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Article

Activity Test of The Combination Papaya Leaf Extract (*Carica papaya* L.) and Soursop Leaf Extract (*Annona muricata* L.) on Decreasing Blood Glucose Levels in Rats (*Rattus norvegicus*)

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Abstract

Diabetes mellitus (DM) is one of the most common health disorders and its prevalence rate is increasing every year. Natural compounds can be an alternative treatment for DM. Previous research reports for papaya leaves (*Carica papaya* L.) and soursop leaves (*Annona muricata* L.) showed activity in lowering blood glucose levels when used alone. Therefore, in this study, the two samples were combined to lower blood glucose levels. Both leaves were extracted using the decoction method. This study aims to identify secondary metabolite compounds in papaya leaf extract and soursop leaf extract, then continued with determining the activity and effectiveness of lowering blood glucose levels. The results of the identification of secondary metabolite compounds showed several groups of compounds such as flavonoids, saponins and tannins. The combination of papaya leaf extract and soursop leaf extract showed a decrease in blood glucose levels. In more detail, EDPS (1:2) and EDPS (2:1) were statistically significant against negative controls. EDPS (1:2) showed the most effective percentage reduction in blood glucose levels at 22.72%.

Keywords: Papaya leaves, soursop leaves, reduce blood glucose levels

1. INTRODUCTION

Diabetes mellitus is one of the most frequent medical conditions in the world. Diabetes, often known as DM, occurs when the body is unable to create enough insulin to meet its own needs [1]. According to the International

Diabetes Federation (IDF), around 537 million persons aged 20 to 97 had diabetes in 2021 [2]. This figure is expected to rise to 634 million in 2030 and 783 million by 2045. Diabetes mellitus, according to the World Health Organisation (WHO), affected around 422 million persons globally in 2014 and is expected to climb to 629 million by 2045 [3]. According to the 2018 Basic Health Research (RISKESDAS) statistics, the average number of DM sufferers in Indonesia was 1.5 percent [4]. East Kalimantan had 2.3% of DM sufferers at the provincial level throughout Indonesia, so it is known that East Kalimantan is ranked third, with DKI Jakarta in first and DI Yogyakarta in second place based on the results of blood sugar examinations based on doctor's diagnosis in residents of all ages. According to RISKESDAS statistics (2018), the average number of DM patients in East Kalimantan was 2.26%. Samarinda, the regency/city level of East Kalimantan province [5], has the highest frequency of DM sufferers based on doctor's diagnosis in residents of all ages and in inhabitants aged 15 and up, at 3.04% and 4.11%, respectively.

Diabetes mellitus (DM) is a metabolic disorder characterized by an increase in blood glucose due to decreased insulin secretion by pancreatic beta cells or insulin resistance/disorders [5]. Diabetes mellitus is also commonly known as hyperglycemia, when in a chronic state certain symptoms can appear. Symptoms that occur in patients with chronic hyperglycemia include polyuria, polydipsia, polyphagia, fatigue, reduced body performance, unexplained weight loss, susceptibility to ketoacidosis or non-ketoacidosis infections, and visual disturbances [7].

Synthetic medicines are commonly used to treat diabetes mellitus. Long-term usage of synthetic medications can result in negative effects such as liver damage with elevated liver enzymes and hypoglycemia, particularly with sulfonylurea treatments. As a result, many people prefer herbal treatment as an alternative to DM therapy. Herbal medicine is generally considered safer than synthetic pharmaceuticals because the negative effects are less severe [8].

Natural substances with antidiabetic properties include papaya trees (*Carica papaya* L.) and soursop (*Annona muricata* L.). Papaya trees and soursop are popular alternatives to manufactured medications. This plant's compound group contains flavonoids, alkaloids, tannins, triterpenoids, steroids, and saponins. Flavonoids can lower blood sugar levels due to their antioxidant activity, which protects pancreatic beta cells and increases insulin sensitivity. Alkaloids can heal injured pancreatic beta cells and stimulate sympathetic nerves, hence enhancing insulin release. Triterpenoids and steroids can promote the release of insulin from the pancreas, lowering blood glucose levels [9]. Tannins increase glycogenesis and can function as an astringent, shrinking the small intestine's epithelial membrane and limiting nutrient absorption [10]. Saponin reduce α-glucosidase enzyme activity, making them effective antidiabetics [11].

Papaya leaves are a component of the papaya plant that is commonly used as an alternative medicine. According to Mahatriny et al. (2014), papaya leaves contain various categories of compounds with potential antidiabetic properties, including flavonoids, alkaloids, triterpenoids, steroids, and tannins [12]. Rahman et al. (2015) discovered that combining papaya seed infusion and avocado seeds reduced blood glucose levels in mice with a 6% v/v concentration by 88.57% after 14 days of infusion therapy [13].

Soursop leaves are a component of the soursop plant that is commonly used as an alternative medicine for diabetes. According to studies by Fadel and Besan (2020), soursop leaves contain active components such as flavonoids, alkaloids, tannins, and saponins [14]. According to research by Hariani et al. (2018), it is known that soursop leaves can reduce blood glucose levels by giving soursop leaf infusion with a concentration of 20% experiencing a decrease of 48.6%, 40% experiencing a decrease of 48%, and 60% experiencing a decrease of 45.5% in mice after being given soursop leaf infusion for 14 days [15].

To avoid the adverse effects of synthetic diabetic medications, a mixture of papaya leaf and soursop leaf plants was developed as an alternative. Hariani et al. (2018) [15] found that soursop leaf infusion had good antidiabetic efficacy against mice, with an average drop of 45.5% at a concentration of 60%. As a result, this study was undertaken to investigate the effect of decreasing blood glucose levels in mice using a combination of papaya leaf extract and soursop leaf extract.

2. MATERIALS AND METHODS

2.1 Materials

Aquadest, citric acid, papaya leaves, soursop leaves, FeCl3, HCl, Metformin, NaOH, sodium citrate, Dragendroff reagent, Lieberman-Bouchard reagent, Mayer reagent, Magnesium powder (Mg), streptozotocin (BioWorld), glucose strips (Auto Check), mice, filter paper, syringes.

2.2 Instrument

Stirring rod, glass funnel, beaker, glucometer (Auto Check), Hot plate, measuring flask, mortar and mortar, pan, dropper, measuring pipette, propipette, test tube rack, probe, iron spatula, syringe, test tube, scales.

2.3 Method

2.3.1 Preparation of experimental animals

The experimental animals were male mice aged 1.5-3 months with an average body weight of 150-250 grammes. Before being utilised, the mice were acclimatised for a week in the animal laboratory of Mulawarman University's Faculty of Pharmacy, with the goal of allowing them to adapt to their new surroundings. A total of 24 mice were employed, divided into six groups of four each. The mice utilised in the study must be healthy.

2.3.2 Sampling and Sample Processing

Papaya leaf and soursop samples were collected in Samarida, East Kalimantan. The samples were collected, sorted until clean, then weighed for the initial weight. The samples were chopped into little pieces and air-dried in a room out of direct sunlight. The dried simplicia was then retrieved, and the samples were pulverised into powder before being stored in an airtight container.

2.3.3 Extraction Process

The extract is prepared utilising a hot extraction process, namely decoction with aquadest solvent. Each finely milled simplicia is placed in a container filled with water. The container is cooked over a water bath at 90°C for 30 minutes, stirring occasionally. To acquire the sample extract results, the boiled and heated results are filtered via filter paper.

2.3.4 Secondary Metabolites Identification

a. Alkaloid

The material was dissolved in HCl, heated, and cooled. The findings were filtered to yield the filtrate. The filtrate collected was separated into two tubes. Tube 1 was treated with 4-5 drops of Dragendorf reagent. Tube 2 was treated with 4-5 drops of Mayer reagent. Tube 3 was treated with 4-5 drops of Wagner reagent. Tube 1 reacts positively, forming an orange-brown precipitate. Tube 2 has a positive reaction, which results in the development of a white or yellow precipitate. Tube 3 produces a brown precipitate, indicating a positive reaction [16].

b. Flavonoid

The sample was dissolved in methanol, followed by magnesium powder (Mg) and three drops of strong HCl. The sample was shaken, and the resulting changes were noted. A positive reaction of flavonoid, namely the production of red, yellow, or orange colours in the sample solution [17].

c. Saponin

The sample is placed in a test tube and then filled with hot water. The sample in the tube is chilled and shook for ten seconds. The favourable reaction of saponin, meaning the development of foam as high as 1-10 cm for at least 10 minutes, and the foam does not dissolve after adding 1 drop of HCl [18].

d. Tannin

The sample is placed in a test tube, which is then filled with hot water and heated for 5 minutes. The filtrate is obtained by boiling, and then 3-4 drops of $FeCl_3$ are added to it. A positive tannin reaction, particularly the production of a blue-green or black-green colour in the solution [18].

e. Steroid/Terpenoid

The sample is placed in a test tube, and Lieberman-Bouchard reagent is applied to it. A positive reaction of steroid produces a green colour, whereas a positive response of terpenoids produces a red or yellow colour [18].

f. Antosianin

The sample is placed in a test tube, and 2M NaOH is added drop by drop. A good reaction of the anthocyanin component is evidenced by the red sample turning blue green or gradually fading after being put to NaOH [19].

2.3.5 Metformin preparation

Metformin pills were ground till smooth, then weighed. The weighted pills were placed in a beaker and dissolved with distilled water, stirring until homogenous. The dissolved tablets were placed in a measuring flask, then distilled water was added to the boundary mark and mixed thoroughly.

2.3.6 Citric Buffer preparation

Citrate buffer is created by combining solution A, which is citric acid solution (2.1 grammes in 100 mL), and solution B, which is sodium citrate solution (2.94 grammes in 100 mL). Citrate buffer is prepared in a 100-mL beaker with a pH of 4.5. Solution A (27.5 mL) is mixed with solution B (22.5 mL) and 100 mL of distilled water is added. The solution is measured with a pH meter to pH 4.5. If the pH remains acidic, it is dripped with sodium citrate; if it remains basic, it is dripped with citric acid, yielding a citrate buffer of pH 4.5.

2.3.7 Streptozotocin solution preparation

Streptozotocin was dissolved in citrate buffer and administered to mice intraperitoneally at a dose of 40 mg/kg body weight.

2.3.8 Streptozotocin administration

Mice were initially starved for 18 hours. Streptozotocin was administered intraperitoneally to mice at a dose of 40 mg/kg body weight, and blood glucose levels increased if they reached 150-200 mg/dl.

2.3.9 Measurement of Blood Glucose Levels

Blood glucose level decreasing activity testing can be completed in stages. A total of 24 white mice were prepared and divided into six groups (normal, negative, positive, EDPS (2:1), EDPS (1:1), and EDPS (2:1)), with each group containing four mice. Group 1 is a normal control, consisting of non-diabetic experimental animals treated just with a routine diet (food and drink). Groups 2–6 are diabetic experimental animal groups (induction with streptozotocin), with group 2 serving as a negative control on a conventional food and water. Group 3 is a positive control, consisting of experimental animals fed a regular diet and administered metformin orally. Groups 4, 5, and 6 are test groups, consisting of experimental animals fed a conventional meal plus a combination of papaya leaf and soursop leaf extracts with concentration ratios of 2:1, 1:1, and 1:2 orally. Blood glucose levels were monitored or tested on days 0, 1, 2, 5, and 8.

Blood glucose levels in mice are measured by drawing blood from the mouse's tail, but the first blood is withdrawn first, followed by the second blood, which is injected into the sugar strip and glucometer. The results are then read using the glucometer. Following the measurement, the data is reported and processed using nonparametric Kruskal Wallis analysis.

3. RESULT AND DISCUSSION

3.1 Identification of Secondary Metabolite Compounds in Papaya Leaf Extract (Carica papaya L.) and Soursop Leaf Extract (Annona muricata L.)

The qualitative identification of secondary metabolite in table 1 indicates that papaya leaves include alkaloid compounds (mayer), flavonoids, saponins, and tannins. Soursop leaves include alkaloids (mayer), flavonoids, and saponins. Alkaloid testing in papaya and soursop leaf decoctions used three types of reagents: dragendorf reagent, which showed a positive reaction in the formation of orange-brown deposits; mayer reagent, which showed a positive reaction in the formation of white or yellow deposits; and Wagner reagent, which showed a positive reaction in the formation of reddish-brown deposits.

Table 1. Secondary Metabolic Compound Content of Papaya Leaf Extract Decoction with Soursop Leaf Extract

Secondary Metabolites	Result	
	Papaya Leaf (*Carica papaya* L.)	Soursop Leaf (*Annona muricata* L.)
Alkaloid		
1. Dragendorf	1. Not detected	1. Not detected
2. Mayer	2. Not detected	2. Terdeteksi
3. Wagner	3. Not detected	3. Not detected
Flavonoid	Detected	Detected
Saponin	Detected	Detected
Tanin	Detected	Detected
Steroid	Not detected	Not detected
Terpenoid	Not detected	Not detected
Antosianin	Not detected	Not detected

The findings of the identification of secondary metabolites in the alkaloids of soursop leaf decoction in all tubes showed that only Mayer's reagent produced a positive reaction, whereas the tubes treated with Dragendorf and Wagner reagents produced no positive results. Meanwhile, no reagent produced a positive reaction in the papaya leaf decoction. This can happen when the number of alkaloid compounds attracted to the sample is small, resulting in only one reagent being sensitive to the sample. This is because alkaloids have nitrogen in their cyclic portions and can bind to other groups such as amine, phenol, amide, and methoxy groups. As a result, alkaloids have semi-polar characteristics, making them more soluble in semi-polar solvents (chloroform, acetyl acetate, alcohol, or acetane), but difficult to dissolve in water [20].

According to the test results, papaya leaf and soursop leaf decoctions produced an orange colour in the test solution after being given magnesium (Mg) powder and concentrated HCl. The test sample turned orange because magnesium powder and HCl reduced the benzopyrone core contained in the flavonoid structure, causing it to change colour [21]. Flavonoid compounds are known to have polar qualities because they have bonds with sugar groups. Flavonoid compounds are easily soluble in polar solvents (such as water) or semi-polar [20].

The results of this test on papaya leaf and soursop leaf decoction samples revealed a positive reaction as evidenced by the development of foam or bubbles, which remained stable after being supplemented with HCl. This is because saponin is a compound with both hydrophilic and hydrophobic groups. When the sample is agitated, the hydrophilic group binds to water, while the hydrophobic group binds to air, resulting in foam. The sample is then supplemented with HCl to increase the polarity so that the hydrophilic group may bind more stably, making the foam created more stable [21].

The findings of this test of papaya leaf decoction and soursop leaf decoction after being dripped with $FeCl_3$ showed that the samples changed colour to blackish green. The colour shift in this sample is induced by tannin reacting with Fe^{3+} ions, resulting in a complex compound of tricyanoferritory potassium. Furthermore, this sample can identify tannin because tannins include numerous OH groups, making them polar and able to dissolve in polar solvents [22].

The findings of this test demonstrate that papaya leaf and soursop leaf decoctions have no modifications in the sample, and no steroid or terpenoid substances have been discovered. This is because the test sample's solvent is polar (water), whereas steroids and terpenoids are non-polar compounds, therefore neither can be detected in papaya leaf decoction or soursop leaf decoction [21].

In this test, papaya leaf decoction and soursop leaf decoction produced no colour changes, indicating that the sample contains no anthocyanin components. This can be caused by the influence of anthocyanin pigment stability, such as heating anthocyanin at a temperature of 50-60 °C, while making the decoction at 90°C, which can disrupt the stability of the anthocyanin pigments in the sample. Furthermore, it can be produced by the action of sunlight because the stability of anthocyanin in its production might affect the anthocyanin pigment included in the sample and exacerbate the damage to the anthocyanin pigment [23].

3.2. Blood Glucose Level Reducing Activity of Papaya Leaf Extract (Carica papaya L.) and Soursop Leaf Extract (Annona muricata L.) in Rats (Rattus norvegicus)

The test findings presented in Figure 1 show that in the mice given a combination of papaya leaf and soursop leaf decoction, blood glucose levels decreased. The test group was separated into three comparative concentration groups: 1:2, 1:1, and 2:1. These three comparison concentrations were administered orally to experimental rats with elevated blood glucose levels (day 1) for seven consecutive days. On day one, the average increase in blood glucose levels in mice was EDPS (1:2) of 332.25 mg/dL, EDPS (1:1) of 354.75 mg/dL, and EDPS (2:1) of 331.75 mg/dL. On the eighth day after receiving papaya leaf and soursop leaf decoction, mice's blood glucose levels reduced as follows: EDPS (1:2) of 204.25 mg/dL, EDPS (1:1) of 298.75 mg/dL, and EDPS (2:1) of 242.5 mg/dL. This demonstrates that the components found in papaya and soursop leaves, specifically flavonoids, saponins, and tannins, can help lower blood glucose levels.

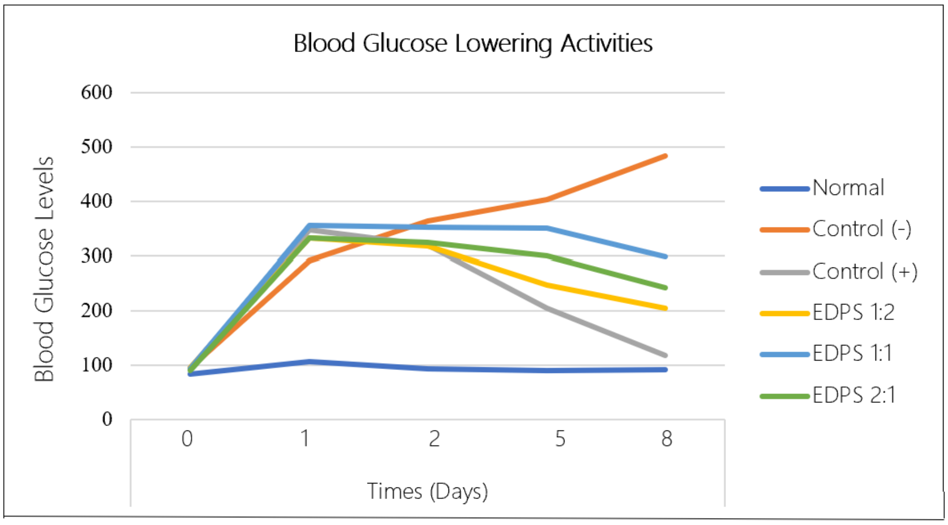

Figure 1. Blood Glucose Level Reduction Activity Test Results Graph

The Kruskal Wallis test resulted in a Sig. < 0.001 value, indicating a significance level of <0.05. As a result, if the significance value is less than 0.05, the averages of each treatment group differ significantly. A Mann-Whitney test was then used as a follow-up. The Mann-Whitney test is designed to determine whether or not there is a significant difference between treatment groups. A Mann Whitney test result of p < 0.05 indicates a significant difference between test groups. Meanwhile, if the value is more than 0.05 (p> 0.05), the data is not substantially different or no significant difference exists between test groups.

The Mann-Whitney test findings may be seen in the data, which reveal that there are both significant and non-significant differences. The normal control group differs significantly from all other groups, including the negative control group, the positive control group, EDPS (1:2), EDPS (1:1), and EDPS (2:1). The negative control group differs significantly from the normal control group, the positive control group, EDPS (1:2), and EDPS (2:1). However, EDPS (1:1) shows no significant difference. The positive control group differs significantly from the normal control group, negative control group, and EDPS (1:1). While EDPS (1:2) and EDPS (2:1) reveal no significant changes. The EDPS 1:2 group differs significantly from the normal control and negative control groups. However, in the positive control group, there are no significant differences between EDPS (2:1) and EDPS (1:1). The EDPS (1:1) group differs significantly from the normal control and positive control groups. Meanwhile, in the negative control group, the EDPS ratios were 1:2 and 2:1. The EDPS 2:1 group had a substantial difference between the normal control and negative control groups. However, in the positive control group, there was no significant difference between EDPS (1:2) and EDPS (1:1).

Based on the findings of statistical analysis using SPSS version 29, it is clear that the EDPS (1:2) and EDPS (2:1) group have pretty good blood glucose reducing action, as they differ significantly from the negative control group. These findings indicate that the test group had activity in decreasing blood glucose levels in mice. This is consistent with the graph of blood glucose lowering activity in Figure 1, which shows that the EDPS (1:2) and EDPS (2:1) group both reduce blood glucose levels. The findings of the secondary metabolite compound test suggest that papaya leaf extract and soursop leaf extract contain flavonoid, saponin, and tannin, which can lower blood glucose levels.

3.3. The Best Comparison of the Combination of Papaya and Soursop Leaf Extract in Reducing Blood Glucose Levels in Rats (Rattus norvegicus)

Table 2 shows the percentage of glucose level drop. The percent decrease data shows that in the normal control group of 13.83%, negative control of -43.25%, positive control of 38.43%, EDPS (1:2) of 22.72%, EDPS (1:1) of 5.97%, and EDPS (2:1) of 12.88%. Based on these findings, the positive control group achieved the highest percentage of blood glucose level reduction. This is possible because metformin is a traditional medicine that increases insulin sensitivity, allowing insulin in the body to bind more easily to its receptors. Furthermore, metformin can enhance glucose utilisation by intestinal cells, lowering blood glucose and inhibiting glucose absorption in the intestine following food intake [24].

Based on the percentage reduction results, it is clear that the combination of papaya and soursop leaves has the potential to reduce blood glucose levels. However, based on the percentage of reduction, the test group with the best reduction effect is EDPS (1:2) because the percentage of reduction is similar to the percentage of reduction of the positive control, with EDPS (1:2) at 22.72% and the positive control at 38.43%. This could be because the sample contains secondary metabolites. The identification test of secondary metabolite components revealed that papaya leaf and soursop leaf extracts include flavonoids, saponins, and tannins.

Papaya leaves contain flavonoids, which imitate insulin and function in the pancreas to repair injured pancreatic beta cells, so increasing insulin output. Saponin functions as an alpha-glucosidase inhibitor. Tannins inhibit the alpha-glucosidase enzyme, which might delay glucose absorption after eating [25]. Soursop leaves contain flavonoid that are known to reduce glucose absorption and enhance peripheral insulin resistance. Saponin compounds can reduce blood glucose levels by decreasing the activity of the alpha-glucosidase enzyme [26]. (Djunarko dkk., 2022). Tannin can reduce glucose absorption, improve glucose tolerance, and stimulate insulin release [27]. (Pandaleke dkk., 2022).

Table 2. Percentage of Decrease in Blood Glucose Levels

Treatment	Average Percentage Decrease		
	2nd Day	5th Day	8th Day
Normal	12.26%	15.33%	13.91%
Average			13.83%
Control (-)	-25.02%	-38.52%	-66.21%
Average			-43.25%
Control (+)	7.93%	41.17%	66.19%
Average			38.43%
EDPS (1:2)	4.29%	25.36%	38.52%
Average			22.72%
EDPS (1:1)	0.85%	1.27%	15.79%
Average			5.97%
EDPS (2:1)	2.03%	9.72%	26.90%
Average			12.88%

4. CONCLUSION

Based on the research, it can be concluded that administering a combination of papaya and soursop leaf extract to rats induced by streptozotocin (STZ) can reduce blood glucose levels, implying that it has the potential as an antihyperglycemic agent. Secondary metabolites found in papaya and soursop leaf extract include flavonoids, saponins, and tannins. The combination of papaya leaf extract and soursop leaf extract has been shown to reduce blood glucose levels in rats in three different sample comparisons. However, EDPS (1:2) and EDPS (2:1) is statistically significant in the negative control group. The combination of papaya leaf extract and soursop leaf at a 1:2 ratio reduces blood glucose levels the most effectively, by 22.72% compared to the other test groups and is not significantly different from the positive group.

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