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Anti-inflammatory and Insulin-sensitizing Effects of Combined *Pandanus amaryllifolius* and *Syzygium polyanthum* Extracts in HFD-STZ Induced Diabetic Rats

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) is a global health crisis characterized by insulin resistance and pancreatic -cell failure, largely driven by chronic low-grade inflammation. Elevated pro-inflammatory markers, particularly TNF- and IL-6, disrupt insulin signaling. While conventional oral hypoglycemics are effective, their long-term use is often hindered by adverse effects. *Pandanus amaryllifolius* and *Syzygium polyanthum* are polyphenol-rich medicinal plants with significant antioxidant potential. This study evaluates the *in vivo* efficacy of a combined ethanolic extract of these plants in reducing TNF-, IL-6, and HOMA-IR levels, alongside *in silico* validation of their bioactive compounds. An experimental posttest-only control group design was employed using HFD-STZ-induced male Wistar rats. Key parameters included blood glucose, HOMA-IR, inflammatory cytokines, and pancreatic histopathology. Molecular docking was conducted to analyze the interaction between bioactive compounds and glucose metabolism receptors. The combined extracts significantly suppressed systemic inflammation, marked by a substantial reduction in TNF- and IL-6. This correlated with improved insulin sensitivity and lower HOMA-IR values. Histopathologically, the 200 mg/kg BW dose showed the most significant recovery of the islets of Langerhans. In silico analysis confirmed that flavonoids like quercetin exhibit strong binding affinities to target proteins. The combination of *P. amaryllifolius* and *S. polyanthum* acts as a potent anti-inflammatory and insulin sensitizer, offering a promising adjuvant therapy for T2DM management.

Key words: In silico; Insulin resistance; *Pandanus amaryllifolius*; *Syzygium polyanthum*; Type 2 diabetes mellitus

INTRODUCTION

Diabetes Mellitus (DM) has emerged as a significant global health challenge (WHO, 2016). The global prevalence is projected to increase significantly, with estimates suggesting a rise to 366 million cases by 2030 (Wild et al., 2004) Indonesia currently ranks among the countries with the highest prevalence, reflecting this global trend. Type 2 Diabetes Mellitus (T2DM) is the most prevalent form, characterized by impaired insulin secretion by pancreatic cells and insulin resistance in peripheral tissues. Pathophysiologically, T2DM is often triggered by modern lifestyle factors, such as the consumption of a High-Fat Diet (HFD), which induces oxidative stress and a state of low-grade chronic inflammation (Alberti & Zimmet, 1998; International Diabetes Federation, 2019).

Inflammation plays a crucial role in the progression of diabetes. Elevated levels of pro-inflammatory cytokines, such as Tumor Necrosis Factor-alpha (TNF-) and Interleukin-6 (IL-6), are known to inhibit insulin receptor signaling pathways, subsequently leading to insulin resistance (Zhang, 2015). Persistent hyperglycemic conditions further exacerbate histopathological damage to the islets of Langerhans in the pancreas through apoptotic mechanisms (Szkudelski, 2001). Although the use of oral antidiabetic drugs, such as Metformin, is effective, long-term administration is often associated with gastrointestinal side effects. Consequently, there is an urgent need to explore safer and more effective adjuvant therapies derived from natural products (Soelistijo, 2015).

Pandan Wangi leaves (*Pandanus amaryllifolius*) and Salam leaves (*Syzygium polyanthum*) are potential herbal plants that have long been used empirically in Indonesia to lower blood

glucose levels (Othman, 2014). *Pandanus amaryllifolius* is rich in alkaloids, flavonoids, and saponins, while *Syzygium polyanthum* contains polyphenolic compounds and tannins (Kusuma, 2011). Previous studies have demonstrated that both plants independently possess antioxidant and hypoglycemic activities (Ningrum, 2015). However, the synergistic effectiveness of their combination in simultaneously suppressing inflammatory mediators, improving insulin sensitivity (HOMA-IR), and restoring pancreatic histopathology has not been extensively explored (Gotto & Moon, 2015; Pickup, 2007). However, despite the documented antidiabetic properties of *Pandanus amaryllifolius* and *Syzygium polyanthum* individually, there is a significant lack of research regarding their synergistic potential in a combined formulation. Current literature predominantly focuses on general glycemic control, often overlooking the underlying molecular mechanisms. Specifically, the combined efficacy of these extracts in simultaneously suppressing key pro-inflammatory mediators (TNF- and IL-6), improving insulin sensitivity through HOMA-IR indexing, and restoring the histopathological integrity of pancreatic islets remains unexplored. The novelty of this research lies in its integrated multi-target approach, combining *in vivo* experimental data with *in silico* validation to address insulin resistance via anti-inflammatory pathways.

Therefore, this study aims to analyze the synergistic effects of the combined ethanolic extracts of *Pandanus amaryllifolius* and *Syzygium polyanthum* on TNF-, IL-6 levels, the HOMA-IR index, and the morphological recovery of pancreatic cells in STZ-HFD-induced diabetic rat models. In addition to *in vivo* studies, this research is supported by an *in silico* approach using molecular docking methods to predict the molecular interactions between the bioactive compounds in the extracts and target proteins involved in inflammatory processes and glucose metabolism (Harborne, 1998; Ramadhan & Phuwaputawat, 2017).

METHODS

This study is experimental laboratory research utilizing a posttest-only controlled group design to evaluate the effects of a combined ethanolic extract of Pandan Wangi leaves (*Pandanus amaryllifolius*) and Salam leaves (*Syzygium polyanthum*) in male white rats. The research was conducted at the Animal House and Biosafety Level 2 (BSL-2) Laboratories, Faculty of Medicine, Universitas Methodist Indonesia, from January to March 2024 (**Figure 1–4**).

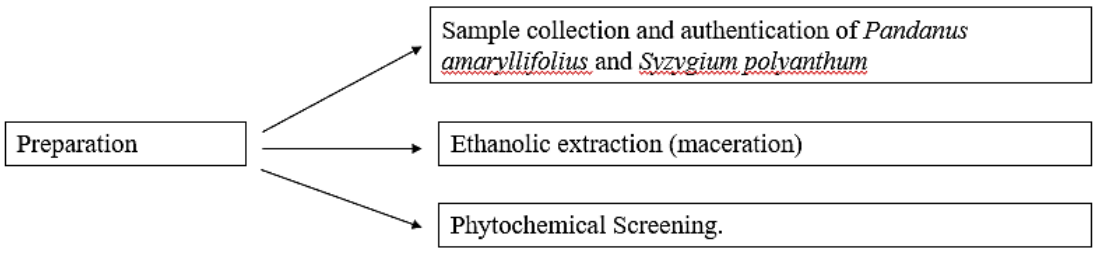

Figure 1. Experimental design and methodology framework of the study

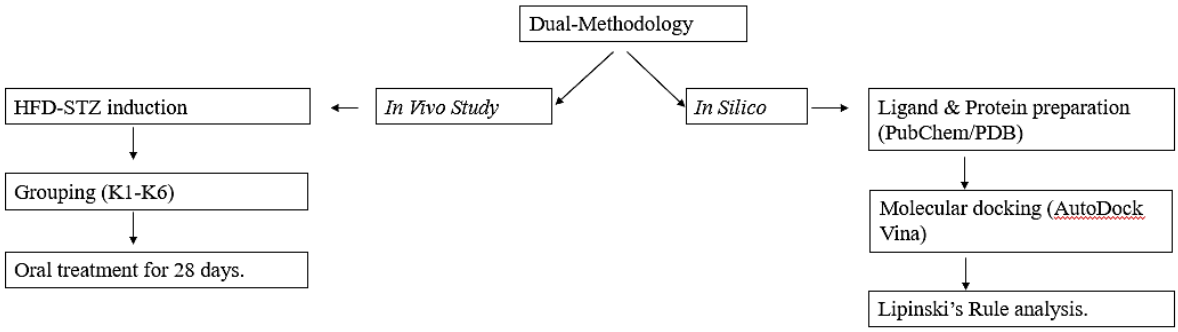

Figure 2. Schematic representation of the dual-methodology approach, showcasing the parallel workflow of the *in vivo* animal study and the *in silico* molecular docking simulation

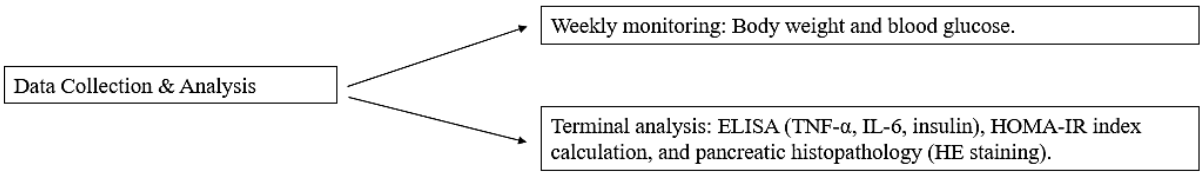

Figure 3. Flowchart of the data collection and terminal analysis stage, including weekly metabolic monitoring, biochemical assays (ELISA), and pancreatic histopathology

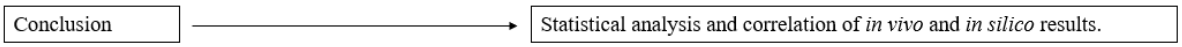

Figure 4. Overview of the data collection and terminal analysis phase, including weekly monitoring of metabolic markers and terminal biochemical/histopathological assays

Materials and equipment

The equipment used included animal cages, oral gavage needles, a glucometer (Easy Touch GCU), ELISA kits (for TNF-, IL-6, and insulin assays), a rotary evaporator, a microtome, and a light microscope. The materials consisted of 30 male Wistar rats, 96% ethanol, Pandan Wangi leaves, Salam leaves, Streptozotocin (STZ), a High-Fat Diet (HFD), 0.5% Na-CMC, and Metformin.

Research procedures

Preparation of Combined Ethanolic Extracts *Pandanus amaryllifolius* and *Syzygium polyanthum* leaves were cleaned, dried (simplisia), and ground into powder. Extraction was performed separately using the maceration method with 96% ethanol for three days (Szkudelski, 2001). The filtrates were then concentrated using a rotary evaporator at to obtain thick extracts. The combined extract was prepared by mixing both extracts at a 1:1 ratio.

Animal preparation and induction

Healthy male Wistar rats, aged 2–3 months and weighing 150–200 grams, were used. Thirty rats were acclimatized for seven days with standard feed. Diabetes was induced by a single intraperitoneal injection of Streptozotocin (STZ), which specifically targets and destroys pancreatic -cells through the accumulation of reactive oxygen species (Al-Hajj, 2016; King, 2012). Diabetes was induced by administering a High-Fat Diet (HFD) for eight weeks, followed

by a single intraperitoneal injection of Streptozotocin (STZ) at a dose of 30 mg/kg BW (King, 2012; Matthews, 1985). Rats were confirmed diabetic if their Fasting Blood Glucose (FBG) levels exceeded 200 mg/dL.

Treatment groups

The experimental rats were randomly assigned into six treatment groups, each consisting of five animals. Group K1 served as the normal control, comprising healthy rats receiving standard laboratory diet and water ad libitum. Group K2, the negative control, consisted of diabetic rats (HFD+STZ-induced) that were administered only 0.5% Na-CMC. Group K3 acted as the positive control, where diabetic rats received the reference drug metformin. Groups K4, K5, and K6 were the treatment groups, receiving the combined ethanolic extracts of *Pandanus amaryllifolius* and *Syzygium polyanthum* at doses of 100, 200, and 300 mg/kg BW, respectively. Treatments were administered orally once daily for 28 days.

Parameter measurement

Several parameters were measured to evaluate the therapeutic effects of the treatment. Metabolic markers, including body weight and blood glucose levels, were monitored weekly throughout the experimental period. At the end of the 28-day treatment, blood samples were collected to analyze inflammatory markers, specifically TNF- and IL-6, using Enzyme-Linked Immunosorbent Assay (ELISA) kits. Additionally, insulin levels were measured via ELISA to calculate the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index. For histopathological examination, pancreatic tissues were harvested, fixed in 10% buffered formalin, and embedded in paraffin blocks. The sections were then stained with Hematoxylin-Eosin (HE) to observe the morphological changes and structural integrity of the islets of Langerhans.

In silico study

Molecular docking simulations were performed to predict the binding affinity between the primary bioactive compounds (flavonoids) from both plants and the target proteins (TNF- and Insulin Receptor). Molecular structures were retrieved from the PubChem and Protein Data Bank (PDB) databases and analyzed using AutoDock Vina software (Berman, 2000; Sudjana, 2005; Trott & Olson, 2010). The bioactive compounds were further evaluated for their drug-likeness properties based on Lipinski's Rule of Five to ensure their potential as oral therapeutic agents (Dallak, 2011). The three-dimensional (3D) crystal structures of the target proteins, namely TNF-α, IL-6, and the Insulin Receptor, were retrieved from the Protein Data Bank (PDB) database, while the bioactive compounds (flavonoids) were obtained from PubChem. (Sudjana, 2005).

Data analysis

Data are presented as mean standard deviation (SD). Normality and homogeneity were assessed using the Shapiro-Wilk and Levene tests, respectively (Berman, 2000). All experimental data were statistically analyzed using One-Way Analysis of Variance (ANOVA) followed by the Tukey HSD post-hoc test to determine significant differences between treatment groups. Non-parametric data were analyzed using the Kruskal-Wallis test. All statistical analyses were performed using SPSS software with a significance level of $p < 0.05$ (Al-Hajj, 2016).

RESULTS

The One-Way ANOVA statistical analysis revealed significant differences in body weight measurements, which were further analyzed using the Tukey Post-Hoc test. Significant differences were observed between the combined extract dose groups and the negative control group, as summarized in **Table 1**. The ANOVA test also demonstrated significant differences in fasting blood glucose (FBG) levels. Post-hoc analysis indicated that the administration of the combined extract at a dose of 200 mg/kg BW resulted in a reduction in glucose levels that most closely resembled the normal control group, as shown in **Table 2**.

Table 1. Average Body Weight of Rats (Mean ± SD)

Groups	Body Weight (g) (Mean ± SD)	p-value
Normal Control	185.4 ± 4.21	
Negative Control (HFD+STZ)	245.8 ± 12.34	
Positive Control (Metformin)	195.2 ± 8.12	0.000
Combined Extract 100 mg/kg BW	215.6 ± 7.45	
Combined Extract 200 mg/kg BW	202.1 ± 5.33	
Combined Extract 300 mg/kg BW	198.5 ± 6.78	

Table 2. Average Fasting Blood Glucose (FBG) Levels of Rats (Mean ± SD)

Groups	FBG Levels (mg/dL)	p-value
Normal Control	95.2 ± 5.07	
Negative Control (HFD+STZ)	285.4 ± 25.42	
Positive Control (Metformin)	115.6 ± 12.74	0.001
Combined Extract 100 mg/kg BW	165.8 ± 18.97	
Combined Extract 200 mg/kg BW	128.4 ± 10.95	
Combined Extract 300 mg/kg BW	122.2 ± 15.49	

Inflammatory markers and insulin resistance

Statistical analysis of inflammatory markers revealed significant differences in TNF- and IL-6 levels. Subsequent post-hoc tests demonstrated a significant reduction in these markers across all treatment groups compared to the negative control group (**Table 3**), indicating the anti-inflammatory potential of the extracts (Berman, 2000). Furthermore, the analysis of the HOMA-IR index showed significant improvements in insulin sensitivity. The group treated with 200 mg/kg BW exhibited effectiveness comparable to the positive control group in reducing insulin resistance and ameliorating pancreatic histopathological damage (**Table 4**) (Morris, 2009).

Table 3. Average TNF- and IL-6 Levels Across Experimental Groups (Mean ± SD)

Groups	TNF-α (pg/mL)	IL-6 (pg/mL)	p-value
Negative Control (HFD+STZ)	145.2 ± 12.5	88.4 ± 6.2	
Positive Control (Metformin)	65.4 ± 8.1	42.1 ± 5.3	0.000
Combined Extract 200 mg/kg BW	72.8 ± 9.4	48.6 ± 4.7	

Table 4. Effect of Combined Extracts on HOMA-IR Index and Pancreatic Histopathological Damage Scores

Groups	HOMA-IR (Mean ± SD)	Pancreatic Damage Score (Mean ± SD)
Negative Control (HFD+STZ)	15.42 ± 2.11	3.8 (Severe)
Positive Control (Metformin)	4.12 ± 0.85	1.2 (Mild)
Combined Extract 200 mg/kg BW	5.65 ± 1.04	1.5 (Mild)

In silico analysis: molecular docking

Molecular docking was performed to elucidate the interaction between bioactive compounds and the target proteins IL-6 (**Figure 5a**) and TNF- (**Figure 5b**). The 3D protein structures were

obtained from the Protein Data Bank (PDB) to predict the binding affinity of the flavonoids present in the extracts (Sudjana, 2005).

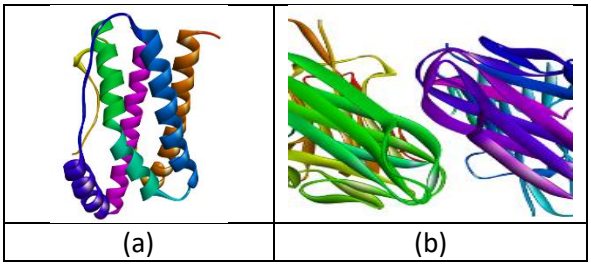

Figure 5. Three-dimensional (3D) structures of the prepared target proteins: (a) IL-6 and (b) TNF-α

Table 5. Free binding energy (ΔG) values of test compounds and Tnf-α

Compound	Free Binding Energy (ΔG) (kkal/mol)
β-sitosterol	-8.4
Steroid	-7.9
Pandamarilactonine A	-7.8
Quercetin	-7.3
Metformin	-5.1
Piperidine	-3.8
Saponin	

The *in-silico* analysis reveals that -sitosterol exhibits the strongest binding affinity (-8.4 kcal/mol) toward TNF-, followed by Steroid and Pandamarilactonine A. Notably, these three compounds show higher binding stability compared to the control drug, Metformin (-5.1 kcal/mol). This suggests that the anti-inflammatory mechanism of the combined extracts is likely mediated by these high-affinity compounds, which effectively bind to TNF- and potentially inhibit its pro-inflammatory signaling pathways (Trott & Olson, 2010; Zhang, 2015).

Table 6. Free binding energy (ΔG) values of test compounds and IL-6

Compound	Free Binding Energy (ΔG) (kkal/mol)
Saponin	-9.4
β-sitosterol	-6.6
Pandamarilactonine A	-6.6
Quercetin	-6.2
Steroid	-5.7
Metformin	-5.2
Piperidine	-3.8

The results indicate that Saponin possesses the highest binding affinity (-9.4 kcal/mol) for the IL-6 protein, significantly outperforming the other compounds and the control drug, Metformin (-5.2 kcal/mol). Additionally, -sitosterol and Pandamarilactonine A showed identical stable binding energies of -6.6 kcal/mol. These findings suggest that Saponin, primarily found in *Pandanus amaryllifolius*, may play a dominant role in suppressing IL-6 activity, thereby contributing to the reduction of low-grade chronic inflammation and the improvement of insulin sensitivity observed in the *in vivo* results (Trott & Olson, 2010; Zhang, 2015).

DISCUSSION

The experimental results demonstrate a significant reduction in body weight and blood glucose levels in groups treated with the combined ethanolic extracts of *P. amaryllifolius* and *S. polyanthum*. Under high-fat diet (HFD) conditions, chronic energy surplus triggers adipocyte hypertrophy, which leads to the release of free fatty acids and systemic inflammation, further exacerbating metabolic dysfunction. These findings align with research by Adnan et al. (2023), which notes that polyphenols in *Syzygium* species enhance lipid metabolism and modulate glucose uptake through the activation of AMPK pathways, thereby preventing the progression of obesity-linked hyperglycemia (Szkudelski, 2001). Furthermore, the administration of *Syzygium polyanthum* has been shown to provide significant metabolic protection by increasing GLUT4 translocation to the cell membrane, helping to stabilize blood glucose levels and weight in diabetic animal models (Morris, 2009). The observed weight loss in treated groups also suggests that the extract may inhibit adipogenesis, providing a multi-faceted approach to managing metabolic syndrome.

The synergism of flavonoids and alkaloids in this combination plays a dual role: protecting pancreatic β-cells from oxidative damage and inhibiting carbohydrate digestion in the gastrointestinal tract. Similar to the mechanism of *S. polyanthum* described by Kusuma et al. (2017), bioactive compounds in these leaves inhibit -amylase and -glucosidase enzymes, effectively delaying the breakdown of complex carbohydrates into monosaccharides and reducing the postprandial glucose load (Trott & Olson, 2010). This delay prevents the sharp glucose spikes that contribute to glucose toxicity in pancreatic tissues. This is further supported by the findings of Chiabchalard & Tencomnao (2010), which highlight that *P. amaryllifolius* extracts can stimulate insulin secretion from pancreatic cell lines by modulating potassium channels, reinforcing the observed improvement in systemic glucose regulation (Ningrum, 2015). The combination, therefore, addresses both the supply of glucose into the bloodstream and the efficiency of its clearance through endogenous insulin modulation.

Regarding the reduction of inflammatory markers, the combined extract effectively lowered TNF-α and IL-6 levels, which are critical mediators in the pathogenesis of Type 2 Diabetes Mellitus (T2DM). The elevated levels of pro-inflammatory cytokines, particularly TNF-α, impair the insulin signaling pathway by inducing the serine phosphorylation of Insulin Receptor Substrate-1 (IRS-1), which subsequently inhibits the downstream PI3K/Akt pathway and leads to systemic insulin resistance. Mechanistically, the flavonoid compounds—such as quercetin and kaempferol—found in the extract inhibit the NF-κB activation pathway, the primary transcriptional regulator for pro-inflammatory cytokine production (Berman, 2000). A study by Sari et al. (2023) on herbal synergies demonstrated that suppressing this inflammatory cascade directly correlates with a decrease in the HOMA-IR index, signifying enhanced insulin receptor sensitivity in peripheral tissues such as skeletal muscle and liver (Ramadhan & Phuwaputawat, 2017). This reduction in chronic low-grade inflammation is essential for restoring long-term metabolic homeostasis.

Histopathological observations showed massive cellular damage and shrinkage of the islets of Langerhans in the negative control group, whereas the 200 mg/kg BW dose exhibited significant structural recovery and increased islet density. This protective effect is consistent with the potent antioxidant capacity of *S. polyanthum* reported by Ramadhan et al. (2020), which neutralizes reactive oxygen species (ROS) and oxidative stress induced by Streptozotocin (STZ) (Trott & Olson, 2010). The recovery of islet morphology suggests that the extract promotes the regeneration of -cells or protects existing cells from further apoptosis. Furthermore, *in silico* molecular docking validated these results, showing stable binding affinities and low binding energies between the extract's active compounds, such as -sitosterol and Saponins, and inflammatory target proteins like TNF-α and IL-6 (Lipinski, 2000; Trott &

Olson, 2010) . The high docking scores indicate a strong molecular interaction, providing a structural basis for the observed anti-inflammatory effects *in vivo*.

Compared to studies using single-plant extracts, this dual-extract approach appears to offer superior cytoprotection by simultaneously modulating multiple metabolic and inflammatory pathways. The synergy between the antioxidant properties of Salam leaves and the insulinotropic potential of Pandan Wangi leaves creates a comprehensive therapeutic effect that surpasses the efficacy of individual treatments. By targeting both insulin resistance (through inflammation reduction) and insulin deficiency (through -cell protection), this combination addresses the core defects of T2DM. These results suggest that the combination of *P. amaryllifolius* and *S. polyanthum* holds significant potential as a standardized herbal formulation for the adjunctive treatment of chronic metabolic disorders, although further clinical trials are required to confirm these effects in humans.

CONCLUSION

Based on integrated in vivo and in silico investigations, it can be concluded that the combined ethanolic extracts of *Pandanus amaryllifolius* and *Syzygium polyanthum* significantly enhance metabolic and histopathological outcomes in rat models of Type 2 Diabetes Mellitus. The administration of the combined extract effectively attenuates pro-inflammatory cytokines, including TNF-α and IL-6, which are key mediators of insulin resistance, and this reduction is closely associated with improvement in the HOMA-IR index, reflecting enhanced insulin sensitivity in glucose regulation. Histopathological evaluation further demonstrates that the extract exerts cytoprotective effects on pancreatic tissue by ameliorating damage to the islets of Langerhans and suppressing necrosis of pancreatic β-cells induced by streptozotocin and a high-fat diet, with the most pronounced tissue-protective effect observed at the dosage of 200 mg/kg body weight. Molecular docking analyses corroborate these biological findings by revealing stable binding affinities of the extracts' bioactive compounds to inflammatory target proteins and metabolic receptors, thereby clarifying the mechanistic role of flavonoids and polyphenols derived from both plants. Collectively, these findings highlight the substantial therapeutic potential of this extract combination as a phytopharmaceutical candidate or herbal adjuvant therapy to support conventional management of Type 2 Diabetes Mellitus while mitigating the risk of chronic inflammation-related complications.

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