Description
K-	1	1	1	Liver damage reaches 0 – 1.5%
	2	1		
	3	1		
	4	1		
K+	1	4	3.75	Liver damage reaches 50%
	2	4		
	3	3		
	4	4		
GN	1	3	3	Liver damage reaches 26-50%
	2	3		
	3	3		
	4	3		
GM	1	3	2	Liver damage reaches 6-25%
	2	2		
	3	1		
	4	2		
GN	1	3	2.25	Liver damage reaches 6-25%
	2	2		
	3	2		
	4	2		
SM	1	1	1.25	Liver damage reaches 0 – 1.5%
	2	2		
	3	1		
	4	1		
SN	1	1	1	Liver damage reaches 0 – 1.5%
	2	1		
	3	1		
	4	1		

4. Discussion

This study aims to determine the glucose levels and histological characteristics of hyperglycemic male Swiss Webster mice (*Mus musculus*) after being given extracts of white teak (*Gmelina arborea*) and sengon (*Falcataria moluccana*) with a polar (methanol) and a non-polar (n-hexane) solvents. Mice were used as test animals in this study because their organs are similar to those of humans, and they are smaller in size and body weight compared to rats, making them easier to handle during the research process. *G. arborea* and *F. moluccana* extracts were chosen as therapies in this study because, based on literature studies, both *G. arborea* and *F. moluccana* contain metabolite compounds that function as antihyperglycemic agents. According to Table 1, the alloxan injection resulted in an increase in blood glucose levels in the mice compared to their baseline levels before the injection. This shows that the intraperitoneal alloxan injection at a dose of 125 mg/kg body weight was able to damage the beta cells of the pancreas. The increase in blood glucose levels occurred because alloxan is a glucose analogue that is toxic to pancreatic beta cells. The structural similarity of alloxan to glucose enables it to enter the cytosol and cross the plasma membrane via GLUT2 transporters.[12] The hyperglycemic condition in alloxan-induced mice occurs due to the formation of free radicals as a byproduct of the high blood glucose reaction. This not only causes hyperglycemia but can also damage pancreatic and liver tissue.[17]

A study by Wadasinghe[12] reported that *G. arborea* extract has benefits as an antidiabetic agent, as it regenerates pancreatic beta cells in test animals. Additionally, the reduction in blood glucose levels in the *F. moluccana* group aligns with research by Shehadeh[13], which found that *G. arborea* and *F. moluccana* contain metabolite compounds such as alkaloids, tannins, triterpenoids, and flavonoids, ehich have antioxidant properties and function as antihyperglycemic agents.[12,13]

Antioxidants are one of the functions of flavonoids, which stabilize free radicals by binding to reactive radical compounds, resulting in more stable and non-reactive compounds in the body. This stability occurs when the hydroxyl groups in flavonoids donate their electrons, making the free radicals more stable.[9] Previous research has proven the hypoglycemic effects of flavonoids, suggesting that plants containing flavonoids can lower blood glucose levels.[14,15] Flavonoid compounds contribute to antioxidant activity, and the higher their concentration, the better the antioxidant activity produced. [18] Antioxidants can inhibit the formation of intracellular free radicals and prevent ROS (reactive oxygen species) caused by diabetes.[12] The mechanism of antioxidant activity is that antioxidants can enhance the insulin effect in plasma by increasing insulin secretion from the remaining beta cells of the pancreas and promoting the regeneration of these beta cells, allowing insulin to function again.

The results of the PostHoc LSD statistical analysis in Table 3 show that the *G. arborea* and *F. moluccana* extract groups, when dissolved in methanol solvent, can provide a better percentage of glucose level reduction compared to extracts dissolved in n-hexane solvent. Meanwhile, based on the results of Mann-Whitney statistical analysis in Tables 2 and 3, it shows that the *G. arborea* and *F. moluccana* extract groups with n-hexane solvent are known to be able to repair liver and pancreas tissue with results close to the negative group.

Pancreatic damage was assessed by damage to the endocrine cells of the islets of Langerhans expressed in the form of abnormal cells, pycnotic cell nuclei, karyorrhexis cell nuclei, karyolysis cell nuclei, uneven cell distribution, and empty spaces between cells, which can be seen in Table 2. The stages of necrosis in pancreatic cells begin with pycnosis (shrinkage of the cell nucleus), followed by karyorrhexis (rupture of the cell nucleus), and karyolysis (loss of the nucleus).[19] Flavonoids have antidiabetic activity that can regenerate cells in the islets of Langerhans. Flavonoid compounds can overcome insulin deficiency, so the presence of flavonoid content has a beneficial effect on diabetes mellitus caused by the absence of insulin or damage to insulin receptors. Flavonoids can stimulate glucose uptake in peripheral tissues, regulate the activity and expression of enzymes involved in carbohydrate metabolic pathways, and act like insulin (insulinomimetic) by affecting the insulin signaling mechanism.[20] Saponins (steroids and triterpenoids) can reduce blood sugar levels by one mechanism, namely inhibiting the release of the α-glucosidase enzyme from the pancreas.[21]Increased blood glucose levels cause damage or changes to the structure of liver tissue after alloxan injection and occur due to two processes, namely the formation of free radicals and damage to the permeability of cell membranes, which results in damage to pancreatic beta cells that function in insulin production. [22]

Damage to the liver and pancreas can be prevented by the antioxidant effects derived from flavonoid compounds.[23] Antioxidant effects protect cells from damage by preventing the formation of free radicals.[24,25] Based on Tables 5 and 7, the results showed that the treatment of *gmelina* and sengon extracts with methanol and n-hexane solvents provided significant improvements in the histology of the pancreas and liver of mice. The p-value <0.05 indicates that there is a significant difference between the control group and the treatment group. This indicates that treatment with these extracts has a positive effect in improving the histological condition of these organs compared to the untreated group. Flavonoid activity relies on the number and position of -OH groups that contribute to balancing free radicals. These antioxidant compounds have the ability to directly scavenge ROS by providing hydrogen atoms.[26]

In histological analysis of liver and pancreas tissues, both polar (methanol) and nonpolar (n-hexane) solvents showed significant changes; however, the n-hexane solvent yielded more significant results ($p < 0.05$). This indicates that the n-hexane extract was more effective in improving the histology of both organs. However, the results of glucose levels in Table 3 show that methanol solvent can reduce blood glucose levels more significant. In the group given *gmelina* extract with methanol solvent, the increase in glucose levels reached 612 mg/dl, indicating that high glucose levels can cause oxidative stress and inflammation, potentially exacerbating tissue damage.[27] This high rise in glucose levels may indicate that more time is needed to repair liver and pancreas tissue, as hyperglycemia can worsen tissue conditions and affect the recovery process.

Mahasuari et al.[28] mentioned that methanol solvent is known to dissolve flavonoid compounds well. This is because the solubility of flavonoid compounds contained in plants is influenced by their ability to form hydrogen bonds with solvents.28 Flavonoids are polar, so they have an affinity for polar solvents such as water and alcohol groups.25 In general, compounds extracted with the proper solvent will produce high purity, which gives rise to greater bioactive effects, but in this study, the nonpolar group (n-hexane) showed better liver repair results than the polar group (methanol). Based on previous studies, the n-hexane fraction of *Voacanga africana* root bark has the highest total phenolic and flavonoid content

at all concentrations (ppm), followed by the ethyl acetate fraction.[17] This is because the highest content of phenolic compounds is not always found in extracts with polar solvents, but depends on the structure of the compound. Antioxidant compounds exhibit varying degrees of polarity, resulting in differences in concentration depending on the solvent used during extraction. Extraction results are significantly influenced by the type of solvent and the extraction method employed.[29]

5. Conclusion

According to the study results, it can be inferred that administering the dosage of *G. arborea* and *F. moluccana* waste extract using methanol and n-hexane solvent (400 mg/kg body weight) for 7 days significantly reduces blood glucose levels and improves the histological structure of hyperglycemic mice (*Mus musculus*). However, statistically, there was no significant difference between the effects of G. arborea and *F. moluccana* extract with methanol or n-hexane solvents on hyperglycemic mice.

Conflict of Interest

The authors declare no conflicts of interest.

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