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Research Article

The Effectiveness of the Combination of Bay Leaf Extract (*Syzygium polyanthum*) and Celery Leaf Extract (*Apium graveolans* L.) on Lowering Blood Sugar Level in Wistar Rats (*Rattus norvegicus*)

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ABSTRACT

Background: Diabetes mellitus is a metabolic disorder marked by high blood glucose levels. According to the WHO, approximately 422 million people worldwide were living with diabetes in 2023, with 1.5 million diabetes-related deaths reported annually. Based on the RISKESDAS data, the prevalence of diabetes in Indonesia was 8.5% in 2018, affecting approximately 20.4 million individuals, and the increase is closely linked to rising obesity rates. Diabetes treatment involves both medication and lifestyle changes. Indonesia has many herbal plants, such as bay and celery leaves, which contain bioactive compounds like flavonoids, alkaloids, saponins, and tannins believed to have antihyperglycemic properties.

Aims: This study aimed to evaluate the effectiveness of the combination of bay leaf extract (*Syzygium polyanthum*) and celery leaf extracts (*Apium graveolans* L.) against lowering blood sugar levels in white male Wistar rats (*Rattus norvegicus*).

Methods: This research is an experimental study using a pre- and post-test control group design. A total of 25 male Wistar white rats (*Rattus norvegicus*) were induced with alloxan and then divided into five groups: Group 1 (G1) as the negative control; Group 2 (G2) as the positive control, treated with the drug glibenclamide; Group 3 (G3) received bay leaf extract at a dose of 300 mg/kgBW; Group 4 (G4) received celery leaf extract at a dose of 300 mg/kgBW; and Group 5 (G5) received a combination of bay leaf and celery leaf extracts at a dose of 300 mg/kgBW. The post-test was conducted twice : Post-test 1 was carried out 60th minutes after treatment, and Post-test 2 was conducted 120th minutes after treatment. Blood glucose levels were measured using a glucometer.

Results: At 60th minutes post-treatment, blood sugar levels decreased by 40 mg/dL in G1, 100 mg/dL in G2, 44 mg/dL in G3, 57.4 mg/dL in G4, and 70.8 mg/dL in G5. At 120th minutes, the decreases were 45 mg/dL (G1), 104.6 mg/dL (G2), 49.2 mg/dL (G3), 62 mg/dL (G4), and 77.6 mg/dL (G5). The Post Hoc LSD test showed a statistically significant average decrease of 5 mg/dL between post-test 1 and post-test 2 *(p < 0.001).*

Conclusion: The combination of bay leaf extract and celery leaf extract at a dose of 300 mg/kgBW is most effective in reducing blood glucose levels in hyperglycemic Wistar rats.

1. Introduction

The Indonesian Society of Endocrinology (PERKENI) definition of diabetes mellitus is a metabolic disease characterized by elevated blood glucose levels caused by impaired insulin secretion, insulin action, or both. Diabetes mellitus is a disease that can lead to various complications, both in large blood vessels (macrovascular) and small blood vessels (microvascular), as well as in the nervous system (neuropathy). These complications can reduce the quality of life for individuals with diabetes mellitus and increase healthcare costs (Perkumpulan Endokrinologi Indonesia, 2021).

According to the World Health Organization (WHO) in 2023, there will be approximately 422 million diabetes patients worldwide, resulting in 1.5 million deaths each year, and this number is expected to continue to rise. According to the International Diabetes Federation (IDF) in 2021, the total number of diabetes mellitus patients worldwide is approximately 537 million. The IDF predicts that the number of diabetes sufferers will increase to 634 million by 2030 and 783 million by 2045. According to the West Java Provincial Health Office in 2022, the number of diabetes mellitus (DM) patients in West Java Province reached 644.704 individuals. The number of diabetes patients in Cirebon City is 9.008 individuals, while in Cirebon Regency, it is 23.174 individuals. The number of diabetes sufferers in Cirebon Regency continues to rise, from 22.465 individuals in 2021 to 23.174 individuals in 2022 (Dinas Kesehatan Provinsi Jawa Barat, 2023; Kemenkes RI, 2019).

Diabetes treatment includes pharmacological and non-pharmacological approaches, including the use of herbal medicines that are widely available in Indonesia. The reason diabetes sufferers prefer herbal treatment for several reasons (Handayani L & Widowati L, 2020). First, herbal medicine has no negative side effects. Second, herbal medicine is easily accessible and affordable. Third, herbal medicine is safe to use. In addition, the community also uses herbal medicine because pharmacological treatments are less effective and have side effects. Therefore, there is currently an increasing trend in the use of herbal medicine for the treatment of various ailments (Ahriyasna R *et al*., 2023; Retta E & Kusumajaya H, 2023).

Indonesia is known for its wealth of herbal plants that are potentially an alternative treatment for diabetes mellitus, one of which is bay leaf and celery leaf. The phytochemical content found in bay leaf includes flavonoids, tannins, alkaloids, saponins, and triterpenoids, which are believed to play a role in lowering blood sugar levels (Meilala L *et al*., 2023; Meldawati, 2022; Nasution PR, 2022; Rissa MM, 2022). Additionally, based on other studies conducted on test animals, it has been proven that celery leaves can also lower blood sugar levels due to the presence of flavonoids, alkaloids, and saponins, which are secondary metabolite compounds (Meutia R *et al*., 2023; Mohsenpour *et al*., 2023; Nelinda R & Wathoni N, 2018).

The combination of bay leaf extract and celery leaf extract is evaluated in this study for its effectiveness in lowering blood sugar levels in male Wistar strain white rats induced with alloxan. The results of this research are expected to provide additional scientific evidence supporting the use of combined herbal plants as an alternative therapy for managing diabetes mellitus. A novel aspect of this study lies in the specific combination of these two extracts and their collective impact on diabetes. This research offers a potential alternative treatment for diabetes mellitus by expanding existing knowledge on traditional medicinal plants and their pharmacological properties.

Furthermore, this study is intended to contribute to the development of future research and enhance the scientific understanding of the benefits of bay leaf and celery leaf extracts in reducing blood glucose levels. In the context of healthcare services, it is anticipated that the findings may support the formulation of natural antioxidant treatments—such as bay leaf and celery leaf extracts—with appropriate dosages for effective blood sugar control. Although previous studies have investigated the individual effects of these extracts, limited research has explored their combined use. Given that both plants contain similar bioactive compounds with potential antihyperglycemic effects, their combination may yield synergistic or additive therapeutic benefits.

2. Methods

Study Design

This research was conducted from March to July 2024 at the Research Laboratory of the Faculty of Medicine, Swadaya Gunung Jati University. The animals used in this study were male Wistar strain rats, selected due to their ease of handling, relatively low maintenance costs, consistent responses to experimental treatments, and higher

metabolic stability. Male rats were specifically chosen to avoid hormonal fluctuations associated with the estrous cycle and potential pregnancy in female rats, making them a reliable model for evaluating the effects of pharmacological and herbal interventions on metabolic conditions such as hyperglycemia.

Glibenclamide was used as the positive control because it has been extensively employed in previous animal studies, especially in rodent models induced with hyperglycemia using agents such as alloxan or streptozotocin (Irawan *et al*., 2022; Widiasari *et al*., 2021). The treatment groups were administered a dose of 300 mg/kg body weight, based on previous studies that found this dosage to be effective (Meilala L *et al*., 2023; Nasution PR, 2022; Rissa MM, 2022).

Tools and Materials

This research utilizes tools such as a mouse cage, gloves, a milligram scale, a blender (Philips), a measuring cup, an Erlenmeyer flask, a funnel, a beaker, filter paper, aluminum foil, a rotary evaporator, a water bath, a glucometer, glucose test strips, an injection syringe, and an oral probe. The materials used in this research are celery leaves, bay leaves, monohydrate alloxan, distilled water, glibenclamide, and 70% ethanol.

Extraction Bay Leaf

7 kg of bay leaves that have been thoroughly washed are then dried under sunlight, and covered with aluminum foil. After that, they are blended, resulting in 518 grams of simplicia powder. The simplicia powder is soaked in a 70% ethanol solvent at a ratio of 1:5 for 3 days with daily stirring, this process is called the maceration method. The obtained extract was then evaporated using a rotary vacuum evaporator at a temperature of 50°C and subsequently concentrated with a water bath until a thick extract of 46 grams was obtained.

Extraction Celery Leaf

8 kg of celery leaves that have been thoroughly washed are then dried under sunlight, and covered with aluminum foil. After that, they are blended, resulting in 567 grams of simplicia powder. The simplicia powder is soaked in a 70% ethanol solvent at a ratio of 1:5 for 3 days with daily stirring, this process is called the maceration method. The obtained extract was then evaporated using a rotary vacuum evaporator at a temperature of 50°C and subsequently concentrated with a water bath until a thick extract of 53 grams was obtained.

Population and Samples

The sample size in this study was determined using the Federer formula, resulting in a requirement of 25 male Wistar strain white rats (*Rattus norvegicus*) induced with alloxan. The rats were randomly assigned using simple random sampling into 5 groups: a negative control group, a positive control group receiving the drug Glibenclamide, treatment group 1 receiving an extract of bay leaves (*Syzygium polyanthum*) at a dose of 300mg/kgBW, treatment group 2 receiving an extract of celery leaves (*Apium graveolans* L.) at a dose of 300mg/kgBW, and treatment group 3 received a combination of bay leaf extract (*Syzygium polyanthum*) and celery leaf extract (*Apium graveolans* L.) at a dose of 300mg/kgBW.

Criteria for Inclusion and Exclusion

The inclusion criteria for this study are: male Wistar strain white rats (*Rattus norvegicus*), weighing between 170-250 grams, aged 2-3 months. Meanwhile, the exclusion criteria for this study are: blood sugar levels in rats >135 mg/dL before being induced with alloxan, weight loss of rats to less than 170 grams during the adaptation period, unhealthy condition of the rats, and any disabilities during the research.

Measurements

The experimental animals used in this study were healthy male white rats. One week prior to testing, the animals were acclimatized in their cages. The purpose of this acclimatization was to allow the rats to adapt to their environment and to visually assess their health status before inclusion in the study. The cages were maintained at a temperature range of 26–28°C with a humidity level of 75–95%, following a 12-hour light/dark cycle. Food and water were provided ad libitum using standard feeding practices (Sinata R *et al*., 2023; Hasim *et al*., 2020). Next,

the blood glucose levels of the rats were measured before induction with alloxan (Pre-1). The rats were then intraperitoneally injected with alloxan at a dose of 150 mg/kgBW across all groups. Thirty minutes after the alloxan injection, blood glucose levels were measured again (Pre-2). Rats were classified as hyperglycemic if their blood glucose level exceeded 135 mg/dL, and as normoglycemic if their blood glucose level ranged from 50–135 mg/dL. Once identified as hyperglycemic, the rats received a single treatment according to their designated group. Blood glucose levels were subsequently measured at 60 minutes (Post-1) and 120 minutes (Post-2) after treatment. Glucose levels were measured using a glucometer. Prior to blood collection, the tip of the rat's tail was cleaned with 70% alcohol, and then punctured with a sterile syringe to obtain approximately 1.0 μL of blood. The blood sample was immediately applied to a glucose test strip inserted into the glucometer, and the result was displayed after 5 seconds.

Ethical Clearance

This study has been ethically approved by the Ethics Committee of the Faculty of Medicine, Swadaya Gunung Jati University, following the seven WHO standards, with number No.5/EC/FKUGJ/IV/2024, on April 8th, 2024.

3. Results

By a simple random sampling method, a total of 25 samples that meets the inclusion and exclusion criteria were involved in this study. The blood sampling of the rats was conducted four times, namely twice for the pre-test and twice for the post-test. Pre-test 1 was before the alloxan induction, Pre-test 2 was 30th minutes after the alloxan induction, Post-test 1 was 60th minutes after the treatment, and Post-test 2 was 120th minutes after the treatment. Here are the results before and after the treatment, which can be seen in **Table 1**.

Table 1. The Result Before and After Treatment

GROUP	SAMPLE	BLOOD SUGAR LEVEL (mg/dL)				DECREASE PRECENTAGE (%)	
		Pre-1	Pre-2	Post-1	Post-2	Pre 2-Post 1	Pre 2-Post 2
G1 (Negative Control)	G1.1	99	168	108	104	36%	38%
	G1.2	88	155	112	107	28%	31%
	G1.3	91	142	120	114	15%	20%
	G1.4	96	145	114	110	21%	24%
	G1.5	82	148	104	98	30%	34%
G2 (Positive Control)	G2.1	95	156	54	50	65%	68%
	G2.2	87	144	47	43	67%	70%
	G2.3	84	166	53	47	68%	72%
	G2.4	83	145	58	56	60%	61%
	G2.5	104	164	60	55	63%	66%
G3 (Treatment of Bay Leaf Extract at a Dose of 300 mg/kgBW)	G3.1	82	137	109	105	20%	23%
	G3.2	79	149	108	103	28%	31%
	G3.3	89	143	102	97	29%	32%
	G3.4	103	153	104	100	32%	35%
	G3.5	116	159	96	90	40%	43%
G4 (Treatment of Celery Leaf Extract at a Dose of 300 mg/kgBW)	G4.1	109	147	102	98	31%	33%
	G4.2	104	154	98	90	36%	42%
	G4.3	98	173	107	104	38%	40%
	G5.4	109	160	95	93	41%	42%
	G5.5	92	161	106	100	34%	38%
G5 (Treatment of the Combination of Bay Leaf Extract and Celery Leaf Extract at a Dose of 300 mg/kgBW)	G5.1	98	162	92	85	43%	48%
	G5.2	96	142	85	78	40%	45%
	G5.3	87	205	90	84	56%	59%
	G5.4	89	138	84	76	39%	45%
	G5.5	88	140	82	76	41%	46%

Table 1 shows the results of blood sugar levels with an average pre-test blood sugar level 1 (before alloxan induction) for G1 (Negative control) at 91.2 mg/dL, and G2 (Positive control) at 90.6 mg/dL, while for G3 (Treatment of bay leaf extract at a dose of 300 mg/kgBW) it is 93.8 mg/dL, for G4 (Treatment of celery leaf extract at a dose of 300 mg/kgBW) it is 102.4 mg/dL, and for G5 (Treatment of the combination of bay leaf extract and celery leaf extract at a dose of 300 mg/kgBW) it is 91.6 mg/dL. In pre-test 2 (30 minutes after alloxan induction), the average blood sugar level for G1 (Negative control) is 151.6 mg/dL and G2 (Positive control) is 155 mg/dL, while for G3 (Treatment of bay leaf extract at a dose of 300 mg/kgBW) it is 148.2 mg/dL, for G4 (Treatment of celery leaf extract at a dose of 300 mg/kgBW) it is 159 mg/dL, and for G5 (Treatment of the combination of bay leaf extract and celery leaf extract at a dose of 300 mg/kgBW) it is 157.4 mg/dL. The average blood sugar level in post-test 1 (60 minutes after treatment) for G1 (Negative control) is 111.6 mg/dL, and G2 (Positive control) is 54.4 mg/dL, while for G3 (Treatment of bay leaf extract at a dose of 300 mg/kgBW) it is 103.8 mg/dL, for G4 (Treatment of celery leaf extract at a dose of 300 mg/kgBW) it is 101.6 mg/dL and for G5 (Treatment of the combination of bay leaf extract and celery leaf extract at a dose of 300 mg/kgBW) it is 99.8 mg/dL. In post-test 2 (120 minutes after treatment), the average blood sugar level for G1 (Negative control) is 106.6 mg/dL, and G2 (Positive control) is 50.2 mg/dL, while for G3 (Treatment of bay leaf extract at a dose of 300 mg/kgBW) it is 99 mg/dL, for G4 (Treatment of celery leaf extract at a dose of 300 mg/kgBW) it is 97 mg/dL, and for G5 (Treatment of the combination of bay leaf extract and celery leaf extract at a dose of 300 mg/kgBW) it is 95 mg/dL. The graph of the average blood sugar levels before and after treatment can be seen in **Figure 1**.
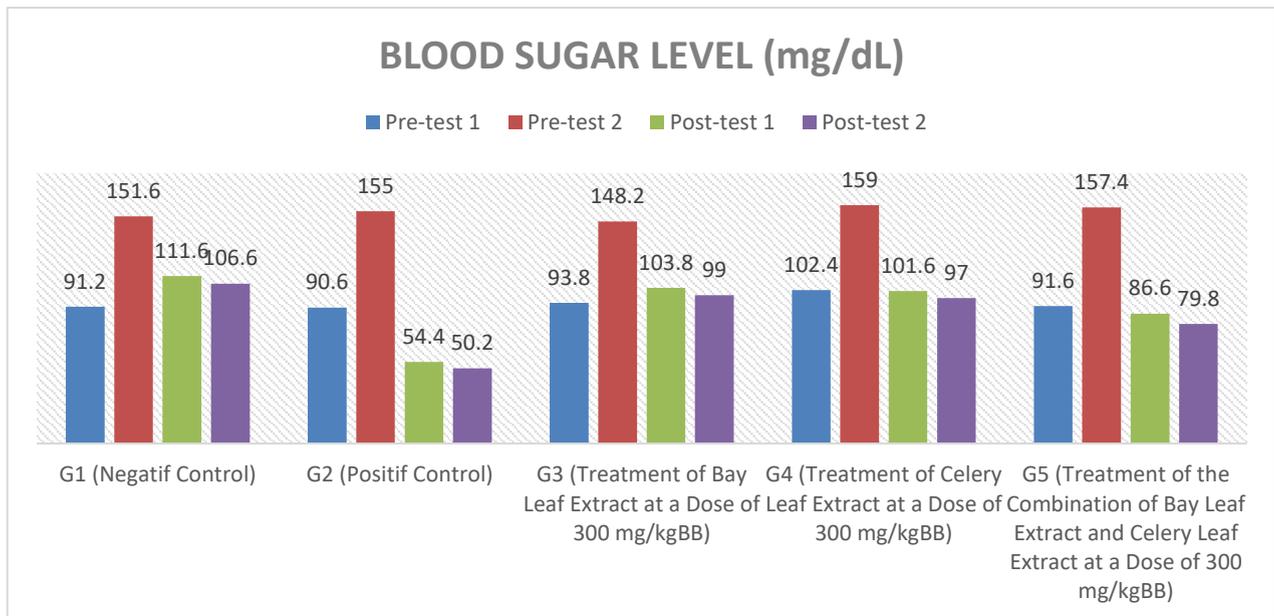
Figure 1. Average Blood Sugar Level Measurement Graph.

Figure 1 shows that Group 5 (Treatment of the combination of bay leaf extract and celery leaf extract at a dose of 300 mg/kgBW) experienced the greatest reduction in blood sugar levels, which was followed by Group 4 (Treatment of celery leaf at a dose of 300 mg/kgBW) and Group 3 (Treatment of bay leaf at a dose of 300 mg/kgBW). Based on **Table 2,** the output data from the Normality Test *Shapiro-Wilk* shows $p<0.05$, indicating that data is not normally distributed. Therefore, the Friedman test was conducted.

Table 2. Normality Test *Shapiro-Wilk*

Group	p-value
Pre-2	0.002
Post-1	0.005
Post-2	0.009

Based on **Table 3,** the output data from the *Friedman test* shows *p*<0.001, indicating that there is a change in the average blood sugar levels of each group before and after the intervention. The *Post Hoc LSD* test was conducted to evaluate the differences in blood glucose reduction based on the timing of measurement. Based on **Table 4,** there was an average decrease in blood glucose levels of 63 mg/dL when comparing pre-test 2 to post-test 1. When comparing pre-test 2 to post-test 2, the average decrease was 68 mg/dL. Meanwhile, a comparison between post-test 1 and post-test 2 showed an average decrease of 5 mg/dL. These differences in blood glucose level reduction were statistically significant, with a p-value of < 0.001.

Table 3. *Friedman Test*

GROUP	SAMPLE TOTAL	*p-value*
G1 (Negatif Control)	5	
G2 (Positif Control)	5	
G3 (Treatment of Bay Leaf Extract at a Dose of 300 mg/kgBW)	5	<.001
G4 (Treatment of Celery Leaf Extract at a Dose of 300 mg/kgBW)	5	
G5 (Treatment of the Combination of Bay Leaf Extract and Celery Leaf Extract at a Dose of 300 mg/kgBW)	5	

Table 4. *Post Hoc LSD Test*

(I) INTERVENTION	(J) INTERVENTION	*Mean Difference*	*Sig.*
***Pre-test* 2 (t30)**	*Post-test* 1 (t60)	63	
	Post-test 2 (t120)	68	
Post-test 1 (t60)	Pre-test 2 (t30)	-62.64	<.001
	Post-test 2 (t120)	5.08	
Post-test 2 (t120)	Pre-test 2 (t30)	-67.72	
	Post-test 1 (t60)	-5.08	

4. Discussion

The findings of each group's blood glucose level tests are displayed on the graph in **Figure 1**. According to a study by Nasution PR in 2022, the rats blood sugar levels rose after 30th minutes for all groups. Aloksan functions by a mechanism akin to that of glucose, enabling it to collect specifically in the β pancreatic cells. This is shown by a decrease in insulin granules in the β pancreatic cells and a reduction in the diameter of the Langerhans islet cells. Because of these similarities, alloxan can enter the cytosol and travel toward the β cell plasma membrane via the glucose transporter (GLUT2). Alloxan initiates redox processes inside the cell that result in superoxide radicals. These radicals subsequently generate hydroxyl compounds, which cause fast destruction to the β cells of the pancreas. Blood glucose levels rise as a result of the disruption of insulin synthesis caused by injury to the pancreatic β cells. Aloksan also lowers the amount of glycogen in the liver; the pancreas is harmed by its cytotoxic effects, which are mostly brought on by the conversion of radical anions. This shows that alloxan induction has caused the rat's body to absorb glucose (Nifadila Dachi *et al*., 2022; Rukminingsih *et al*., 2023).

The glibenclamide-treated positive control group blood glucose levels significantly decreased, especially between minutes 60th and 120th, as the graph in **Figure 1.** This happens because Glibenclamide, an oral antihyperglycemic drug belonging to the type 2 sulfonylurea family, works by inhibiting the production of insulin in the pancreas and reducing blood glucose levels. By depolarizing K^{+} channels and promoting insulin secretion, it can cause insulin to be released via exocytosis. Based on their insulinotropic potential, sulfonylureas bind to particular receptors on the surface of pancreatic β cells. Insulin secretion is stimulated by exocytosis and pancreatic β cells are depolarized as a result of the receptors closing the potassium channels. This process can actively aid in the release of insulin by bringing potassium into the cells. Glibenclamide can both raise insulin secretion and decrease alloxan-induced blood glucose levels (Irawan *et al*., 2022; Widiasari *et al*., 2021).

Studies have shown that the extract from bay leaves (*Syzygium polyanthum*) can reduce blood sugar levels. The average blood sugar levels decreased by 44.4 mg/dL at the 60th minute, and 49.2 mg/dL at the 120th minute respectively. The findings of this investigation align with those of a 2022 study by Nasution PR on the efficacy of 300 mg/kgBW of bay leaf extract in reducing blood sugar levels in male white rats used as test subjects after alloxan induction. The outcomes of this investigation are also consistent with the findings of Meilala L et al., 2023 study, which found that the best way to reduce blood sugar levels was to use a bay leaf extract at a dose of 750 mg/kgBW. The phytochemical composition of bay leaf (*Syzygium polyanthum*) extract, which comprises flavonoids, tannins, alkaloids, saponins, and triterpenoids, can reduce blood sugar levels. The extract has a 0.512% flavonoid content, 0.34% alkaloids, 0.1258% phenols, and 0.1688% tannins (Al-Ishaq RK *et al.*, 2019; Rivai & Yulianti, 2019).

Celery leaf extract (*Apium graveolens* L.) has been shown in studies to have the capacity to reduce blood sugar levels. It is demonstrated by a drop in average blood sugar levels of 62 mg/dL at the 120th minute and 57.4 mg/dL at the 60th minute. The outcomes of this investigation align with the studies carried out by Meutia R et al., 2023, about the efficaciousness of celery leaf ethyl acetate fraction at a dosage of 300 mg/kgBW in reducing blood glucose levels.

According to study findings, combining celery leaf extract (*Apium graveolans* L.) with bay leaf extract (Syzygium polyanthum) is more effective in lowering blood sugar levels than giving either extract alone. A drop in average blood sugar levels of 70.8 mg/dL at the 60-minute mark and a drop of 77.6 mg/dL at the 120-minute mark are indicators of it. This is due to the presence of triterpenoids, alkaloids, flavonoids, and tannins in bay leaves. Celery leaves, on the other hand, have flavonoids, alkaloids, and saponins; therefore, the two leaves operate in concert to reduce blood sugar. When the two extracts are combined, their antioxidant capacity increases three to four times, which is probably what causes the synergistic effect. Furthermore, the distinctions in the sites of action and the effectiveness of the drug-receptor complexes that each agent possesses complement one another, which is a key factor in creating synergistic effects (Alkadri *et al.*, 2019).

Flavonoids, bioactive compounds found in the leaves, play a vital role in protecting the body against oxidative stress caused by Reactive Oxygen Species (ROS). They achieve this by halting the chain reactions of free radicals and promoting the body's natural antioxidant defenses, particularly the enzymes glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT), while also reducing levels of malondialdehyde (MDA), a marker of lipid peroxidation. Flavonoids are categorized into several subclasses, such as flavones, flavanones, and flavonols. Among flavonols, compounds like kaempferol, quercetin, and myricetin are notable, with quercetin being especially recognized for its glucose-lowering potential. Quercetin acts by scavenging oxygen radicals through hydrogen ion donation, thereby preventing oxidative DNA damage in healthy cells. Immunohistochemical studies further reveal that quercetin can reverse β-cell degeneration, improve insulin secretion, and enhance glucose uptake by peripheral tissues (Nugroho A, *et al.*, 2019). Common flavonoids include hesperidin, fisetin, genistein, daidzein, cyanidin, naringenin, apigenin, luteolin, tangeretin, morin, and rutin (Al-Ishaq RK, *et al.*, 2019; Meutia R, *et al.*, 2023). Quercetin, in particular, can inhibit glucose absorption through the GLUT2 receptor in the intestinal mucosa and reduce glucose uptake. It also inhibits phosphodiesterase, leading to increased cyclic AMP (cAMP) in pancreatic β-cells, which activates protein kinase A (PKA) and boosts insulin secretion (Azzahra *et al.*, 2022).

Saponins and alkaloids are two classes of bioactive compounds known for their substantial antidiabetic properties through multiple biochemical pathways. Saponins contribute to blood glucose regulation by influencing intracellular calcium (Ca²⁺) levels and stimulating insulin secretion from pancreatic β-cells. Their mechanism closely resembles that of sulfonylurea drugs, as they inhibit K^+-ATP channels, leading to membrane depolarization, increased calcium influx, and activation of calmodulin enzymes that trigger insulin exocytosis. Moreover, saponins hinder the activity of α-glucosidase enzymes in the small intestine, slowing the breakdown of carbohydrates and delaying glucose absorption. They may also alter the structure of cell membranes, thereby interfering with glucose transporter function and reducing glucose uptake. Alkaloids, on the other hand, exhibit a broader range of antidiabetic effects through both pancreatic and extra-pancreatic mechanisms. Within the pancreas, they promote the regeneration of damaged β-cells, enhancing insulin production and secretion, partly by stimulating the sympathetic nervous system. Outside the pancreas, alkaloids help regulate peripheral glucose levels by facilitating glucose uptake into cells, which lowers blood glucose concentrations. They also reduce glucose absorption in the

intestines, minimizing postprandial glucose spikes. In addition, alkaloids support glycogen synthesis in the liver and muscles, aiding in glucose storage and further decreasing blood glucose levels. A critical aspect of their function is the suppression of gluconeogenesis, achieved by inhibiting key enzymes such as glucose-6-phosphatase and fructose-1,6-bisphosphatase. Alkaloids also enhance glucose oxidation by activating glucose-6-phosphate dehydrogenase, an enzyme crucial for converting glucose into usable energy. These combined actions highlight the therapeutic potential of both saponins and alkaloids in managing diabetes effectively (Meilala L, *et al.*, 2023; Rissa MM, 2022; Saputra M, *et al.*, 2021).

Future studies are encouraged to expand upon the current findings by investigating a broader spectrum of extract dosages to determine the most effective and safest therapeutic levels. It is also important to conduct phytochemical analyses to identify and measure the specific bioactive constituents, such as flavonoids, alkaloids, and saponins, that contribute to the antihyperglycemic effects. Additionally, histopathological analysis of pancreatic tissue, especially the islets of Langerhans, is vital to gain insight into the cellular and tissue-level responses to these herbal interventions. Employing these approaches would offer a more in-depth understanding of the underlying mechanisms and support the advancement of scientifically validated herbal treatments for diabetes. Prior research has highlighted the critical role of identifying active compounds and evaluating histological changes in confirming the therapeutic value of medicinal plants (Agustina M, 2017; Metasari, S, 2017; Manuntung A, *et al.*, 2021).

5. Conclusion

This study found that combining bay leaf (*Syzygium polyanthum*) and celery leaf (*Apium graveolens* L.) extracts at a dose of 300 mg/kgBW significantly reduced blood glucose levels in alloxan-induced male Wistar rats. The combination proved more effective than either extract alone or the negative control, indicating a potential synergistic effect between their active components, such as flavonoids, alkaloids, and saponins. While both extracts individually showed antihyperglycemic properties, their combined use resulted in a greater glucose-lowering effect, as observed at 60th and 120th minutes after treatment. These findings support the potential of using combined herbal extracts as a natural alternative for managing hyperglycemia. However, limitations include the absence of phytochemical analysis and histopathological examination, which leaves the exact active compounds and tissue-level effects unidentified. Future studies should explore different dosages, conduct compound identification, and evaluate pancreatic histology to better understand the mechanisms and therapeutic potential.

Conflict of Interest

The research is no conflict from the researchers and the organization and also the funders for the research.

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