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EFFECTIVENESS OF THE COMBINATION OF BINAHONG LEAF EXTRACT (*Anredera Cordifolia* (TEN.) Steenis) AND ORANGE PEEL EXTRACT (*Citrus Nobilis* L.) ON BLOOD GLUCOSE LEVELS IN RATS

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Abstrak

Diabetes Mellitus merupakan penyakit dengan pengobatan sepanjang hidup, sedangkan obat antidiabetes yang dikonsumsi dapat menimbulkan efek samping dalam penggunaan jangka panjang sehingga membutuhkan alternatif terapi dengan tanaman obat tradisional seperti tanaman binahong (*Anredera cordifolia* (Ten) Steen.) yang mengandung flavonoid dan saponin serta tanaman dan kulit jeruk (*Citrus nobilis*. L). Senyawa tersebut mempunyai kemampuan menurunkan kadar gula darah. Penelitian ini bertujuan untuk mengetahui adanya efek antidiabetes ekstrak etanol daun binahong pada tikus (*Rattus novergicus*) yang diinduksi streptozotocin. Jenis penelitian ini eksperimental dengan metode *pre and post test with controlled group design*, menggunakan hewan uji tikus 25 ekor yang dibagi menjadi 5 kelompok. Kontrol negatif, kontrol positif (Glibenklamid), kelompok perlakuan ekstrak etanol daun binahong, kelompok perlakuan ekstrak etanol kulit jeruk dan kelompok perlakuan kombinasi ekstrak etanol daun binahong dan ekstrak kulit jeruk. Hasil penelitian menunjukkan bahwa ekstrak daun binahong (24,5 mg/KgBB) dan ekstrak kulit jeruk (150 mg/KgBB) efektif menurunkan glukosa darah pada tikus. Kombinasi keduanya dengan dosis masing-masing 12,25 mg/KgBB dan 75 mg/KgBB (perbandingan 50:50) terbukti paling efektif menurunkan kadar gula darah. Kesimpulannya kombinasi ekstrak daun binahong dan ekstrak kulit jeruk dapat digunakan untuk menangani diabetes melitus pada tikus yang diinduksi streptozotocin.

Kata kunci: Diabetes mellitus; *Anredera cordifolia*; *Citrus nobilis*; Gula Darah; Streptozotocin

Abstract

Diabetes mellitus is a lifelong disease that requires continuous treatment. However, the long-term use of antidiabetic drugs may cause side effects, thereby encouraging the search for alternative therapies using traditional medicinal plants such as binahong (Anredera cordifolia (Ten.) Steenis), which contains flavonoids and saponins, and tangerine peel (Citrus nobilis L.). These compounds are known to possess blood glucose-lowering properties. This study aimed to determine the antidiabetic effect of ethanol extract of binahong leaves in rats (Rattus norvegicus) induced with streptozotocin.This research was an experimental study using a pre- and post-test with controlled group design, involving 25 rats divided into five groups: negative control, positive control (glibenclamide), treatment with binahong leaf ethanol extract, treatment with tangerine peel ethanol extract, and treatment with a combination of both extracts.The results showed that binahong leaf extract (24.5 mg/KgBW) and tangerine peel extract (150 mg/KgBW) effectively reduced blood glucose levels in rats. The combination of both extracts at doses of 12.25 mg/KgBW and 75 mg/KgBW, respectively (50:50 ratio), was the most effective in lowering blood glucose levels. The combination of ethanol extracts of binahong leaves and tangerine peel can be used as a potential alternative therapy for diabetes mellitus in streptozotocin-induced rats.

Keywords: ***Diabetes mellitus; Anredera cordifolia; Citrus cobilis; Blood sugar; Streptozotocin***

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INTRODUCTION

Many herbal plants contain antidiabetic compounds or exhibit hypoglycemic activity, which can effectively lower blood glucose levels (Firdausya et al., 2019). One such herbal plant possessing antidiabetic compounds is binahong leaf (*Anredera cordifolia* (Ten.) Steenis), which is known to contain flavonoids, oleanolic acid, protein, saponins, and ascorbic acid (Suhadi et al., 2019). Binahong's ability to treat various diseases is attributed to the active compounds it contains. All parts of the binahong plant, including its roots, stems, and leaves, are known to possess medicinal properties that have been validated through various laboratory studies. Specifically, ethanol extract of binahong leaves has been demonstrated to reduce blood creatinine and urea levels, and to facilitate the repair of damaged kidney cells.

Several studies in animal models have shown that binahong plant extract can help control and lower blood glucose levels. Research conducted by Rissa et al. (2022) reported that the ethanol extract of binahong leaves demonstrated the best ability to reduce blood glucose at a dose of 35 mg/KgBW. Furthermore, various studies evaluating ethanol extract for reducing blood glucose in male Wistar rats, such as that by Rollando et al. (2022), have indicated that binahong leaf ethanol extract is capable of lowering blood glucose levels in test animals.

Another herbal plant with antidiabetic activity is orange peel. Tangerine peel (*Citrus* nobilis L. or *Citrus reticulata* L.) has been shown to contain high concentrations of flavonoids, including hesperidin, naringin, and narirutin (Alaa M. Ali et al., 2020). Taxonomically, tangerines belong to the division Spermatophyta, class Dicotyledonae, order Rutales, family Rutaceae, genus *Citrus*, and species *Citrus reticulata* L. (Dari, A.W et al., 2020). This plant is a local citrus fruit widely cultivated in Indonesia. Beyond its antibacterial properties, tangerine peel is also rich in vitamin C and various secondary metabolites such as alkaloids, flavonoids, saponins, tannins, phenols, and terpenoids (Dari, A.W et al., 2020). Previous research indicates that orange peel contains hesperidin, a compound proven to reduce intestinal glucose absorption and inhibit gluconeogenic pathways, thus making it a potential antidiabetic agent in humans (R. P. Constantin et al., 2014; H. Parhiz et al., 2015). Tangerine peel possesses a distinctive and appealing aroma, making it highly promising for development into herbal medicinal preparations, such as teabags (Qomariah Kulsum U and Wulandari A, 2020). While oranges are commonly consumed directly or as juice, their peels are often discarded as waste, despite containing a higher concentration of vitamin C (136 mg per 100 g) compared to the fruit pulp (71 mg) (Elfariyanti et al., 2022).

Flavonoid yang ditemukan dalam kulit jeruk terbagi menjadi flavanon, flavonol, dan flavon (Alaa M. Ali et al, 2020). Penelitian lain menyebutkan kandungan konsentrasi tertinggi flavonoid dari kulit jeruk keprok adalah hesperidin, naringin dan narirutin (Alaa M. Ali et al, 2020). Kandungan flavonoid inilah yang memiliki aktivitas sebagai antidiabetes. Aktivitas flavonoid sebagai antidiabetes diduga meregenerasi kerusakan sel beta pancreas dan merangsang sel beta pancreas untuk memproduksi insulin. Penelitian yang dilakukan oleh Ali dkk menyebutkan bahwa ekstrak hidroetanol kulit jeruk keprok (Citrus reticulata) memiliki aktivitas sebagai antidiabetes dan antihiperlipidemia lebih kuat daripada herperidin dan quercetin pada tikus diabetes yang diinduksi dengan Streptozotocin (Alaa M. Ali et al, 2020).

RESEARCH METHODOLOGY

This was an experimental study employing a pre- and post-test with a controlled group design. The study obtained ethical approval from the Research Ethics Committee of Ahmad Dahlan University (KEP UAD) with approval number 022408107, concerning the Use of Experimental Animals as Research Subjects. Ethical approval is required before conducting research involving humans and animals to ensure

that the study is feasible and meets specific requirements, particularly when animal testing is involved, as in this research.

The equipment used in this study included containers, an oven, a powder grinder, 500 mL glass bottles, stirring rods, aluminum foil, beakers, a Soxhlet extractor, funnels, an analytical balance, filter paper, a 60-mesh sieve, a rotary evaporator, a water bath, a mortar, a pestle (or "stanfer" if it's a specific local term, otherwise "pestle"), a flow tester, a stopwatch, a tapped density tester, a jolting volumeter, and a disintegration tester. The materials used were fresh binahong leaves, tangerine peel, 96% ethanol, Streptozotocin, glibenclamide, and distilled water.

Plant Determination

The determination of binahong and tangerine plants was carried out at the Biology Laboratory, Universitas Ahmad Dahlan (UAD). Plant determination was conducted to confirm the authenticity of the plants used in the study, thereby preventing errors in sample collection. Ensuring the correct plant species is a prerequisite that must be fulfilled in research (Stevani and Rissa, 2024). Based on the results of this determination, it was confirmed that the plants used in this study were *Anredera cordifolia* (Ten.) Steenis and *Citrus reticulata*.

Extract Preparation

Fresh binahong leaves and tangerine peels were subjected to wet sorting to separate impurities and other unwanted materials from the plant parts. Subsequently, the leaves and peels were thoroughly washed with running water to remove any attached dirt or dust. The extraction method employed in this study was maceration. The ratio of dried binahong leaf powder to 96% ethanol solvent for this method was 1:5 (w/v). One thousand grams (1000 g) of the dried material were weighed and placed into a maceration vessel, followed by the addition of 5 L of 96% ethanol solvent. The mixture was then stirred using an electric stirrer for 2 hours. The maceration vessel was covered and left undisturbed for 3x24 hours (or 3 days), protected from light (Rahayuningsih et al., 2020). After 3 days, the mixture was filtered using filter paper. The resulting macerate was then concentrated and evaporated using a rotary evaporator at 60°C and 80 rpm until a thick extract was obtained (Tahar et al., 2019). The extract was further evaporated on a water bath at 60°C. Importantly, the extraction process avoided the use of high heat to prevent degradation of thermolabile flavonoid compounds (Riwanti et al., 2020).

Induction

After an adaptation period, the experimental rats were induced with diabetes using streptozotocin administered intraperitoneally. Streptozotocin is utilized for diabetes induction because it is a diabetogenic compound that functions by damaging pancreatic β-cells, thereby reducing insulin secretion from these cells and consequently increasing blood glucose levels. The streptozotocin dose employed for induction in this study was 45 mg/KgBW.

RESULTS

The thick extract obtained from binahong leaf extraction was dark green. This intense color is attributed to the solvent's absorption capacity; a higher concentration of compounds extracted during maceration results in a more concentrated color. Similarly, the tangerine peel extract was dark yellow or brownish-yellow. The yield of the thick binahong leaf extract was 50.2 grams, and the tangerine peel extract yield was 88.4 grams.

Table 1. Yield of Binahong Leaf Extract and Tangerine Peel Extract

Name of the raw material	Weight of the raw material	Extract weight	Percentage yield (%)	Indonesian Herbal Pharmacopoeia (%)
Binahong leaf	500 gram	50,2 gram	10,04	At least 7,2
Orange peel	1.016 gram	88,4 gram	8,70	

The thick extract of binahong leaves yielded 50.2 grams, with a percentage yield of 10.04%. The tangerine peel extract yielded 88.4 grams, with a percentage yield of 8.70%. The yields from both extracts met the requirements of the Indonesian Herbal Pharmacopoeia, which specifies a minimum yield of 7.2% (Depkes RI, 2010). The identification of binahong leaf and tangerine peel extracts involved organoleptic examination of the binahong leaf extract, assessing its form, color, and odor. The results of the binahong leaf extract identification are presented in Table 4.

Table 2. Results of Organoleptic Examination of Binahong Leaf Extract

Examination	Result	
	Binahong leaf	Orange peel
Smell	Characteristic smell	Characteristic smell
Shape	Thick	Thick
Color	Dark greenish-black	Orange-yellow to dark brown

The table above presents the results of the organoleptic examination of binahong leaf extract and tangerine peel extract. These characteristics indicate that binahong leaf extract contains bioactive compounds such as flavonoids, saponins, and tannins, which typically impart a dark color to the extract (Hasibuan et al., 2019). Furthermore, tangerine peel extract contains bioactive flavonoids and polyphenol compounds.

Evaluation of the Antidiabetic Effect of Binahong Leaf Ethanol Extract and Orange Peel Ethanol Extract

This study investigated the antidiabetic effects of binahong leaf ethanol extract at a dose of 24.5 mg/KgBW, tangerine peel ethanol extract at a dose of 150 mg/KgBW, and a 50:50 combination of both extracts. The combination consisted of 50% of the binahong leaf extract dose (12.25 mg/KgBW from a total of 24.5 mg/KgBW) and 50% of the tangerine peel extract dose (75 mg/KgBW from a total of 150 mg/KgBW). The testing was conducted using male rats as experimental animals. Male rats were chosen due to their faster drug metabolism and more stable biological conditions compared to female rats. An adaptation period of 7 days was implemented for the rats in the animal house. The purpose of this adaptation was to prevent stress and allow the rats to acclimate to their new living environment. During adaptation, the rats were provided with food and water, and their cages were cleaned every 2 days. The rats were weighed daily to monitor changes in their body weight throughout the experiment, which was crucial for determining the volume used for treatment administration. Rat body weight measurements were performed using a balance and expressed in grams.

A total of 25 male rats were used in this study, divided into 5 groups. Group I served as the negative control, administered with 0.5% CMC Na orally. The negative control group is defined as a group that shows no influence or effect on the test animals, serving as a comparative substance that yields no effect (Kartikawati et al., 2021). The comparative substance used in this study was 0.5% CMC Na, which

functioned as a suspending agent in the preparation of test substance suspensions, as the test substances used had limited solubility in distilled water.

Group II, the positive control group, received Glibenclamide at a dose of 0.65 mg/KgBW via oral administration. Glibenclamide, as a positive control, was used as a comparator to assess the effect of an established oral antidiabetic drug known to lower blood glucose levels. The dose of Glibenclamide used was based on the effective human oral dose of 5 mg/day, which was then converted to a rat dose (20 g), resulting in 0.45 mg/KgBW. Group III was administered binahong leaf extract at a dose of 24.5 mg/KgBW orally. Group IV received tangerine peel extract at a dose of 150 mg/KgBW orally. Lastly, Group V was given a 50:50 combination of binahong leaf extract and tangerine peel extract, specifically comprising 50% of the binahong leaf extract dose (12.25 mg/KgBW, derived from the total of 24.5 mg/KgBW) and 50% of the tangerine peel extract dose (75 mg/KgBW, derived from the total of 150 mg/KgBW).

Blood glucose levels were measured both before and after induction to monitor the increase in blood glucose following streptozotocin administration in rats. Blood glucose levels were determined by measuring fasting blood samples collected from the ocular venous plexus. Prior to each blood glucose measurement, rats were fasted for 8 hours, but access to water was maintained to prevent dehydration in the experimental animals (mice/rats – *please clarify consistency*). The purpose of fasting the rats was to ensure an empty digestive system, which would not interfere with drug absorption (Febrina et al., 2019). The blood glucose levels recorded by the device were then noted to observe the increase in blood glucose in the mice/rats after streptozotocin induction. A comparison of the average initial blood glucose levels and those after streptozotocin administration in the experimental animals can be observed, and data analysis performed accordingly.

Based on the research findings, the average blood glucose levels in each group of rats after treatment are presented. The diabetes mellitus (DM) group exhibited the highest blood glucose level, with an average of 268.29 ± 3.65 mg/dL, which was significantly different from all other treatment groups (indicated by letter b). The group treated with glibenclamide as a positive control showed a reduction in blood glucose levels to 111.29 ± 1.83 mg/dL (indicated by letter a, signifying a significant difference compared to the DM group). Treatment with binahong leaf extract (110.29 ± 3.24 mg/dL), tangerine peel extract (112.64 ± 1.51 mg/dL), and the combination of both extracts (98.64 ± 0.92 mg/dL) also demonstrated a significant reduction in blood glucose levels compared to the DM group. Notably, the combination of binahong and tangerine peel extracts produced the most substantial reduction in blood glucose levels. This difference was significant when compared to the DM group (a) and approached significance when compared to the positive control/glibenclamide group (ab). This suggests that the combination of both extracts possesses better potential in lowering blood glucose levels than the single administration of each extract.

Table 3. Average Blood Glucose Levels

Group	Mean Blood Glucose Levels (mg/dL)
Diabetes mellitus	268.29 ± 3.65^{b}
Glibenklamide (Positive control)	111.29 ± 1.83^{a}
Binahong extract	110.29 ± 3.24^{a}
Orange peel extract	112.64 ± 1.51^{a}
Combination of binahong and orange peel	98.64 ± 0.92^{ab}

a= Significantly different from the DM group
b= significantly different from the positive control group/glibenclamide

According to the International Diabetes Federation, hyperglycemia is defined as a fasting blood glucose level of ≥ 126 mg/dL. Based on Table 4, a decrease in fasting blood glucose levels was observed in groups II, III, IV, and V after treatment. Among these four groups, the combination of binahong and tangerine peel extracts at a dose of 12.25:75 mg/KgBW showed the greatest effectiveness in reducing rat blood glucose levels, reaching 98.64 mg/dL, which was significantly lower than the diabetic (DM) group (Group I) and the positive control group (Group II). This was followed by Group III (binahong extract) at 110.29 mg/dL, Group II (positive control) at 111.29 mg/dL, and Group IV (tangerine peel extract) at 112.64 mg/dL.

Research conducted by Stevani and Rissa (2024) demonstrated a reduction in blood glucose levels in mice after administration of binahong leaf extract at a dose of 17.5 mg/KgBW. Binahong leaves contain flavonoid compounds that act as inhibitors of α-glucosidase, maltase, and α-amylase enzymes, which can increase insulin secretion, thereby capable of lowering blood glucose levels. Ethanol extract of orange peel also possesses the potential to reduce blood glucose levels through the inhibition of α-glucosidase and α-amylase in rats, as compared to the positive control/Acarbose (Ghauri et al., 2021).

Table 4. Comparison of Blood Glucose Reduction by Treatment Effects

Group	Mean Blood Glucose Levels (mg/dL)		
	H0	H1	H2
Diabetes Mellitus (Negative Control)	68.41 ± 1.05[b]	267.23 ± 3.56[a]	268.29 ± 3.65[ba]
Glibenclamide (Positive Control)	67.33 ± 1.67[b]	267.80 ± 3.643[a]	111.29 ± 1.83 [a b]
Binahong Extract	67.40 ± 3.96 [b]	265.00 ± 3.569 [a]	110.29 ± 3.24 [a b]
Orange Peel Extract	68.79 ± 1.404 [b]	268.11 ± 5.24 [a]	112.64 ± 1.51 [a b]
Combination of Binahong and Orange Peel Extracts	69.45 ± 1.691 [b]	269.55 ± 2.218 [a]	98.64 ± 0.92 [a b]

Keterangan : H1 = Glucose Level
a= Significant difference compared to H0 ($p < 0.05$)
b= Significant difference compared to H1

Based on Table 4, observations at H0 and H1 revealed a significant increase in blood glucose levels across all groups after streptozotocin induction, indicating that the rats had developed a diabetic condition. The normal blood glucose range for rats is 50-135 mg/dL (Nangoy, Queljoe, & Yudistira, 2019), and all groups exhibited blood glucose levels above 135 mg/dL, consistent with hyperglycemia. Streptozotocin is a free radical that causes necrosis of pancreatic beta cells and inhibits insulin production, making it widely used for inducing diabetes mellitus in experimental animals (Nugraha & Hasanah, A. N, 2018). In this study, the streptozotocin dose administered was 45 mg/kgBW. Previous studies have indicated that streptozotocin doses of 40-55 mg/kgBW can cause partial insulin secretion impairment, leading to a Type 2 Diabetes mellitus-like condition (Husna, Suyatna, F. D, Arozal, W, & Purwaningsih, E. H, 2019). Streptozotocin induction can cause damage to pancreatic beta cells within 2-4 days (Putri, 2017).

Subsequently, observations at H2 showed a significant decrease in blood glucose levels compared to H1 in the positive control, binahong extract, tangerine peel extract, and combination (binahong-tangerine peel extract) groups. Their respective levels were 111.29 ± 1.83 mg/dL, 110.29 ± 3.24 mg/dL, 112.64 ± 1.51 mg/dL, and 98.64 ± 0.92 mg/dL, which had reached normal blood glucose levels. Only the negative control group did not experience a reduction in blood glucose levels (268.29 ± 3.65 mg/dL) and remained in a hyperglycemic state. These results indicate that the positive control group (glibenclamide), binahong

extract, tangerine peel extract, and the combination extract are capable of lowering blood glucose levels in diabetic conditions. The most substantial reduction occurred in the binahong-tangerine peel extract combination group.

This enhanced effect is attributed to the antioxidant properties of compounds present in both binahong and tangerine peel extracts. Binahong extract contains several compounds with antidiabetic activity, including Boussingoside A, saponins, and flavonoids such as 8-glucosylapigenin (orientoside) and vitexin (K, Krisanti E, & Muhammad F, 2017). Flavonoids are known to stimulate insulin secretion and regenerate damaged pancreatic beta cells (Rahmawati, Fachriyah E, & Kusrini D, 2013). Meanwhile, the antidiabetic mechanism of saponins involves inhibiting the alpha-glucosidase enzyme. Alpha-glucosidase plays a role in converting carbohydrates into glucose; therefore, inhibiting this enzyme can reduce blood sugar levels (MA, 2018). Furthermore, tangerine peel contains flavonoids like naringin, which has antidiabetic effects (Shwaish, Farhan, & Mohammed, 2022). Consequently, the combination of both extracts provides a more optimal effect.

CONCLUSION

Binahong leaf extract (24.5 mg/KgBW) and tangerine peel extract (150 mg/KgBW) showed yields within standard ranges and contain active compounds such as flavonoids and saponins. Both extracts were effective in reducing blood glucose levels in rats. The combination of these two extracts at respective doses of 12.25 mg/KgBW and 75 mg/KgBW (50:50 ratio) proved to be the most effective in lowering blood glucose levels in diabetic rats, surpassing the effects of individual extracts and glibenclamide. This observed effect is supported by proposed mechanisms including increased insulin secretion, regeneration of pancreatic beta cells, and inhibition of carbohydrate-digesting enzymes. This combination holds potential as a herbal therapy for type 2 diabetes mellitus.

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