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Antidiabetic Activity of Cep-Cepan Leaf Extract Nanoparticles (*Castanopsis costata*) in Streptozotocin-Induced White Rat Models

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Abstract: The cep-cepan plant (*Castanopsis costata*) from the Fagaceae family is traditionally used by the Karo community in Medan, North Sumatra, to treat diabetes mellitus, although its efficacy has not yet been scientifically proven. This study aimed to evaluate the effectiveness of the antidiabetic activity of cep-cepan leaf extract nanoparticles (*Castanopsis costata*) in a streptozotocin-induced white rat model. A total of 25 male white rats were divided into five treatment groups: a positive control group, a negative control group, and three experimental groups treated with extract concentrations of 25, 75, and 150 mg/kg body weight, respectively. Plasma glucose levels were measured every 72 hours for 15 days using blood samples taken from the tail. Pancreatic tissue was then examined, and the data were analyzed using one way anova. The findings showed significant antidiabetic activity in all treatment groups, with $p < 0.001$. The nanoparticle extract of cep-cepan leaves exhibited the highest antidiabetic potential at a dosage of 150 mg/kg, reducing blood glucose levels by 59.39%. These results suggest that the nanoparticle extract of cep-cepan leaves demonstrates antidiabetic activity in the streptozotocin-induced white rat model, and it has the potential to be developed as an alternative treatment for diabetes mellitus.

Keywords: Cep-cepan; Extract; Nanoparticles; STZ; Type 2 DM

Introduction

Diabetes is a global health condition characterized by elevated blood sugar levels due to insulin dysfunction. This disease disrupts the body's metabolic processes and is one of the leading causes of premature death worldwide. It leads to a loss of glucose homeostasis and metabolic disorders involving carbohydrates, fats, and proteins (Famurewa et al., 2023; Tafesse et al., 2017). The International Diabetes Federation (IDF) states that elevated blood glucose levels are the third leading risk factor for premature death globally, following high blood pressure and tobacco use (Tafesse et al., 2017). Diabetes mellitus has emerged as a leading cause of disease and mortality worldwide, with cases projected to reach 642 million by 2040, predominantly in low- and middle-income countries (Ogurtsova et al., 2017). Currently, commonly used medications for diabetes treatment face several limitations, including reduced effectiveness, high costs, and various side effects (Zeru et al., 2021). A study by Piero et al. highlights over 1,200 species of medicinal plants used by ethnic groups worldwide as traditional treatments for diabetes (Piero et al., 2015). Indonesia boasts the second-largest forest biodiversity in the world, featuring approximately 28,000 plant species, of which 2,500 are used for medicinal purposes, including Castanopsis costata, commonly referred to as "Cep-cepan" (Alkandahri et al., 2019, 2021). *C. costata* belongs to the Fagaceae family and is recognized for its therapeutic activities, including antipyretic effects, digestive aid, and analgesic properties (Salim et al.,

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2017). Previous studies have shown that *C. costata* possesses various biological properties, including antioxidant activity, anti-inflammatory activity and antimalarial (Alkandahri et al., 2021).

In a streptozotocin-induced diabetic rat model, this work is the first to scientifically evaluate the antidiabetic potential of nano-formulated *Castanopsis costata* (Cep-Cepan) leaf extract, showing considerable blood glucose reduction (up to 59.39%) and pancreas regeneration. In contrast to earlier research, this study identifies flavonoids, alkaloids, tannins, and terpenoids as important bioactive substances that improve insulin sensitivity and inhibit α-glucosidase while also providing histological proof of beta-cell protection. Because of its increased bioavailability, the nano-formulation is a viable option for an all-natural, reasonably priced diabetes treatment. This study opens the door for new plant-based antidiabetic treatments by bridging the gap between contemporary nanotechnology and traditional herbal therapy (Furman, 2015).

In addition, this plant is frequently used in North Sumatra for diabetes treatment, although further research is lacking. Consequently, the researchers aim to investigate the antidiabetic activity of cep-cepan leaf extract nanoparticles (*Castanopsis costata*) in a streptozotocin-induced white rat model.

Diabetes is still a major worldwide health concern with rising prevalence and few effective treatment options that are sometimes expensive and associated with side effects, which makes this research crucial (Zhao et al., 2020). Although they have been used for generations, traditional herbal treatments such as *Castanopsis costata* (Cep-Cepan) leaves have not been scientifically validated. This study intends to improve the plant's bioavailability and therapeutic potential by creating a nano-formulated extract, offering a safe, efficient, and reasonably priced substitute for the treatment of diabetes. In order to help create safer and more easily accessible herbal-based diabetes treatments, the objective is to investigate its potential for pancreas regeneration, comprehend its mechanisms, and scientifically validate its antidiabetic effects.

Method

This study employs an experimental research design using a Post Test Only Control Group Design, conducted on white rats induced with streptozotocin at the Integrated Laboratory of Prima Indonesia University. The research flow is illustrated in Figure 1.

This study utilized materials including a 96% ethanol solution, cep-cepan leaves, filter paper, and a 70% alcohol solution. The research flow can be seen in Figure 1. Additionally, the study involved using materials such as alloxan monohydrate, distilled water, chitosan, sodium tripolyphosphate (NaTPP), metformin, and streptozotocin. The equipment used in this research included a rotary vacuum evaporator, blender, closed maceration device, extraction containers, stirring rods, separating funnels, beakers, scales, scissors, measuring cylinders, ovens, water baths, evaporating dishes, 16 mesh sieves, spatulas, pipettes, trays, mortars, and pestles, as well as animal cages, masks, and gloves (Ghasemi et al., 2023).

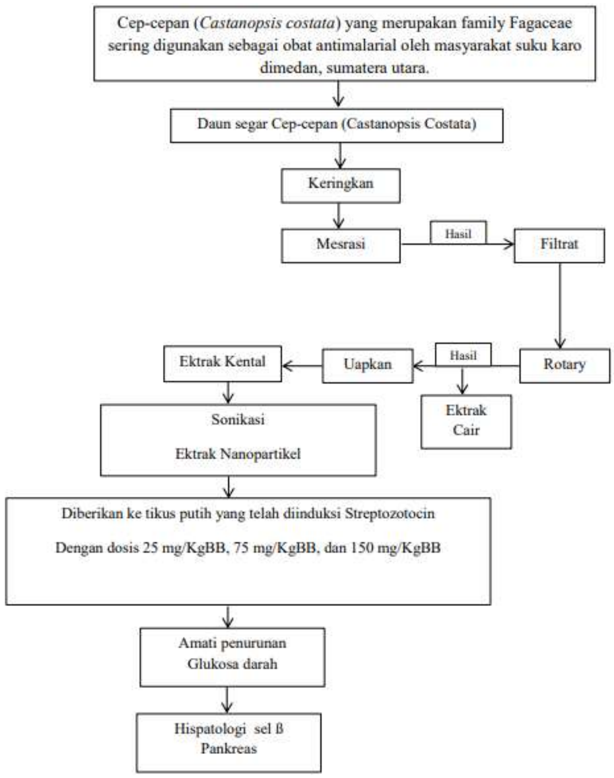

Figure 1. Research flow

The study commenced with the extraction process of cep-cepan leaves (*Castanopsis costata*). The extraction was performed using the maceration method, where 500 grams of dried plant powder, previously sieved through a 40 mesh sieve, were immersed in 5 liters of 96% ethanol. The soaking process was carried out in a closed container for 72 hours. After this period, the mixture was filtered to obtain the macerate, while the residue was subjected to maceration two additional times using the same procedure (Chiuman et al., 2023; Mutia et al., 2021).

All macerates from each filtration were collected in containers corresponding to the type of natural material being extracted. The macerate was then evaporated using a rotary vacuum evaporator at 45°C until no solvent condensation occurred in the condenser. After the rotary vacuum evaporation, the process continued with water bath evaporation at 70°C for approximately

12 hours to obtain a concentrated extract (Nasri et al., 2024; Sari et al., 2019). Following the concentration, phytochemical screening was conducted.

Simultaneously, 1 gram of cep-cepan leaf extract (*Castanopsis costata*) was weighed and dissolved in 35 ml of ethanol and 15 ml of distilled water. Chitosan of varying weights was dissolved in 100 ml of 1% glacial acetic acid. The ratio of the extract, chitosan, and NaTPP in the solution was set at (1:1:1). After the components were thoroughly mixed, stirring was continued using a magnetic stirrer for 2 hours. Particle size and zeta potential were measured using a Malvern particle size analyzer (UK) (Maulina, 2013; Tanessa et al., 2023).

Before treatment, all male Wistar rats were acclimatized for one week to the environmental conditions and the provided diet. Only rats with fasting blood glucose levels above 200 mg/dL were included in this study. For measuring fasting blood glucose, the rats were divided into five groups, each consisting of five animals. Three days after the injection, all groups except the diabetes control group received the plant extract. Blood samples were taken from each group on days 0, 3, 9, 12, and 15 to assess blood glucose levels. Group 1 managed their diabetes through physical activity, such as swimming three times a week for two weeks, while Group 2 received a standard dose of metformin (500 mg/kg body weight orally every day). Groups 3, 4, and 5 were administered ethanol extract at doses of 25, 75, and 150 mg/kg body weight for two weeks.

Result and Discussion

The results of the phytochemical screening of the powdered simplicia and ethanol extract revealed the presence of secondary metabolites, as shown in Table 1.

Table 1. Phytochemical Screening

Phytochemical Constituent	Extract
Alkaloids	+
Flavonoids	+
Saponins	+
Tannin	+
Steroids / Triterpenoids	+

Phytochemical compounds in plants possess specific biological activities, such as flavonoids and terpenoids/steroids, which have been demonstrated to inhibit the activity of the enzyme alpha-glucosidase (Dalimunthe et al., 2023; Lubis et al., 2023).

Alpha-glucosidase enzyme is responsible for supplying glucose in the small intestine by breaking down polysaccharides into monosaccharides (glucose). Inhibition of this enzyme reduces the amount of glucose that can be absorbed by the small intestine, thereby decreasing blood glucose levels (A. Kumar et al., 2023).

Flavonoids can improve lipid profiles by enhancing the activity of lipoprotein lipase enzymes, which catalyze the formation of very low-density lipoprotein (VLDL) cholesterol. This VLDL transports triglycerides (TG) and hydrolyzes them into fatty acids and glycerol. The fatty acids circulating in the blood are then absorbed by skeletal muscles and other tissues for storage and used as a source of energy/catabolism. Additionally, flavonoids have the ability to inhibit fatty acid synthesis (FAS), directly preventing the formation of fatty acids and triglycerides (Fitri et al., 2023).

Flavonoids also help reduce LDL levels by inhibiting the oxidation of LDL and 3-Hydroxy-3-Methyl-Glutaryl-Coenzyme A (HMG-CoA), which is involved in cholesterol synthesis. Additionally, they increase LDL receptors on liver cell membranes to facilitate the transport of lipids in the blood (Famurewa et al., 2023).

Additionally, flavonoids play an important role in increasing HDL cholesterol levels by enhancing the activity of Lecithin Cholesterol Acyl Transferase (LCAT). LCAT converts free cholesterol into cholesterol esters, making them more water-soluble so they can interact with lipoproteins as core particles of new HDL cholesterol. This process can also contribute to weight loss in rats.

According to the research findings, the average body weight of rats in the diabetes mellitus model showed a decrease; however, statistical analysis of the average weight loss did not yield significant results. The body weight of the rats can be seen in Table 2.

Table 2. Results of Rat Body Weights

Time	Mean±SD					p-value
	PC	NC	EDCCI	EDCCII	EDCCIII	
Day-0	151.40±2.07	151.80±5.07	150.60±2.30	151.00±2.23	152.40±2.30	0.223
Day-3	151.40±2.07	151.80±5.07	150.60±2.30	151.00±2.23	152.40±2.30	0223
Day-6	153.60±4.09	153.60±8.87	141.80±15.80	147.40±3.36	146.80±4.49	0.068
Day-9	149.80±15.86	151.80±12.05	132.40±18.92	144.80±9.20	142.20±3.70	0.273
Day-12	149.20±13.55	151.60±19.29	136.20±18.45	139.20±10.18	137.00±7.34	0.443
Day-15	149.20±13.55	151.60±19.29	135.00±18.41	139.20±10.96	136.00±6.78	0.470

Delphinidin is an anthocyanin aglycone and a type of flavonoid found in cep-cepan leaves. It has the ability to reduce body fat by lowering the expression of biomarkers related to adipogenesis and lipogenesis, such as peroxisome proliferator-activated receptor-gamma (PPAR-γ) (M. N. Kumar et al., 2019).

Additionally, delphinidin can inhibit body fat accumulation (adipogenesis) by reducing the expression of PPAR-γ, helping to prevent weight gain during intervention (Parra-Vargas et al., 2018).

Meanwhile, cyanidin-3-O-glucoside is another anthocyanin aglycone also found in cep-cepan leaves that has similar effects. However, this study did not assess the quantity of cyanidin-3-O-glucoside present in cep-cepan leaves. Consequently, the research on weight loss in rats did not yield significant results based on statistical analysis using ANOVA. The data can be seen in Table 2. Results of Rat Body Weights.

Blood glucose levels were measured using a glucometer. The data from these measurements were analyzed with SPSS, and significance was determined using one-way ANOVA ($p<0.05$) and Bonferroni post hoc tests. The results of the blood glucose tests on rats with the diabetes mellitus (DM) model treated with various interventions indicated that the administration of ethanol extract nanoparticles of Castanopsis costata (EDCC) effectively reduced blood glucose levels. Doses of EDCC at 50 mg/kg body weight and 75 mg/kg body weight significantly lowered blood glucose levels compared to the positive control, which was less effective than metformin, a commercial diabetes medication.

Table 3. Results of Blood Glucose Reduction

Time	Mean±SD					p-value
	PC	NC	EDCCI	EDCCII	EDCCIII	
Day-0	94.60±6.34	92.60±9.94	94.20±6.76	96.20±6.68	86.00±9.61	0.332
Day-3	255.40±37.48	328.00±57.81*d	252.00±46.19	244.40±30.90*b	265.00±25.75	0.029
Day-6	255.40±37.48*b	386.40±60.67*a,c	246.80±38.3*b	307.00±90.48	308.00±18.45	0.005
Day-9	200.40±10.35*b	384.00±96.34*a,c	240.60±45.05*b	283.00±74.35	281.00±14.40*a	0.001
Day-12	177.60±16.07*b	313.00±71.91*a,c,d,e	161.20±27.26*b	172.40±20.84*b	158.40±37.23*b	0.000
Day-15	177.60±16.07*b,c,d,e	286.80±15.94*a,c,d,e	145.80±19.74*a,b,e	132.40±3.36*a,b	107.60±4.39*a,b,c	0.000

The data indicating a reduction in blood glucose levels over 3, 6, 9, 12, and 15 days revealed that treatment group K1 exhibited significant differences compared to the other treatment groups ($p<0.05$). This difference may be attributed to various factors, including the pathophysiological conditions of the test animals, the absorption capacity of the test substances, and the animals' adaptation to hyperglycemic conditions (Alaofi, 2020; Lubis et al., 2022). While increasing the dosage and duration of medication typically enhances the response, it is possible for the response to diminish after reaching an optimal dosage threshold. Previous research has indicated that natural medicinal substances often contain a variety of bioactive compounds that work synergistically, unlike chemical drugs that generally contain a single active ingredient. A limitation of natural medicines is the variability in their compound content, which can affect their effectiveness. Analysis results showed that on day 3, all treatment groups exhibited significant differences compared to the negative control group. Similarly, on days 6, 9, 12, and 15, all treatment groups also demonstrated significant differences relative to the negative control group. This suggests that the ethanol extract of cep-cepan leaves (*Castanopsis costata*) possesses antihyperglycemic activity. The compounds found in cep-cepan leaves may lower blood glucose levels due to antioxidant phytochemicals such as flavonoids, polyphenols, and tannins. These compounds act as free radical scavengers and are believed to function similarly to insulin in peripheral tissues. Thus, several hypotheses from this study were confirmed: the administration of active fractions of the ethanol extract of cep-cepan leaves (*Castanopsis costata*) at doses of 25 mg/kg body weight, 75 mg/kg body weight, and 150 mg/kg body weight resulted in a reduction of blood glucose levels in streptozotocin-induced male Wistar rats compared to the negative control group. Doses of 75 mg/kg body weight and 150 mg/kg body weight of the active fractions of the ethanol extract of cep-cepan leaves (costata) proved to be effective as antihyperglycemic agents when administered for 15 days.

The Effect of Cep-Cepan Leaf Extract on Pancreatic Histopathological Features. Histopathological observations of the pancreatic organs in rats were conducted using the Hematoxylin-Eosin staining method. Hematoxylin and eosin are dyes commonly used to color tissues for easier observation under a microscope. The principle of this staining method is that the acidic cell nuclei attract basic dyes, resulting in a blue color, while the basic cytoplasm attracts acidic dyes, resulting in a red color. In this study, histopathological observations were made using a microscope with a magnification of 400x. The test animals with diabetes mellitus exhibited distinct histopathological features compared to normal test animals, which could be seen in the number of endocrine cells and the shape of the endocrine cells that showed signs of necrosis and degeneration.

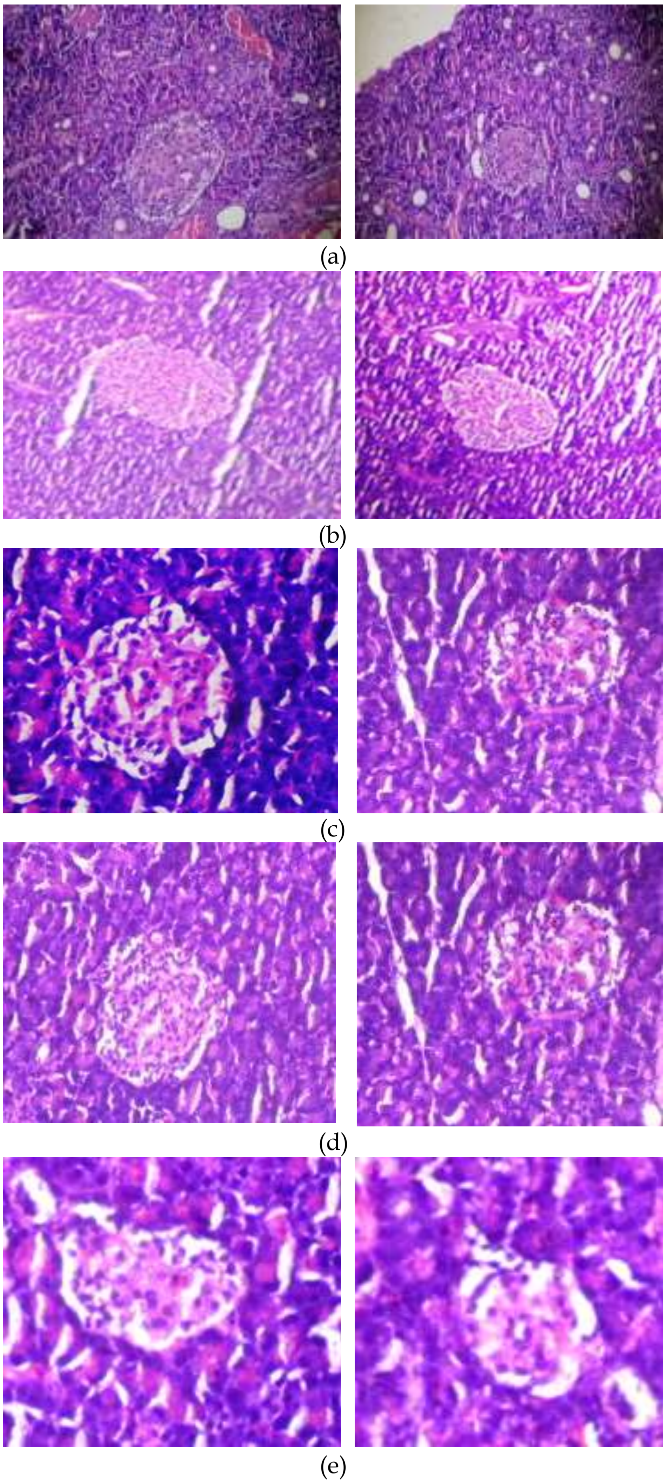

Figure 2. (a) Group K1: Streptozocin induction; (b) Group K2: Streptozocin induction plus metformin; (c) Group K3: Streptozocin induction plus cep-cepan leaf extract at 25 mg/kg body weight; (d) Group K4: Streptozocin induction plus cep-cepan leaf extract at 75 mg/kg body weight; (e) Group K5: Streptozocin induction plus cep-cepan leaf extract at 150 mg/kg body weight

Based on the histopathological observation of the rats' pancreas, it was found that in diabetic rats (K1), which were induced with Streptozotocin, there were signs of vascular congestion, severe infiltration of lymphocytic inflammatory cells, and the Langerhans islets remained within normal limits. In group K2, which involved rats treated with STZ and metformin, there was still evidence of vascular congestion with minimal infiltration of lymphocytic inflammatory cells, while the Langerhans islets remained normal. In groups K3, K4, and K5, where the rats were administered 25 mg/kg BW of Nano Cep-Cepan Leaf Extract in a Streptozotocin-induced model, vascular congestion and minimal infiltration of lymphocytic inflammatory cells were observed, with the Langerhans islets still within normal limits.

The degeneration and necrosis observed were responses of the cells after exposure to toxins in the form of high doses of glucose, which can disrupt metabolic pathways in rats. Consequently, microscopic examination revealed changes in the shape of endocrine cells in the islets of Langerhans in the rats.

The improvement of the islets of Langerhans is not only observed through histopathological findings but is also supported by the morphology of the endocrine cells. The number of endocrine cells in the islets of Langerhans is influenced by the capabilities of secondary metabolites found in the nanoparticle extract of cep-cepan leaves, particularly flavonoids. The secondary metabolites present in red hibiscus leaves play a role as antioxidants, helping to regenerate damaged pancreatic beta cells. Flavonoids are known for their antioxidant activity, which is believed to protect the body from damage caused by reactive oxygen species, thereby inhibiting the onset of degenerative diseases such as diabetes mellitus. They can lower blood glucose levels due to their antioxidant properties. Furthermore, flavonoids provide protective effects against damage to β cells, which produce insulin, and can restore insulin receptor sensitivity in cells, potentially enhancing insulin sensitivity (Sasmita et al., 2017).

Conclusion

The administration of nanoparticle extract from cep-cepan leaves (*Castanopsis costata*) has demonstrated antidiabetic effectiveness in white rats induced with Streptozotocin.

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Author Contributions
Conceptualization, C.N.G,; L.C.; A.N.G.; Methodology C.N.G.; G.R.; Software, A.N.G.; L.C. Validation C.N.G,; L.C.; A.N.G.; Formal analysis, C.N.G.; G.R.; Investigation, A.N.G.; and L.C.; Resources, C.N.G; and A. N. G; Data curation, C.N.G; and A. N. G; Writing—original draft preparation, A. N. G.; Writing—review and editing A. N. G; and C.N.G.; Visualization, C.N.G; and A. N. G.; Supervision, L.C; and G.R.; Project administration, G.R. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest
The authors declare no conflict of interest.

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