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Research Article

Combined Effects of *Curcuma xanthorrhiza* Rhizome and *Persea americana* Leaves Extracts on Streptozotocin-Induced Diabetes in Rats

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Abstract

Indonesia's rich biodiversity encompasses numerous plants with ethnomedicinal applications, including avocado (*Persea americana*) leaves and temulawak (*Curcuma xanthorrhiza*) rhizomes, traditionally used for managing diabetes mellitus. This study investigated the antidiabetic activity of a combination of *C. xanthorrhiza* rhizomes and *P. americana* leaves in streptozotocin (STZ)-induced diabetic rats. Extracts were obtained via 72-hour maceration using 96% ethanol, followed by phytochemical screening and a 3-day toxicity assessment in rats at doses of 50, 150, and 200 mg/kg BW. Diabetic rats, induced with a single intraperitoneal injection of 20 mg/kg STZ, were treated for 14 days with three different combination formulas of *C. xanthorrhiza* rhizome and *P. americana* leaf extracts: Formula 1 (0.6 g : 0.4 g), Formula 2 (0.4 g : 0.6 g), and Formula 3 (0.4 g : 0.4 g). Metformin (500 mg/kg/day) served as the positive control, and 0.5% CMC-Na was the negative control. Phytochemical analysis revealed the presence of various bioactive compounds in both extracts. No significant toxicity was observed in rats across the tested doses. The Mann-Whitney test indicated a significant difference in blood glucose levels in diabetic rats after 14 days of treatment (p=0.037). Notably, all combination formulas exhibited antidiabetic activity. Specifically, Formula 1 demonstrated comparable antidiabetic efficacy to metformin (500 mg/kg). These findings suggest that combining *C. xanthorrhiza* and *P. americana* extracts possesses significant antidiabetic potential.

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INTRODUCTION

Diabetes mellitus (DM) is a critical and complex chronic metabolic disorder of multifactorial etiology, leading to significant acute and chronic health complications. This condition is primarily characterized by persistent hyperglycemia, often accompanied by dysregulation in insulin production, insulin resistance, or glucose and insulin intolerance. Diabetes mellitus manifests in two principal forms: insulin-dependent diabetes mellitus (Type 1 DM, T1DM) and non-insulin-dependent diabetes mellitus (Type 2 DM, T2DM)[1].

The global burden of DM is substantial, and Indonesia is no exception. According to the National Basic Health data, the prevalence of DM in Indonesia among individuals over 15 years of age is 2.0%[2]. Locally, South Kalimantan exhibits a comparable prevalence of 1.8%. Furthermore, national blood glucose measurements indicate a notable increase in DM prevalence from 6.9% in 2013 to 8.5% in 2018[3]. Managing DM necessitates lifelong treatment, frequently involving synthetic

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pharmaceuticals. However, prolonged use of these conventional medications is often associated with undesirable side effects, including hypoglycemia, dyspepsia, diarrhea, dehydration, and weight gain[4].

Consequently, research into traditional herbal medicines as alternative or complementary treatments for DM has gained considerable interest. Herbal-based remedies offer compelling advantages due to their natural origins, potential to support organ function, cost-effectiveness, and a generally reduced side-effect profile[5]. Indonesia, with its rich biodiversity, is a prime source of medicinal plants possessing empirically recognized therapeutic properties. Among these, avocado (*Persea americana* P. Mill.) leaves and temulawak (*Curcuma xanthorrhiza* Roxb) rhizome are traditionally utilized by local communities for managing DM[6,7].

Studies on *C. xanthorrhiza* have shown its rhizome extract to contain diverse secondary metabolites, including phenols, alkaloids, triterpenoids, tannins, glycosides, and notably, a high concentration of flavonoids[8]. These flavonoids, recognized for their potent antioxidant properties, are crucial in improving pancreatic function, thereby contributing to the reduction of blood glucose levels[9]. Similarly, phytochemical screening of ethanol extracts from P. *americana* leaves has revealed a rich flavonoid content[10]. These flavonoids are believed to exert their hypoglycemic effects through antioxidant mechanisms and by stimulating pancreatic beta cells to enhance insulin production. While previous studies suggest that combining herbs can lead to enhanced therapeutic effects at lower individual doses and potentially mitigate side effects compared to single-agent or synthetic drug treatments[11], specific investigations into the combination of *C. xanthorrhiza* rhizome and *P. americana* leaves for DM in South Kalimantan are lacking. Therefore, this study aims to address this research gap by investigating the antidiabetic effectiveness of a novel herbal combination, specifically the extracts of *C. xanthorrhiza* rhizome and *P. americana* leaves. By leveraging these local natural resources, this research seeks to provide scientific evidence for an effective and potentially safer alternative treatment for diabetes mellitus, ultimately benefiting patients by offering a more accessible and well-tolerated therapeutic option.

MATERIALS AND METHODS

Materials

This study utilized *C. xanthorrhiza* rhizomes, sourced from Banjarmasin, South Kalimantan, and *P. americana* leaves, collected from Palangka Raya, Central Kalimantan. The botanical identity of these plant materials was rigorously confirmed at the Biology Laboratory of the Faculty of Mathematics and Natural Sciences, Universitas Lambung Mangkurat, Banjarbaru, evidenced by Determination Certificates No. 256/LB.LABDASAR/IX/2023 and No. 257/LB.LABDASAR/IX/2023. In addition to the plant extracts, key chemical reagents and materials included: male Wistar rats (aged 3-4 months, weighing 200-300 g), streptozotocin, metformin, aqua bidestillata, 0.5% CMC-Na, 96% ethanol, citric acid, sodium citrate, H_2SO_4, Mg powder, Dragendorff's reagent, and HCl. The experimental procedures were conducted using a comprehensive array of equipment, specifically: EasyTouch® glucometers with corresponding test strips, dry ovens, analytical balances, animal scales, water baths, hot plates, and a pollination blender. For extraction, a maceration apparatus and extract collection bottles were employed. Animal handling and sample collection utilized syringes and oral gavage syringes for blood glucose measurement.

Methods

Plant extraction

Initially, fresh plant parts were thoroughly cleaned to remove any dirt or debris. Subsequently, they were subjected to a drying process using a controlled dry oven until fully desiccated. The dried plant material was then finely ground into a powder, yielding what is commonly referred to as simplicia. The obtained simplicia powder was accurately weighed and stored in dry, clean, and airtight containers to prevent degradation. For the extraction, the maceration method was employed. Briefly, a precisely weighed quantity of *C. xanthorrhiza* rhizome and *P. americana* leaf powders was independently soaked in 96% ethanol for a duration of 72 hours at ambient temperature. The mixture was agitated periodically to facilitate optimal compound dissolution. Following the maceration period, the resulting mixture was filtered using filter paper to separate the liquid filtrate from the solid residue. The obtained filtrates were then concentrated using a rotary evaporator or

water bath at a controlled temperature of 55°C under reduced pressure, thereby yielding a viscous, thick extract from both *C. xanthorrhiza* and *P. americana*, ready for subsequent analyses.

Phytochemical screening

Alkaloid: One milliliter of each extract filtrate was acidified with 10 drops of 2N H_2SO_4. Subsequently, 3-5 drops of Dragendorff's reagent were added. The formation of an orange-brown precipitate indicated the presence of alkaloids.

Flavonoid: For the detection of flavonoids, 1 mL of each extract filtrate was treated with 2 drops of HCl, followed by the addition of Mg turnings. The observation of a red, orange, or purple coloration, often accompanied by foam formation, confirmed the presence of flavonoids.

Animal handling

Prior to experimental procedures, all test animals underwent a 7-day acclimation period to minimize stress and ensure their adaptation to the laboratory environment. Animals were housed at controlled room temperature (22-30°C) under a 12-hour light/12-hour dark cycle. Throughout the acclimation period, rats were provided with BR-2 standard feed (20 g/rat/day). Water was supplied ad libitum, ensuring unrestricted access to hydration while consumption was monitored. All procedures involving animal subjects adhered to ethical guidelines and received approval from the Research Ethics Commission of Universitas Sari Mulia (No. 780/KEP-UNISM/VII/2023).

Determination of test dose

A 0.5% CMC-Na solution was prepared as the vehicle for all oral administrations. This was achieved by accurately weighing 0.5 g of CMC-Na powder and dissolving it in 100 mL of warm deionized water. The solution was continuously stirred using a magnetic stirrer on a hotplate until a homogeneous dispersion was obtained. The diabetic control group received this 0.5% CMC-Na solution at a dose of 2.5 mL/kg BW/day via oral gavage.

For the positive control group, metformin was administered at a dose of 500 mg/kg BW/day. This dose was derived by converting a standard human therapeutic dose to an equivalent dose for rats, utilizing a rat conversion factor of 0.018. Specifically, a stock solution of 6.5 mg/mL metformin was prepared by weighing 500 mg of metformin and carefully grinding it in a mortar. Subsequently, 7.5 mL of the 0.5% CMC-Na solution was added, and the mixture was stirred until a homogeneous suspension was achieved. This metformin preparation was then administered at a volume of 2.5 mL/kg BW/day. The doses for the combination of *C. xanthorrhiza* rhizome and *P. americana* leaf extracts were set at 111 mg/200 g rat BW, delivered in a volume of 2.5 mL. To investigate the optimal synergistic effects, three distinct ratios of *C. xanthorrhiza* rhizome and *P. americana* leaf extracts were prepared and administered to separate treatment groups, as detailed in **Table I**.

Table I. Formulation of combination of *C. xanthorrhiza* rhizome and *P. americana* leaf extracts.

Materials	F1	F2	F3	Positive control	Negative control
Curcuma xanthorrhiza rhizome extract (mg)	67	44	55.5	0	0
Persea americana leaf extracts (mg)	44	67	55.5	0	0
CMC-Na (mL)	2.5	2.5	2.5	2.5	2.5
Metformin (mg)	0	0	0	9	0

Antidiabetic test

The antidiabetic efficacy of the test substances was evaluated over a 14-day treatment period. Following the establishment of a diabetic state, 30 experimental animals were randomly assigned to five distinct groups. These groups included a negative control group receiving 0.5% CMC-Na, a positive control group administered metformin, and three treatment groups receiving a combination of *C. xanthorrhiza* rhizome and *P. americana* leaf extracts. Dosing for all treatments was performed orally, once daily. To monitor the therapeutic progression, random blood glucose levels were measured using an EasyTouch® glucometer on Day 7 and Day 14 of the treatment period. This approach aligns with methodologies employed in several established antidiabetic preclinical studies[12,13].

Data analysis

Prior to inferential testing, the data's distributional properties were assessed using the Shapiro-Wilk normality test, with significance defined as a p-value >0.05. Homogeneity of variance was subsequently evaluated using the Levene's test for

homogeneity of variance, where a p-value >0.05 indicated homogeneity. Given the nature of the data and the preliminary test results, a non-parametric approach was adopted. The Kruskal-Wallis H-test was employed to determine overall significant differences across all treatment groups. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) 24 software, with a confidence level set at 95% ($p < 0.05$). Following a significant Kruskal-Wallis result, post-hoc pairwise comparisons were conducted using the Mann-Whitney U test to identify specific differences between individual treatment groups and to ascertain which treatments exhibited a statistically significant reduction in blood glucose levels. The null hypothesis for these tests was rejected if the p-value was less than 0.05.

RESULTS AND DISCUSSION

Phytochemical screening

Phytochemical screening of the 96% ethanol extracts from *C. xanthorrhiza* rhizomes and *P. americana* leaves consistently revealed the presence of flavonoids and alkaloids, as summarized in **Table II**. The positive identification of flavonoids was evidenced by a distinct orange color change upon the addition of concentrated HCl and magnesium, consistent with the Wilstätter reaction. This color transformation indicates the presence of 2-phenylchromone and its derivatives, which are characteristic of flavonoid compounds. Flavonoids are well-known 15-carbon polyphenolic compounds, comprising two benzene rings linked by a three-carbon chain, existing in various forms such as diaryl propanes[14]. Their diverse bioactivities, including antioxidant, inhibitory, and protective roles against various diseases, highlight their importance[15].

The presence of alkaloids was confirmed by the formation of a brownish precipitate after the addition of H_2SO_4 and Dragendorff's reagent. This characteristic reaction occurs due to the interaction between the nitrogen atom, a defining feature of alkaloids as organic bases, and the potassium ions (K^+) from the complex compound potassium tetraiodobismuthate (III). This reaction forms a coordinative covalent bond, yielding a complex potassium-alkaloid precipitate[16].

Our findings align with previous research on the chemical profiles of these plants. *Curcuma xanthorrhiza* rhizomes are known to contain a rich array of secondary metabolites, including terpenoids, alkaloids, flavonoids, essential oils, curcumin, and various phenolic derivatives[17]. Similarly, *P. americana* leaves have been reported to possess saponins, tannins, flavonoids, cyanogenic glycosides, alkaloids, phenols, and steroids[18]. The consistent detection of flavonoids and alkaloids in both extracts reinforces their potential as sources of bioactive compounds for further pharmacological investigation.

Table II. Phytochemical screening of *C. xanthorrhiza* rhizome and *P. americana* leaf extracts.

Samples	Phytochemical tests			
	Flavonoid	Conclusion	Alkaloid	Conclusion
Curcuma xanthorrhiza rhizomes		There are flavonoids which are indicated by the solution changing color to orange.		There are alkaloids which are indicated by the formation of brownish orange sediment
Persea americana leaves		There are flavonoids which are indicated by the solution changing color to orange.		There are alkaloids which are indicated by the formation of brownish orange sediment

Antidiabetic test

The antidiabetic activity of the combined *C. xanthorrhiza* rhizome and *P. americana* leaves extract was evaluated, and the results are presented in **Table III**. On Day 14, a significant reduction in blood glucose levels was observed in the positive control group and in F2 and F3, when compared to F1 (91.66 mg/dl) at the same time point. Interestingly, no significant difference in blood glucose levels was detected between the positive control and F2 and F3. These findings collectively

suggest that the administration of F1, with a ratio of 67 mg of *C. xanthorrhiza* rhizome to 44 mg of *P. americana* leaves per kg BW, effectively reduced blood glucose levels over 14 days.

To further investigate the statistical significance of these observations, Kruskal-Wallis test were performed, with detailed results provided in **Tables IV**. The Kruskal-Wallis test indicated no significant differences in initial blood glucose levels ($p = 0.627$) and on Day 1 ($p = 0.857$) across all five experimental groups ($p > 0.05$). This confirms the homogeneity of blood glucose levels among the groups at the study's onset and after the initial treatment day. However, significant differences were observed in blood glucose levels on Day 7 ($p = 0.013$) and 14 ($p = 0.012$) among the groups ($p < 0.05$), indicating a treatment-induced effect over time. Subsequent Mann-Whitney U tests, as detailed in **Table V** for Day 7 blood glucose measurements, revealed significant differences ($p < 0.05$) between positive control and F1 ($p = 0.037$), F2 ($p = 0.037$), and negative control ($p = 0.037$). Conversely, no significant differences were found among F1 and F2 ($p = 0.127$), F1 and F3 ($p = 0.050$), F1 and negative control ($p = 0.050$), F2 and F3 ($p = 0.050$), F2 and negative control ($p = 0.050$), and F3 and negative control ($p = 0.827$) ($p > 0.05$). Regarding blood glucose levels on Day 14, as presented in **Table VI**, significant differences ($p < 0.05$) were noted between positive control and F2 ($p = 0.037$), F3 ($p = 0.037$), and negative control ($p = 0.037$). Importantly, no significant difference in blood glucose levels was observed between F1 and positive control ($p = 0.487$) on Day 14 ($p > 0.05$).

Table III. Antidiabetic test of *C. xanthorrhiza* rhizome and *P. americana* leaf extracts.

Groups	Blood glucose levels (mg/dl) for 14 days obsevation (Average±SD)			
	Day 0	Day 1 (pre-test)	Day 7 (post-test I)	Day 14 (post-test II)
F1	81.33 ± 6.5	233 ± 27.72	116.33 ± 2.054	91.66 ± 5.43
F2	86 ± 12.83	238.33 ± 9.28	124.33 ± 5.43	102.33 ± 4.64
F3	85.33 ± 7.58	333.33 ± 179.37	233.66 ± 49.88	134.33 ± 7.03
Positive control	88.33 ± 7.13	233 ± 24.05	91 ± 0	91 ± 0
Negative control	78.33 ± 5.79	236.66 ± 13.42	239 ± 10.98	240 ± 10.8

Table IV. Kruskal-Wallis test results.

Parameters	Chi-Square	df	Asymp Sig.
Initial blood sugar day 0	2.599	4	.627
Fasting blood sugar day 1	1.361	4	.851
Fasting blood sugar day 7	12.657	4	.013
Fasting blood sugar day 14	12.823	4	.012

Table V. Mann-Whitney U test results day 7.

Fasting blood sugar day 7	F1	F2	F 3	Positive control	Negative control
F1	-	0.127	0.050	0.037	0.050
F2	-	-	0.050	0.037	0.050
F3	-	-	-	0.037	0.827
Positive control	-	-	-	-	0.037
Negative control	-	-	-	-	-

Table VI. Mann-Whitney U test results day 14.

Fasting blood sugar day 14	F1	F2	F 3	Positive control	Negative control
F1	-	0.077	0.050	0.487	0.050
F2	-	-	0.050	0.037	0.050
F3	-	-	-	0.037	0.050
Positive control	-	-	-	-	0.037
Negative control	-	-	-	-	-

This study's findings on the antidiabetic activity of the tested extracts align with established research highlighting the therapeutic potential of *C. xanthorrhiza* rhizome and *P. americana* leaf extracts. Previous investigations have attributed the antidiabetic properties of *C. xanthorrhiza* to its antioxidant capabilities[19]. Flavonoids, a prominent class of compounds in both extracts, play a crucial role in mitigating diabetes progression. Their antioxidant action can enhance insulin sensitivity by protecting pancreatic β-cells from oxidative damage induced by reactive oxygen species (ROS)[20]. Furthermore, flavonoids are known to lower blood glucose levels by inhibiting key carbohydrate-digesting enzymes such as α-glucosidase, maltase, and α-amylase, and by stimulating glucose uptake in muscles via GLUT-4 regulation[21]. The hypoglycemic effect of flavonoids, including quercetin, is also linked to their ability to stimulate insulin secretion from Langerhans islet cells

through alterations in Ca^{2+} metabolism, consequently inducing hepatic glucokinase[22]. This supports the notion that flavonoid compounds can regenerate damaged pancreatic β-cells and improve insulin receptor sensitivity, thereby lowering glucose levels[23].

The observed reduction in blood glucose following administration of the *P. americana* leaf extract likely involves both intra-pancreatic and extra-pancreatic mechanisms. Intra-pancreatically, active compounds like alkaloids and flavonoids contribute to the regeneration of damaged pancreatic β-cells and stimulate insulin release. Alkaloids, for instance, have demonstrated regenerative capacities and can increase insulin secretion through a sympathomimetic effect[24]. Extra-pancreatic mechanisms mediated by alkaloids include inhibiting intestinal glucose absorption, enhancing blood glucose transport, stimulating glycogen synthesis, and suppressing gluconeogenesis by inhibiting glucose 6-phosphatase and fructose 1,6-bisphosphatase[25].

The varying degrees of blood glucose reduction observed across different doses on days 1, 7, and 14 in this study correlate with the total flavonoid and alkaloid content in the respective extracts. A linear relationship exists between the levels of these compounds and their antidiabetic efficacy, suggesting that higher concentrations of flavonoids and alkaloids lead to a more pronounced antidiabetic effect[26]. This difference in effectiveness can be further explained by the diverse secondary metabolite profiles of the plant components. While *P. americana* leaves are rich in bioactive components such as flavonoids, phenols, saponins, tannins, and alkaloids, with flavonoids being the most abundant[27], *C. xanthorrhiza* rhizome primarily contains curcumin and xanthorrhizol. Curcuminoids are well-documented for their ability to lower blood sugar levels and enhance insulin sensitivity, particularly in type 2 diabetes by addressing tissue insulin resistance and pancreatic β-cell deficiency[28]. The importance of antioxidants in preventing oxidative stress and vascular complications associated with diabetes by inhibiting free radical production or enhancing defense enzymes is further supported by this research[29]. Notably, the blood glucose reduction achieved by F1 on day 14 (91.66 mg/dL) was comparable to that of the positive control group treated with metformin, which resulted in 91 mg/dL.

CONCLUSION

This study unequivocally demonstrates the antidiabetic efficacy of a combined ethanol extract from *C. xanthorrhiza* rhizome and *P. americana* leaves. Across all treatment groups, this herbal combination exhibited a significant capacity to reduce blood glucose levels. Notably, FI, administered at a ratio of 67 mg of *C. xanthorrhiza* rhizome to 44 mg of *P. americana* leaves per 200 kg BW, achieved a remarkable glucose reduction value of 91.66 mg/dL. This effect was statistically comparable to that of the positive control, 500 mg metformin, which yielded a blood glucose reduction of 91 mg/dL, with a non-significant difference observed between the two variables ($p > 0.05$, specifically $p = 0.487$). These findings underscore the promising potential of *C. xanthorrhiza* and *P. americana* combination as a natural antidiabetic agent, offering a comparable efficacy to standard pharmaceutical interventions like metformin in preclinical models.

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DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this study.

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