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Combination of Red Betel (*Piper crocatum*) Leaf and Sambiloto (*Andrographis paniculata* Ness) Herb Extract on Reduction of Lipid Profile in Diabetic Rats

[1]Kusmiyati Tjahjono, [2]Nesti Rahmawati, [3]Diana Nur Afifah, [4*]Larasati Sekar Kinasih

[1]Department of Biochemistry, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia
[2,3]Department of Nutrition Science, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia
[3]Departement of Biomedical Sciences, Faculty of Medicine and Health Sciences, Universitas Islam Negeri Maulana Malik Ibrahim, Malang, Indonesia
**Corresponding Author e-mail: larasatisekark@kedokteran.uin-malang.ac.id*
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Abstract: This study aims to determine the antihyperlipidemic effect of a combination of red betel extract and sambiloto herb in an experimental animal model of Type 2 Diabetes Mellitus (T2DM). This study was a randomized pre-post-test experiment with a control group design on 25 male Sprague-Dawley rats. Rats experienced T2DM with a high-fat diet for 14 days and Streptozotocin (STZ) induction of 55 mg/kgBW preceded by nicotinamide (NA) 100 mg/kgBW. We confirmed T2DM if the rats' fasting glucose levels were less than 200 mg/dl. The rats were randomly divided into 5 groups: negative control (K1), positive control (K2), combination of red betel leaf and sambiloto herb extract 75:25 (P1), 50:50 (P2), and 25:75 (P3). The combination of red betel leaf and sambiloto herb extract at any dose was able to significantly reduce total cholesterol, LDL cholesterol, and triglyceride levels ($p<0.05$). The combined extract of red betel leaf and sambiloto herb at a ratio of 75:25 yielded the effective dose for reducing total cholesterol, triglyceride levels, and LDL. In T2DM rats, the combination of these extracts has the potential to increase total cholesterol, LDL, and triglyceride levels.
Keywords: Lipid profile; red betel leaf; sambiloto herbs; T2DM

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INTRODUCTION

Deficits in insulin production, insulin action, or both in pancreatic beta cells cause Diabetes Mellitus (DM), a chronic metabolic disorder characterized by abnormal blood glucose levels (Bhayya & Sanjay, 2022). It is a chronic non-communicable disease that generally appears slowly over a long period of time, often without causing symptoms, so it is often referred to as a "silent killer" (Todkar, 2016). According to the International Diabetes Federation (IDF), the number of individuals with diabetes was 537 million in 2021, with projections indicating an increase to 643 million by 2030 (IDF, 2021). More than 90% of diabetes mellitus cases are Type 2 Diabetes Mellitus (T2DM) (Galicia-Garcia et al, 2020).

The administration of insulin injections and oral antidiabetic drugs is a common therapeutic method for DM. However, these methods often cause side effects such as dizziness, nausea, and anorexia, prompting some patients to seek alternative treatments using herbal or natural remedies (Wang et al., 2017; Ansari et al., 2022). Two plants considered effective for DM treatment are red betel (*Piper crocatum*) and sambiloto (*Andrographis paniculata*). Natural antioxidants from these plants not only aid in DM treatment but also prevent damage from free radicals and reduce the risk of chronic diseases (Premanath & Laksmidevi, 2015; Jusup, 2016).

Red betel leaf extract has antioxidant activity, with 73.41% inhibition of 1,1-diphenyl-2-picrylhydrazyl (DPPH) (Lister et al., 2019). This extract contains various phytochemical compounds, including alkaloids, saponins, tannins, and flavonoids, which function as antihyperglycemics and antioxidants. Furthermore, studies have demonstrated the effectiveness of red betel leaf extract at a dose of 250 mg/kgBW in lowering blood glucose levels in diabetic mice (Thirumalai et al., 2014). Sambiloto has a high antioxidant content, ranging from 20% to 65% (Rais, 2016). Sambiloto also has volatile compounds, phenolic acids, flavonoids, triterpenes, and terpenoid lactones. It also has the bioactive compound andrographolide (14-deoxy-11,12-didehydrographolide), which helps the immune system, fights infections, and lowers the risk of atherosclerosis (Kumar et al., 2021). A study demonstrated the antidiabetic and antihyperlipidemic properties of sambiloto leaves in T2DM mice fed a high-fat diet (Thakur et al., 2013; Akhtar et al., 2016).

The combination of red betel and sambiloto is expected to provide better effects and safety when used alone (Rahmawati et al., 2021). This is because the andrographolide content in sambiloto has side effects such as nausea, vomiting, and loss of appetite, and can cause antifertility if consumed in high doses (Hidayat & Patricia, 2022). Based on this background, this study was conducted with the aim of evaluating the impact of red betel leaf extract and sambiloto herb on T2DM model rats given a high-fat diet and Streptozotocin (STZ) injection on the observation of Triglyceride, Low Density Lipoprotein (LDL), and Total cholesterol levels.

METHOD

This study used a randomized pre-post-test experimental design with a control group, involving 25 male Sprague-Dawley rats. This study has obtained Ethical Clearance approval from the Health Research Ethics Commission of the Faculty of Medicine Diponegoro University (Dr. Kariadi General Hospital Semarang) No.114/EC/H/FK-RSDK/X/2018. This research was conducted from October to December 2019.

Materials

Sambiloto herb extracts with a certificate of analysis (COA) were obtained from PT. Borobudur Herbal Industry, Semarang, Central Java. Betel leaves were obtained at the Center for Research and Development of Medicinal Plants and Traditional Medicines (B2P2TOOT) Tawangmangu, Karanganyar, Central Java, and determined at the Faculty of Biology, Gajah Mada University, with letter number 01416/S.Tb/X/2018. Ethanol 70% (Merck), streptozotocin (STZ), and nicotinamide (NA) obtained from Nacalai Tesque, Japan. Meanwhile, the tools used in this study were a macerator container, vacuum rotary evaporator, freeze dryer, and glassware.

Data procedures

Betel leaf extraction method, Betel leaf powder was macerated using 70% ethanol solvent with a ratio of 1:10 for two days while stirring and filtered using filter paper to obtain the maceration filtrate. The maceration residue was then re-macerated using 70% ethanol with the same procedure. All maceration filtrates obtained were evaporated using a vacuum rotary evaporator at a temperature of 40 °C. The resulting extract was in the form of a thick ethanol extract, which was then dried using a freeze dryer to obtain a dry extract in powder form (Yulinta et al., 2013; Rahmawati et al., 2021).

Experimental study, We induced T2DM in rats by providing high-fat feed for 14 days, followed by an injection of nicotinamide (NA) at a dose of 100 mg/kgBW. After 15 minutes, STZ induction was carried out at a dose of 55 mg/kgBW (Skovsø, 2014;

Gheibi et al., 2017). The experimental mice were randomly divided into five groups: negative control group without treatment (K1), positive control group of diabetes (K2), treatment group of combination of red betel leaf extract and sambiloto herb with a ratio of (75:25) dose of 237.5 mg/kgBW (P1), (50:50) 225 mg/kgBW (P2), and (25:75) 212.5 mg/kgBW (P3). The intervention was given through a tube for 21 days.

Blood sampling was carried out after 3 days of STZ induction and 21 days after the intervention. The mice were fasted overnight before blood was taken through the orbital plexus. The blood samples were centrifuged at 4000 rpm for 15 minutes, then the serum was taken to analyze triglyceride, low-density lipoprotein (LDL), and total cholesterol levels. Triglyceride levels were measured using GPO-PAP, while LDL and total cholesterol levels were measured using the CHOD-PAP method spectrophotometrically and expressed in mg/dL units.

Data Analysis

Data processing and analysis were performed using SPSS for Windows version 22.0. The obtained levels of data were analyzed using the one-way ANOVA method at a 95% confidence level, then continued with the Bonferroni post hoc test. The significance value is stated as $p < 0.05$.

RESULTS AND DISCUSSION

Triglyceride levels

The Triglyceride Level Examination in Table 1 reveals a significant difference (p=0.000) between the average values before and after the intervention.

Table 1. Mean of triglyceride levels before and after intervention

Group	Triglyceride (mg/dL)		Δ	%Δ	*P'*	*P*
	Before	After				
K1	63.6±3.07	65.9±3.51	2.3±0.96	3.5	0.006	
K2	129.1±2.97	131.0±2.85	1.8±0.75	1.4	0.005	
P1	126.6±2.47	93.6±2.85	-33±3.37	-35.3	0.000	0.000**
P2	127.6±2.67	119.8±3.55	-7.8±4.36	-6.5	0.016	
P3	127.5±2.04	125.7±2.45	-1.8±4.33	-1.4	0.405	

Description:
P': Paired T-test, p<0,05 = significantly different
P: One Way ANOVA Test, p<0,05 = significantly different**

Based on the one-way Anova test, there was a significant difference between the treatments, and the results of the posthoc analysis showed a significant difference between groups K2, P1, P2, and P3 (p=0.000). The largest change in triglyceride levels after the intervention was in the P1 treatment, which was 93.6 mg/dL (35.3%).

Low Density Lipoprotein (LDL) levels

Examination of LDL levels in table 2 shows that the average comparison before and after the intervention showed a significant difference (p = 0.000).

Table 2. Mean of LDL levels before and after intervention

Group	LDL (mg/dL)		Δ	%Δ	*P'*	*P*
	Before	After				
K1	24.5±2.21	25.4±2.05	0.9±0.57	3.5	0.027	
K2	75.7±1.05	77.9±1.80	2.2±0.81	2.8	0.004	
P1	75.2±2.28	35.8±2.28	-39.3±2.23	-109.8	0.000	0.000**
P2	74.7±4.51	45.1±2.15	-29.7±6.00	-65.9	0.000	
P3	73.9±2.10	53.7±1.90	-20.2±1.53	37.6	0.000	

Description:
LDL: Low Density Lipoprotein
P': Paired T-test, p<0,05 = significantly different
P: One Way ANOVA Test, p<0,05 = significantly different**

Based on the one-way Anova test, there was a significant difference between the treatments, and the results of the posthoc test analysis showed a significant difference (p = 0.000) between groups K2 and P1, P2, and P3. The largest decrease in LDL levels was in the P1 treatment group, which was 35.8 mg/dL (39.3%).

Total cholesterol level

Examination of total cholesterol levels in table 3 shows that the average comparison before and after the intervention showed a significant difference (p=0.000).

Table 3. Mean of total cholesterol levels before and after intervention

Group	Total Cholesterol (mg/dL)		Δ	%Δ	*P'*	*P*
	Before	After				
K1	82.6±2.03	85.1±2.80	2.5±0.94	2.9	0.004	
K2	190.7±3.92	194.0±4.84	3.3±1.27	1.7	0.004	
P1	186.9±2.88	116.8±2.67	-70.1±4.37	-60.0	0.000	0.000**
P2	193.1±2.32	145.9±4.49	-47.2±4.68	-32.4	0.000	
P3	192.5±2.17	159.7±2.59	-32.8±3.99	-20.5	0.000	

Description:
P': Paired T-test, p<0,05 = significantly different
P: One Way ANOVA Test, p<0,05 = significantly different

Based on the one-way Anova test, there was a significant difference between the treatments, and the results of the posthoc test analysis showed a significant difference (p=0.000) between groups K2 and P1, P2, and P3. The greatest decrease in cholesterol levels was in the P1 treatment group, which was 98.2 mg/dL (91.8%).

A high-fat diet and STZ-NA induction in T2DM conditioning can lead to obesity and insulin resistance (Gheibi et al., 2017; Rahmawati et al., 2021). A high-fat diet can result in increased body weight, higher body fat, and the risk of insulin resistance (Skovsø, 2017). On the other hand, STZ-NA induction is used for T2DM induction, where the administration of NA before STZ can prevent T1DM due to NA's ability to prevent the reduction of the number or activity of rat β cells (Rais et al., 2022).

Red betel leaves and sambiloto are commonly used as herbal medicines in Indonesia (Sholikhah, 2016; Setyawati et al., 2023). Sambiloto herb contains andrographolide. Red betel leaf extract contains a variety of active compounds such as polyphenols, alkaloids, saponins, flavonoids, tannins, carbohydrates, and essential oils (Anggi & Magfirah, 2019; Suri et al., 2021; Navirius et al., 2023; Irawan et al., 2024).

Studies have shown that a combination of red betel leaf extract and sambiloto significantly reduces triglyceride (TG), LDL, and total cholesterol levels. Preliminary research indicates that the hypolipidemic effects of this extract combination operate through two primary pathways: antioxidant and anti-inflammatory. This has been proven to increase antioxidant levels in DM model rats compared to the T2DM control group. The combination of these extracts can enhance total antioxidant levels while simultaneously lowering blood glucose, insulin, and the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) (Li et al., 2015; Rahmawati et al., 2021; Safithri et al., 2023).

The results of this study align with research showing that sambiloto extract administration in fructose-fed rats significantly decreases TG, LDL, and total cholesterol levels (Nugroho et al., 2012). Another study indicated that andrographolide could minimize oxidative stress by inhibiting the activation of extracellular signal-regulated kinase (ERK) 1/2, p38, mitogen-activated protein kinase (MAPK), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) in ox-LDL-induced macrophage foam cells (Li & Li, 2012). Additionally, flavonoid and alkaloid compounds can regenerate damaged pancreatic beta cells (Prameswari& Widjanarko, 2014).

Research on red betel leaf extract shows promising effects, similarly, sambiloto extract also demonstrates comparable benefits. The alkaloid content in both red betel leaf extract and sambiloto has hypoglycemic activity by increasing insulin levels through the regeneration of damaged pancreatic beta cells, protecting them from damage, and stimulating insulin release. Increased insulin secretion is due to the sympathetic nervous stimulation by alkaloid compounds (Arjadi & Mustofa, 2017). Flavonoid compounds also have hypoglycemic activity that enhances antioxidant enzyme activity and improves insulin receptor sensitivity (Pitriya et al., 2017).

Several compounds in red betel leaf extract function as antioxidants that benefit health, according to various studies. Polyphenols, for instance, protect body cells from free radical damage by binding to free radicals and preventing cellular inflammation (Lister et al., 2019). Red betel leaf extract is also known to have antioxidant activity through DPPH scavenging activity, total phenolic content (TPC), and total flavonoid content (TFC). Furthermore, it has antidiabetic activity by inhibiting alpha-amylase and alpha-glucosidase (Kamaruzaman et al., 2020). Tannins in red betel leaves can form a protective layer in the intestines, narrowing the intestinal epithelial membrane, thus reducing nutrient absorption and potentially inhibiting carbohydrate intake, leading to a less significant increase in blood sugar levels (Prameswari & Widjanarko, 2014; Pitriya et al., 2017).

CONCLUSION

Based on the research results, it can be concluded that the combination extract of red betel leaf and sambiloto in various doses can reduce LDL cholesterol, triglycerides, and total cholesterol levels. The most optimal results of reducing LDL, triglycerides, and total cholesterol levels were shown in the combination extract of red betel leaf and sambiloto herb with a dose of 237.5 mg/kgBW (P1).

RECOMMENDATION

Further research in the field of molecular biology is needed to intervene the combined effects of red betel leaf extract and sambiloto in overcoming T2DM.

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