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Antidiabetic and Anti-inflammatory Effects of Peperomia pellucida Leaf Extract: Modulation of Blood Glucose, IL-1β, and Pancreatic Histopathology in STZ-Induced Diabetic Rats

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ABSTRACT

Background: Diabetes mellitus (DM) is a significant global health challenge with a rapidly increasing prevalence. Although synthetic antidiabetic drugs remain the standard treatment, long-term use often leads to adverse side effects, prompting exploration of natural alternatives. This study investigated the therapeutic potential of ethanol extract of Peperomia pellucida (L.) Kunth leaves in diabetes management through comprehensive assessment of glycemic control, inflammatory marker (IL-1β), and pancreatic tissue histopathology.

Subjects and Method: Thirty male Wistar rats were randomized into five groups (n=6): normal control, negative control (STZ-induced), positive control (STZ+metformin 50 mg/kg BW), and two treatment groups receiving Peperomia pellucida extract at doses of 40 mg/kg BW and 80 mg/kg BW, respectively. After 7 days of treatment, blood glucose levels, serum IL-1β concentrations, and pancreatic histopathology were evaluated. Phytochemical screening was conducted to identify bioactive compounds in the extract.

Results: Phytochemical analysis confirmed the presence of alkaloids, flavonoids, tannins, saponins, and phenolics. Blood glucose measurements showed significant intergroup differences on day 0 ($p<0.001$) and day 7 ($p<0.001$). The 80 mg/kg BW extract group showed a reduction in blood glucose from day 0 (Mean=312.83; SD=40.92) to day 7 (Mean=281.00; SD=34.86). IL-1β serum analysis revealed significant differences among groups ($p<0.001$), with lower IL-1β levels observed in extract-treated groups compared to the negative control. Histopathological examination demonstrated improved pancreatic tissue structure in extract-treated groups, especially at higher doses.

Conclusion: Ethanol extract of Peperomia pellucida (L.) Kunth leaves exhibits promising antidiabetic and anti-inflammatory properties in STZ-induced diabetic rats, as evidenced by reduced blood glucose, decreased IL-1β levels, and improved pancreatic histology. These findings suggest that Peperomia pellucida (L.) Kunth is a potential candidate for the development of natural therapies for diabetes management.

Keywords: Blood glucose, diabetes mellitus, IL-1β, pancreatic histology, Peperomia pellucida

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BACKGROUND

Diabetes mellitus (DM) is a major global health crisis, showing alarming growth trends and causing significant socio-economic impacts (PERKENI, 2019; Kemenkes, 2018). The International Diabetes Federation (IDF) reported that in 2019, Southeast Asia, including Indonesia, ranked third globally with a DM prevalence of 11.3% among adults aged 20–79 years. Specifically, Indonesia ranked seventh among countries with the highest diabetes burden, with approximately 10.7 million affected individuals (IDF, 2019).

The pathophysiology of type 2 DM involves a complex interplay between insulin resistance and progressive pancreatic β-cell dysfunction (Prameswari & Widjanarko, 2014; Muliasari et al., 2017). Persistent hyperglycemia triggers adverse cascades, including oxidative stress and inflammatory processes that further compromise β-cell integrity and function (Elmore, 2007; Tandi et al., 2017). Recent evidence highlights interleukin-1β (IL-1β) as a critical proinflammatory cytokine in the pathogenesis of type 2 DM, significantly contributing to β-cell damage, apoptosis, and impaired insulin secretion (Alfadul et al., 2022). Current pharmacological interventions for diabetes management, including metformin as first-line therapy, often cause undesirable side effects with long-term use, affecting patient compliance and treatment efficacy (Wang et al., 2017; Gumantara and Oktarlina, 2017; Hemmingsen et al., 2014).

Peperomia pellucida (L.) Kunth, commonly known as "suruhan," has gained attention for its traditional medicinal applications across cultures, including treatment for DM-related conditions (Hakim et al., 2024; Khan et al., 2008; Wei et al., 2011). This herbaceous plant belongs to the Piperaceae family and is widely distributed in tropical and subtropical regions, including Indonesia, where it grows abundantly and is easily accessible to the local population.

Phytochemical analyses have shown that Peperomia pellucida (L.) Kunth contains diverse bioactive compounds such as flavonoids, alkaloids, tannins, and saponins (Nwokocha et al., 2012; Ganugapati et al., 2012; Majumder et al., 2011). These compounds have demonstrated antioxidant, anti-inflammatory, and glucose-regulating properties in preliminary studies. For instance, Sheikh et al. (2013) reported a significant hypoglycemic effect of aqueous Peperomia pellucida (L.) Kunth extract in alloxan-induced diabetic rats, with blood glucose reduction comparable to standard antidiabetic drugs. Similarly, Salma et al. (2013) observed a marked decrease in blood glucose levels in a sucrose-induced hyperglycemia model.

Moreover, Atihuta (2018) found that a combined extract of Peperomia pellucida stems and leaves exhibited notable antidiabetic activity by potentially enhancing insulin sensitivity. However, despite these promising preliminary findings and traditional use, comprehensive scientific investigations into the effects of Peperomia pellucida (L.) Kunth on relevant DM parameters specifically blood glucose regulation, inflammatory markers, and pancreatic tissue integrity remain limited.

While earlier studies have demonstrated certain hypoglycemic effects of Peperomia pellucida (L.) Kunth, empirical gaps remain in understanding its comprehensive therapeutic mechanisms, especially regarding simultaneous effects on glycemic control, inflammation, and pancreatic tissue regeneration. Studies by Sheikh et al. (2013) and Salma et al. (2013) primarily focused on blood glucose reduction without assessing inflammatory

markers or histopathological changes. Previous research often evaluated metabolic or inflammatory parameters independently, rather than adopting an integrated approach to understand possible synergistic mechanisms.

Therefore, this study was designed to address these empirical gaps by systematically evaluating the effects of ethanol extract of Peperomia pellucida (L.) Kunth leaves on blood glucose levels, serum IL-1β concentrations, and pancreatic histopathology in STZ-induced diabetic Wistar rats (Almalki et al., 2019; Mostafavinia et al., 2016).

Findings from this investigation are expected to contribute to the scientific validation of Peperomia pellucida (L.) Kunth's traditional use in DM management and may provide a foundation for developing standardized natural therapies with fewer side effects than conventional treatments. Furthermore, the study may offer new insights into cellular and molecular mechanisms that inform future drug discovery efforts targeting metabolic regulation and inflammation in diabetes.

SUBJECTS METHOD

1. **Study Design**
   This study employed a laboratory experimental design using a post-test randomized controlled group design**.**
2. **Population and Sample**
   The study population comprised healthy male Wistar rats (Rattus norvegicus), aged 2.5–3 months and weighing 150–220 grams. A total of 30 rats were included in the sample and divided into five groups (n=6 per group) using the Federer formula: $(n-1)(t-1) \geq 15$.
3. **Inclusion and Exclusion Criteria**
   Inclusion criteria: healthy and active male Wistar rats aged 2.5–3 months, weighing 145–220 grams. Exclusion criteria: rats that were inactive or died during the study period.
4. **Study Variables**
   Independent variables: doses of ethanol extract of Peperomia pellucida leaves (40 mg/kg BW and 80 mg/kg BW). Dependent variables: blood glucose levels, serum IL-1β levels, and pancreatic histopathology scores.
5. **Operational Definition of Variables**
   Blood glucose levels: glucose concentration in the blood measured with an Easy Touch glucometer, expressed in mg/dL
   IL-1β levels: serum concentration of interleukin-1β measured by ELISA, expressed in ng/mL.
   Pancreatic histopathology: microscopic assessment of pancreatic tissue damage scored from 0 to 4 based on the degree of necrosis.
6. **Data Analysis**
   Data were analyzed using SPSS software. Shapiro-Wilk test was used for normality, followed by homogeneity test, one-way ANOVA, and LSD post hoc test. Results are presented as mean ± standard deviation, and $p<0.05$ was considered statistically significant.
7. **Research Ethics**
   The study protocol was approved by the Institutional Animal Ethics Committee of the Faculty of Medicine, Universitas Methodist Indonesia (Approval No. 93/-KEPK-FKUMI/EC/2024).

RESULTS

Phytochemical screening of ethanol extract of Peperomia pellucida (L.) Kunth leaves confirmed the presence of alkaloids, flavonoids, tannins, saponins, and phenolic compounds (Table 1).

Table 1. Phytochemical Screening of Ethanol Extract of Peperomia pellucida (L.) Kunth Leaves

Phytochemical Constituents	Result	Intensity*
Alkaloids	+	+
Flavonoids	+	+++
Tannins	+	++
Saponins	+	++
Phenolic Compounds	+	+++

*Intensity levels: (+) low concentration, (++) moderate, (+++) high concentration

Blood glucose levels were measured on day 0 and day 7 of treatment. The results showed a significant difference among the groups ($p<0.001$) (Table 2).

Table 2. Blood Glucose Levels Before and After Treatment with Peperomia pellucida Leaf Extract in STZ-Induced Diabetic Rats

Group	Day 0	p	Day 7	p
	Mean ± SD		Mean ± SD	
Normal control	103.83±6.04		109.00±2.97	
Negative control	291.67±44.31		285.67±69.12	
Positive control	377.00±71.43	<0,001	293.00±59.82	<0.001
Treatment I	329.00±66.50		295.67±50.80	
Treatment II	312.83±40.92		281.00±34.86	

The extract-treated groups showed a reduction in blood glucose levels compared to the negative control, with the higher dose (80 mg/kg BW) showing a more pronounced effect. Inflammatory marker analysis revealed significant differences in serum IL-1β levels among experimental groups ($p<0.001$) (Table 3). The extract-treated groups had lower IL-1β levels than the negative control, suggesting potential anti-inflammatory effects.

Table 3. Serum IL-1β Levels After Treatment with Peperomia pellucida Leaf Extract in STZ-Induced Diabetic Rats

Group	Mean ± SD	p
Normal control	5.64±1.30	
Negative control	9.14±1.07	
Positive control	8.68±1.26	<0.001*
Treatment I	9.08±1.06	
Treatment II	8.87±1.25	

Histopathological analysis revealed varying levels of pancreatic tissue damage among the groups. Damage was scored based on the degree of necrosis (Table 4). Extract-treated groups, especially the high-dose group, demonstrated improved pancreatic histology compared to the negative control, indicating protective effects on pancreatic tissue. These findings indicate that the ethanol extract of Peperomia pellucida (L.) Kunth leaves has potential antidiabetic and anti-inflammatory properties, as evidenced by decreased blood glucose levels, reduced IL-1β concentrations, and improved pancreatic histology in STZ-induced diabetic rats.

Table 4. Pancreatic Histopathology Damage Scores in STZ-Induced Diabetic Rats After Treatment with Peperomia pellucida Leaf Extract

Group	Pancreatic Histopathology Damage Scores				
	Score 0	Score 1	Score 2	Score 3	Score 4
Normal control	6	0	0	0	0
Negative control	0	0	1	3	2
Positive control	0	3	1	2	0
Treatment I	0	1	2	3	0
Treatment II	0	2	1	2	1

DISCUSSION

This study aimed to evaluate the effects of ethanol extract of Peperomia pellucida (L.) Kunth leaves on blood glucose levels, serum IL-1β levels, and pancreatic histopathology in streptozotocin-induced diabetic rats. The results demonstrated the extract's potential as both an antidiabetic and anti-inflammatory agent.

Phytochemical Screening of Ethanol Extract of Peperomia pellucida (L.) Kunth Leaves

Phytochemical analysis identified alkaloids, flavonoids, tannins, saponins, and phenolic compounds in the leaf extract. These bioactive constituents are known for their antidiabetic and anti-inflammatory properties through various mechanisms (Nwokocha et al., 2012; Ganugapati et al., 2012; Majumder et al., 2011).

The presence of these constituents aligns with previous research by Majumder and Kumar (Majumder et al., 2011). Flavonoids, in particular, exhibit antioxidant effects that may help restore insulin sensitivity in cells (Nwokocha et al., 2012), which may explain the observed decrease in blood glucose levels in groups treated with the extract. In addition, alkaloids have also been reported to reduce gluconeogenesis, thereby lowering blood glucose levels and insulin requirements (Dewi et al., 2021).

Glycemic Control Mechanism

The study found a decrease in blood glucose levels in groups administered with Peperomia pellucida extract, especially at the higher dose (80 mg/kg BW) (Table 2). This hypoglycemic effect may result from several mechanisms. Flavonoids in the extract may enhance insulin sensitivity and stimulate glucose uptake in peripheral tissues (Atihuta, 2018). Saponins may also reduce blood glucose levels by inhibiting intestinal glucose transport and stimulating insulin secretion from pancreatic beta cells (Dewi et al., 2021). The observed decrease in blood glucose levels is consistent with previous studies by Salma et al. (2013) and Sheikh et al. (2013), which also reported antihyperglycemic effects of Peperomia pellucida extract in diabetic rats.

Anti-inflammatory Properties and IL-1β Modulation

Chronic inflammation plays a key role in the pathogenesis of type 2 diabetes, with pro-inflammatory cytokines such as IL-1β contributing to beta-cell dysfunction and insulin resistance (Alfadul et al., 2022). Our results indicate that treatment with Peperomia pellucida extract reduces serum IL-1β levels in diabetic rats, suggesting a potential anti-inflammatory effect.

This effect is likely attributed to the extract's flavonoid content, which has been shown to inhibit pro-inflammatory enzymes such as cyclooxygenase and lipoxygenase, thereby reducing arachidonic acid metabolism and the subsequent production of inflammatory mediators (Al-Khayri et al., 2022). Furthermore, flavonoids may

modulate the activation of nuclear factor-κB (NF-κB), a key transcription factor regulating the expression of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 (Al-Khayri et al., 2022). By suppressing these inflammatory pathways, Peperomia pellucida extract may help reduce the inflammatory components of diabetes and improve overall metabolic function

Pancreatic Protective Effects

Histopathological analysis revealed that Peperomia pellucida extract, particularly at higher doses, could improve STZ-induced pancreatic tissue damage. This protective effect may be attributed to the antioxidant properties of the extract's constituents, which help neutralize oxidetive stress caused by STZ (El-Bassossy et al., 2018; Zhang et al., 2012). Flavonoids in the extract may protect pancreatic beta cells from oxidative injury and support regeneration of damaged cells (Dipa et al., 2015; Dewi et al., 2011). Alkaloids have also been reported to promote regeneration of damaged beta cells (Arjadi and Susatyo, 2010).

The pancreatic protective properties observed in this study are consistent with previous investigations involving Peperomia pellucida under inflammatory and oxidative stress conditions. Wei et al. (2011) demonstrated significant tissue-protective effects in hepatic models, while Khan et al. (2008) reported protective activity in inflammatory models. Our findings extend these protective effects to pancreatic tissue in diabetic conditions, highlighting the broader therapeutic potential of this plant. These protective mechanisms are similar to those reported with Artocarpus communis extract by Dipa et al. (2015), although this study is the first to demonstrate such effects specifically with Peperomia pellucida in diabetic pancreatic tissue.

This study provides compelling evidence of the antidiabetic and anti-inflammatory properties of ethanol extract of Peperomia pellucida (L.) Kunth leaves in STZ-induced diabetic rats. The extract significantly reduced blood glucose levels, attenuated inflammatory responses (as indicated by decreased IL-1β levels), and improved pancreatic tissue damage. These therapeutic effects were more pronounced at the higher dose (80 mg/kg BW), indicating a dose-dependent relationship.

The phytochemical profile—marked by the presence of alkaloids, flavonoids, tannins, saponins, and phenolics—likely contributes to the extract's multifaceted pharmacological activity through complementary mechanisms involving metabolic regulation, anti-inflammatory action, and tissue protection. The comparable efficacy of high-dose extract and metformin suggests that Peperomia pellucida (L.) Kunth may represent a promising natural alternative or adjuvant therapy for diabetes management, potentially offering benefits with fewer side effects than conventional medications.

AUTHOR CONTRIBUTIONS

Ria Oktavia: Conceptualization, Methodology, Data curation, Investigation, Formal analysis, Writing – original draft, Resources, Project administration. Endy Juli Anto: Supervision, Validation, Writing (review & editing), Methodology, Final approval. Jekson Martiar Siahaan: Supervision, Validation, Writing (review & editing), Methodology, Final approval.

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CONFLICT OF INTEREST

The authors declare no conflict of interest related to this research.

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