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Antihyperglycemic Activity of Hydro-ethanolic Extract of *Anamirta cocculus* against Glucose-Induced Hyperglycemia in Rats

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ABSTRACT

Anamirta cocculus, an endemic plant of Papua, Indonesia, has long been used empirically by indigenous Papuan communities to manage various health problems, including diabetes mellitus. This study aimed to evaluate the antihyperglycemic activity of the hydroethanolic extract of *Anamirta cocculus* stem in glucose-induced hyperglycemic rats. A total of twenty-five rats were divided into five groups, each consisting of five animals. Group I served as the control (5% CMC-Na, 5 mL/kg, p.o.), Group II received glibenclamide (0.45 mg/kg, p.o.), while Groups III, IV, and V were treated with Anamirta cocculus extract at doses of 20, 40, and 80 mg/kg (p.o.), respectively. All animals were fasted for 12 hours before the experiment. Hyperglycemia was induced by administering oral glucose at 3 g/kg body weight, and treatments were given immediately after induction. All interventions were administered as a single oral dose. Blood samples were collected before treatment and at 30, 60, 90, 120, 150, and 180 minutes post-treatment via venipuncture to assess blood glucose levels using a glucometer. Bivariate analysis using the independent-samples t-test compared the control and intervention groups, while paired-samples t-tests evaluated pre- and post-treatment changes within each group. The glucose load produced a significant elevation in fasting blood glucose ($p < 0.05$), confirming hyperglycemia. The results demonstrated that *Anamirta cocculus* extract at 40 and 80 mg/kg exhibited significant antihyperglycemic effects ($p < 0.05$) comparable to glibenclamide. These findings suggest that *Anamirta cocculus* may offer potential benefits for diabetes management.

Keywords: Hyperglycemia, *Anamirta cocculus*, Antihyperglycemic, Fasting blood glucose

Introduction

The World Health Organization (WHO) reports that diabetes mellitus (DM) has become a serious threat to global health. Based on WHO's prediction, the number of patients with type 2 diabetes mellitus will increase from 171 million people in the year 2000 to 366 million in 2030. [1] Although diabetes mellitus is a non-communicable disease, it is often referred to as a silent killer because many people with diabetes do not know they have it. [2]

Data from the International Diabetes Federation (IDF) records that 537 million adults or 1 in 10 people, worldwide live with DM, and the disease caused 6.7 million deaths or 1 death every 5 seconds. The IDF also mentioned in 2021 that Indonesia ranks 5th globally with 19.47 million people living with DM, and the country's diabetes prevalence rate is 10.6 percent. [3] The use of antidiabetic drugs is increasing along with the rising prevalence of DM. The treatment pattern for DM involves the routine and long-term use of medication. [4] Synthetic oral medication still remain the best choice in terms of cost effectiveness. [5] These include biguanides (e.g., metformin), sulfonylureas (e.g., glibenclamide, glipizide), DPP-4 inhibitors (e.g., sitagliptin), SGLT-2 inhibitors (e.g., empagliflozin), and thiazolidinediones (e.g., pioglitazone), which work through various mechanisms to improve glycemic control. [6] The potential for side effects from the use of synthetic antidiabetic medications is also increasing. [7] The most frequent side effects include nausea, vomiting, bloating, fatigue, headache, and hypoglycemia. [8] Hypoglycemia is a particular concern, particularly in rural settings, where limited health literacy and restricted access to health services may reduce patients' awareness of this side effect. [9]

The issue of side effects poses a particular challenge in the healthcare sector, prompting the search for safe alternative antidiabetic drugs based on natural ingredients. The growing trend of using herbal-based antidiabetic treatments in developing countries has encouraged researchers to explore the hidden potential of plants found in nature, as these herbal alternatives tend to be safer and have a low risk of side effects. [10] The World Health Organization (WHO) encourages the use of traditional plant-based medicines to maintain public health, treat, and prevent chronic, degenerative diseases, and cancer. Indonesia is blessed with extraordinary natural wealth, possessing 30,000 plant species out of the 40,000 species found worldwide. Of this number, 9,600 plants have medicinal benefits. Approximately 300 species of plants in Indonesia have been utilized as raw materials for the *jamu* (traditional herbal medicine) and traditional medicine industries. This makes traditional medicine a popular choice for many Indonesian people. [11]

One of the regions that has abundant natural resources is the Papua region in Indonesia. The Papuan forests possess rich biological natural resources, including plants with medicinal properties. [12] Yellow rope plant or by its scientific name *Anamirta cocculus (A. cocculus)* is an endemic plant that has been empirically used by the Papuan people as medicine. [13] *A. cocculus* has a yellow stem, and is traditionally used by local residents throughout almost all regions of Papua to treat and prevent the symptoms of malaria. The practice of utilizing this herbal

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plant is a form of local wisdom that is deeply ingrained in the community. [14]

Although its direct traditional use for diabetes has not been documented, several phytochemical investigations have revealed that this species contains a rich profile of secondary metabolites with well-established antidiabetic mechanisms. *Anamirta cocculus* ontains the dominant bioactive compound berberine, an alkaloid with a concentration of about 12.04% of its dry material (powder) at 12% moisture content. This concentration is higher than that of the widely known berberine-producing plant, the bark of Amur corktree (*Phellodendron amurense*.R), which only has a berberine concentration of 8.17% of its dry weight at 8% moisture content. [15] Recent research also shows that the ethanol extract of *Anamirta cocculus* stems contains flavonoids, alkaloids, terpenoids, and tannins.[16,17] Ethanol extract of *Anamirta cocculus* stem, when tested in vitro using UV-Vis spectrophotometry, was shown to have excellent antioxidant activity. [18] These compound classes are widely reported to contribute to antihyperglycemic effects through mechanisms such as inhibition of α-glucosidase and α-amylase, enhancement of insulin sensitivity, protection of pancreatic β-cells from oxidative damage, and improvement of glucose uptake in peripheral tissues. [19] Additionally, UV–Vis spectrophotometry revealed that the ethanol extract of *A. cocculus* stem exhibits excellent antioxidant activity. Since oxidative stress plays a central role in the pathogenesis of diabetes mellitus—particularly in β-cell dysfunction and glucose homeostasis—plants exhibiting strong antioxidant capacity often demonstrate significant antidiabetic potential. [20] The antidiabetic pharmacological effect can originate from secondary metabolites such as polyphenols, tannins, flavonoids, and alkaloids. [21] This study aims to investigate the potential antidiabetic activity of the *Anamirta cocculus* extract in glucose-induced hyperglycemic rats.

Materials and Methods

The research was conducted from July to August 2025 at the Pharmacy Laboratory of Universitas Pendidikan Muhammadiyah Sorong, Papua in Indonesia.

Plant Collection and Identification

The stems of *Anamirta cocculus* were collected from the forest area of Misool Island, Raja Ampat Regency, Southwest Papua Province, Indonesia during the period of May 2025 – June 2025. Folley village (is at the coordinates): -1.7899350105285654º (Latitude), 130.3293199034863º (Longitude). dr. Ratna, Head of the Batu Herbal Materia Medica Laboratory, identified the original specimen of this plant with the determination letter number: 000.9.3/3864/102.20/2025

Experimental Animals

For seven days, 25 adult male Wistar rats (*Rattus novergicus*) weighing between 155 and 316 grammes were placed in cages with natural light to aid in their adjustment to the new surroundings. Male Wistar rats were obtained from Bandung, West Java, Indonesia, in healthy condition and certified as specific pathogen-free (SPF). The animals were accompanied by an official veterinary health certificate with registration number TN.01.01.011/3122-DKPP/IX/2025. During the acclimatization period, test animals were given standard feed with an adequate supply of clean water that changed periodically. The research obtained health research ethical clearance for animal subjects from The Research Ethics Committee of Sekolah Tinggi Ilmu Farmasi Makassar with ethical approval number: 09.176/KOMETIK/STIFA/IX/2025.

Preparation of Extracts

The *Anamirta cocculus* stems collected were dried using an oven at a temperature of 50ºC. The sample was powdered and 500 mg of the powdered simplicia was extracted via maceration using 2 L of 70% ethanol solvent with a ratio of 1:4. The mixture was allowed to stand for 3×24 hours in a sealed container, protected from direct light, then occasionally stirred and filtered. After the extraction process was complete, the extract was evaporated using a rotary evaporator at 50^0C until a thick extract was obtained. The percentage yield was calculated and recorded.

Antihyperglycemic testing

The rats were acclimated, then fasted for 12 hours before the experiment (withdrawal of just food). Following this, the rats' body weight was measured. Fasting blood glucose (basal) levels were measured for each rat. Blood was collected by clipping the tip of the rat's tail. [22,23] The blood obtained was placed on a test strip that was inserted into a glucometer (EasyTouch GCU® glucometer (Bioptik Technology Inc., Taiwan)) and left for a few seconds; the device automatically measured the blood glucose level. The number that appeared on the glucometer screen was recorded as the blood glucose level (mg/dL). [24]

A total of 25 rats were used in this study, where all rats experienced hyperglycemia due to oral glucose administration at a dose of 3 g/kgBW. [25] The 25 rats were divided into 5 groups, with each group consisting of 5 rats. Group I: Negative Control (5% CMC Na 5 mL/kg, oral (po)), Group II: Glibenclamide (0.45 mg/kg, oral (po)) [26,27], Group III: *Anamirta cocculus* (AC) (20 mg/kg, oral (po)), Group IV: *Anamirta cocculus* (AC) (40 mg/kg, oral (po)), Group V: *Anamirta cocculus* (AC) (80 mg/kg, oral (po)). The rats were administered glucose at a dose of 3 g/kgBW orally. They were then allowed to rest for 30 minutes, after which their fasting blood glucose levels were checked following the glucose administration. Subsequently, the oral preparations of the extract/drug were administered to the rats in a single dose. The negative control group received only 0.5% CMC Na. The positive control group received glibenclamide at a dose of 0.45 mg/kgBW. The *Anamirta cocculus* (AC) plant extract groups received the plant extract at doses of 20 mg/kgBW (AC20), 40 mg/kgBW (AC40), and 80 mg/kgBW (AC80). Fasting blood glucose levels were then checked at 30, 60, 90, 120, and 180 minutes after the rats were given the oral preparations. [24]

Statistical analysis

All research data were analyzed using the IBM SPSS version 25 for Windows program. The bivariate analysis used was the independent-samples t-test to compare data between the control group and the intervention groups, while the paired-samples t-test was used for statistical analysis to compare pre- and post-test data within each group. The results were then presented as mean ± SD. A p-value <0.05 was concluded to be statistically significant.

Results and Discussion

Induction of hyperglycemia in rats by administering glucose at a dose of 3 g/kgBW caused a significant increase in blood glucose levels ($p<0.001$). The mean data for fasting blood glucose level are presented in Table 2.

The result of the statistical analysis using the paired-samples t-test, which compared pre- and post-treatment data within each group, showed a significant decrease in blood glucose levels ($p<0.05$) in all test groups (Table 1).

The result of the statistical analysis using the independent-samples t-test, which compared Group II (glibenclamide 0,45 mg/kg), Group III (*Anamirta cocculus* (AC) 20 mg/kg, po), Group IV (*Anamirta cocculus* (AC) 40 mg/kg, po), and Group V (*Anamirta cocculus* (AC) 80 mg/kg, po) compared to Group I (negative control) in hyperglycemic induced in rats (Table 2), showed that at the 30th minute of blood glucose testing, a significant decrease ($p<0.05$) occurred in groups II, IV, and V. Testing at the 60th, 90th, 120th, 150th, and 180th minutes of testing, there was a significant decrease in blood glucose levels ($p<0.05$) in all treatment groups (Groups II, III, IV, and V).

The testing data comparing Group III (*Anamirta cocculus* (AC) treatment dose 20 mg/kg, po), Group IV (*Anamirta cocculus* (AC) 40 mg/kg, po), and Group V (*Anamirta cocculus* (AC) 80 mg/kg, po) with Group II (glibenclamide treatment dose 0,45 mg/kg, po) (Table 2) showed that at the 30, 60, 90, 120, 150, and 180 minute testing points, Group II was significantly ($p<0.05$) more effective in lowering fasting blood glucose levels compared to the other groups. Meanwhile, the testing at the 60th minute showed that Group IV was more effective ($p<0.05$) in lowering fasting blood glucose levels compared to Group III and Group V.

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Table 1: Effect of Glucose Administration on Fasting Blood Glucose Levels in Rats

Groups	Pre-Induction (mg/dl)	Post- Induction (mg/dl)	Δ (mg/dl)	P-Value
Group-I (Negatif control)	93.00 ± 11.97	208.40 ± 14.55	115.40 ± 17.34	< 0.001*
Group-II (Glibenclamide Treatment)	97.40 ± 9.39	199.80 ± 4.97	109.28 ± 16.12	< 0.001*
Group-III (AC 20 mg/kg Treatment)	91.60 ± 8.35	211.20 ± 19.76	119.60 ± 17.37	< 0.001*
Group-IV (AC 40 mg/kg Treatment)	98.60 ± 4.93	205.60 ± 25.59	107.00 ± 21.71	< 0.001*
Group-V (AC 80 mg/kg Treatment)	100.20 ± 9.91	202.20 ± 6.53	102.00 ± 8.91	< 0.001*

Values are expressed as Mean ± SD, **Δ**= Difference between pre-glucose administration and post- glucosa administration, *p<0.05 paired-samples t-test. AC = *Anamirta cocculus*

Table 2: Effect of *Anamirta cocculus* hydro-ethanolic Extract Administration on Blood Glucose Levels in Hyperglicemic-Induced Rats

Variable	Group-I (Negative control)	Group-II (Glibenclamide)	Group-III (AC 20mg/kg)	Group-IV (AC 40mg/kg)	Group-V (AC 80mg/kg)
Pre-treatment (mg/dl)	208.40 ± 14.55	199.80 ± 4.97	211.20 ±19.766	205.60±25.59	202.20±6.53
Post-treatment (mg/dl)					
At 30 Minutes	208.00±11.55	160.60±7.13*	183.40±7.12	183.80±14.30*	182.40±10.66*
At 60 Minutes	212.80±18.24	155.00±8.69*	174.20±5.26*	169.40±10.62*	170.20±7.53*
At 90 Minutes	204.60±6.50	148.40±7.16*	166.40±7.09*	158.80±10.25*	158.80±6.83*
At 120 Minutes	200.60±6.14	141.40±8.01*	158.20±6.66*	152.00±11.51*	150.00±6.51*
At 150 Minutes	206.80±9.85	132.60±6.22*	150.60±10.06*	141.40±11.71*	141.00±7.21*
At 180 Minutes	205.00±10.07	127.00±5.70*	144.80±11.563*	135.00±11.04*	130.40±6.73*
Δ (mg/dl)					
At 30 Minutes	0.40±7.79 [b**]	21.80±17.92 [a**]	27.80±24.75 [a**]	21.80±13.44 [a**]	19.80±5.06 [ab**]
At 60 Minutes	-4.40±10.64 [b**]	29.12±21.97 [a**]	37.00±23.74 [a**]	36.20±16.08 [a**]	32.00±3.53 [a**]
At 90 Minutes	3.80±9.78 [b**]	38.04±22.49 [a**]	44.80±26.24 [a**]	48.80±18.13 [a**]	43.40±3.36 [a**]
At 120 Minutes	7.80±10.37 [b**]	45.00±23.62 [a**]	53.00±26.22 [a**]	53.60±17.18 [a**]	52.20±3.27 [a**]
At 150 Minutes	1.60±8.23 [b**]	50.96±28.85 [a**]	60.60±28.55 [a**]	64.20±15.06 [a**]	61.20±4.54 [a**]
At 180 Minutes	3.40±8.4 [b**]	57.00±30.95 [a**]	66.40±29.76 [a**]	70.60±15.63 [a**]	71.80±4.49 [a**]

Values are expressed as Mean ±SD, n=5, **Δ**= Difference between pre-treatment and post-treatment, ∗p < 0.05 paired-samples t-test, ∗∗p < 0.05 independent-samples t-test. [a]vs. Negative control, [b]vs. Glibenclamide treatment. AC=*Anamirta cocculus*

The testing at the 90th minute showed that Group IV and V (*Anamirta cocculus* (AC) 40 and 80 mg/kg respectively) were more effective (p<0.05) in lowering fasting blood glucose compared to Group III (*Anamirta cocculus* (AC) 20 mg/kg, po). The testing at the 150th and 180th minutes showed that Group V (*Anamirta cocculus* (AC) treatment dose 80 mg/kg, po) was more effective (p<0.05) in lowering blood glucose levels compared to Group III and IV (*Anamirta cocculus* (AC) 20 and 40 mg/kg, po respectively).

In this study, the blood glucose levels after the administration of the *Anamirta cocculus* (AC) stem extract at doses of 20, 40, and 80 mg/kg, clearly showed that blood glucose levels decreased significantly (p<0.05) compared to the negative control group. However, among these three dose variations, only the 40 and 80 mg/kg doses, had an effectiveness comparable of glibenclamide (0,45 mg/kg, po). Therefore, it is assumed that *Anamirta cocculus* administered for the treatment of hyperglycemia in glucose-loaded hyperglycemic rats, may be improving blood glucose levels due to the presence of flavonoids and alkaloids.

Flavonoids are believed to have therapeutic potential in preventing and treating hyperglycemia or DM. Flavonoids possess favorable defense capabilities for the body by reducing lipid peroxidation, thereby preventing damage to body cells caused by free radicals and oxidative stress. [28] The flavonoids contained in the *A. cocculus* plant are thought to have a protective effect against *β*-cell damage, allowing for the regeneration of damaged pancreatic β-cells. Furthermore, they can increase insulin sensitivity and improve the function of insulin receptors. Another mechanism is the ability of flavonoids, particularly quercetin, to inhibit glucose absorption via the GLUT2 transporters in

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the intestinal mucosa, thereby decreasing glucose uptake. Flavonoids are also capable of inhibiting phosphodiesterase, which leads to an increase in (cyclic AMP) cAMP in the pancreatic *β*-cells. The rise in cAMP stimulates the release of protein kinase A (PAK), further enhancing insulin secretion. [29] As antidiabetics, flavonoids and alkaloids are capable of regenerating damaged pancreatic beta cells. The *A. cocculus* stem hydro-ethanolic extract can lower blood glucose levels in diabetic rats. Alkaloids work by stimulating the hypothalamus to increase the secretion of Growth Hormone Releasing Hormone (GHRH), thereby increasing the secretion of Growth Hormone (GH) in the pituitary gland. High levels of GH will stimulate the liver to release insulin-like growth factor-1 (IGF-1). IGF-1 influences the induction of hypoglycemia and reduces gluconeogenesis, thereby decreasing blood glucose levels and insulin requirement. IGF-1, through a negative feedback system, will then normalize GH levels. [30,31]

Conclusion

Oral administration of the *Anamirta cocculus* hydro-ethaanolic stem extract at doses of 40 and 80 mg/kg demonstrated significant anti-hyperglycemic activity in glucose-induced hyperglycemic rats. The reduction in fasting blood glucose level by *Anamirta cocculus* extract suggests the presence of bioactive component(s) with anti-hyperglycemic activity, which is useful for managing hyperglycemia. Consequently, *Anamirta cocculus* hydro-ethanolic extract exerts a beneficial effect against high blood glucose levels. Further research, involving the isolation of phytochemical compounds combined with *in vivo* antidiabetic evaluation, is necessary to elucidate the precise mechanism of the antihyperglycemic effect of the isolated compounds. Additionally, toxicity testing of *Anamirta cocculus* hydro-ethanolic extract should be performed.

Conflict of Interest

The authors declare no conflicts of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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