Antihyperlipidemic Activity of *Archidendron pauciflorum* Fruit Peel Extract in Streptozotocin-induced Diabetes Female Wistar Rats

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**Abstract.** The relationship between diabetes and hyperlipidaemia is a well-recognized phenomenon. Djengkol (*Archidendron pauciflorum*) fruit peels have been used traditionally as medicinal plant for treats diabetes. The present study investigated the antihyperlipidemic activity of ethanol extract from *A. pauciflorum* fruit peel on the diabetic female Wistar rats. The diabetic condition was induced by intravenous injection of streptozotocin at a dose of 65 mg/kg BW. The ethanol extract of Djengkol at a dose of 385, 770, and 1540 mg/kg BW as well as glibenclamide as reference administered daily for 14 days to the diabetic rats. The result did not show dose-response manner, which the extract treatment at a dose of 770 mg/kg BW slightly decreased the cholesterol total, triacylglycerol, LDL cholesterol and atherogenic indices, as well as significantly increased HDL cholesterol compared with the reference group (p<0.05). Overall, our data suggest that *A. pauciflorum* fruit peel extract has an antihyperlipidemic potency in streptozotocin-induced diabetic female Wistar rats rather than “In conclusion, the *A. pauciflorum* fruit peel extract has an antihyperlipidemic potency in streptozotocin-induced diabetic female Wistar rats.

**1. Introduction**

Diabetes mellitus (DM) is a disease with combinations of various disturbances in the body's metabolic system due to chronic hyperglycemia conditions associated with abnormal metabolism of carbohydrates, fats, and proteins resulting from deficiency or decrease the effectiveness of insulin [1]. Diabetes causes microvascular complications including diabetic retinopathy, nephropathy, neuropathy, and diabetic foot disorders, as well as macrovascular complications include cardiovascular disease [2]. Accumulation of lipids in diabetes are mediated through various impaired in the metabolic and regulatory processes, especially insulin deficiency, leading to diabetic patient more susceptible to hyper-cholesterolemia and hypertriglyceridemia. The major pathogenesis of disrupted lipid metabolism in diabetes is the increased mobilization of fatty acids from adipose tissue and secondary elevation of free fatty acid level in the blood [3].

Hyperlipidemia is characterized by increased total serum cholesterol, as well as low-density lipoprotein (LDL) cholesterol, and very low-density lipoprotein (VLDL) cholesterol levels. Hyperlipidemia-associated lipid disorders are considered as the cause of atherosclerotic cardiovascular disease [4]. Hyperlipidemia is a determinant of the development of atherosclerosis and an important risk factor for cardiovascular disease. This constellation, often refer to as the 'lipid triad', specifically
generated atherogenic changes in the arterial wall and promoted the instability of plaque, thus influenced acute cardiovascular events [5]. The risk for the development of atherosclerosis is generally associated inversely with levels of high-density lipoprotein (HDL) cholesterol. The major anti-atherosclerotic effect of HDL is known to be reverse cholesterol transport by scavenged cholesterol from the peripheral vasculature with transport to the liver, where it is excreted in the biliary system. However, HDL exhibits multiple other physiologic effects that may play a role in the reduced risk for atherosclerosis [6].

Studies of the antihyperlipidemic potency of the Fabaceae plant have been carried out using diabetic test animals, e.g. *Cassia fistula* [7], *Clitoria ternatea* and *Vigna mungo* [8], *Tamarindus indica* [9], *Senna auriculata* [10]. Extracts from the Fabaceae plant were known to contain alkaloid compounds, antraquinone, catenin, flavonoids, phenols, saponins, steroids, tannins, terpenoids, xantroproteins and glycosides. The results of the study showed decreased blood glucose, triacylglycerol, total cholesterol, LDL cholesterol, and VLDL cholesterol, as well as increased HDL cholesterol levels after treatment the extract in diabetic animals [7-10].

*Archidendron pauciflorum* (Fabaceae) fruit peel has been used traditionally as medicinal plant, i.e for diabetes treatment [11]. Our previous study showed that LD50 value from acute toxicity test of *A. pauciflorum* fruit peel extract on female Wistar rats estimated as 15382,412 mg/kg body weight (BW) [12]. In this study, we investigated the antihyperlipidemic potency of Djengkol (*Archidendron pauciflorum*) fruit peel in diabetic rats. The dosages used were 2.5, 5, and 10% of the LD50 value or approximately 385, 770, and 1540 mg/kg BW, respectively. Diabetic condition in test animals could be induced by diabetogenic agent, eg streptozotocin (STZ). Streptozotocin (2-deoxy-2-[3- (3-methyl-nitrosourea)-D-glucopyranose]) is a toxic molecule causes damage to pancreatic β cells. Streptozotocin is widely used as diabetogenic agent since it could applied at low doses and has higher success rate (up to 95%) than other inducer substances, such as alloxan [13].

2. Materials and Methods
2.1 Collection and extraction of plant materials
*Archidendron pauciflorum* fruit peels were collected from Karangwangi village, Cianjur West Java. Identification of the plant material was performed by the Taxonomy laboratory in Biology Department, Faculty of Mathematics and Natural Sciences, Padjadjaran University. Dried fruit peels were powdered mechanically using a commercial blender and extracted with ethanol. Dried extract was obtained using a rotary evaporator (EYELA, N1100SWD, Tokyo Rikakiai Co., LTD, Japan) at 40°C.

2.2 Experimental design
Twenty-four female Wistar rats (160-180 g) were obtained from the animal house of the Bio System Laboratory, Universitas Padjadjaran. The rats were weighted and sorted into six groups (Table 1). They were nurtured in a cage based on a standard environmental condition. In this study, piglet standard diets (CP-551, PT. Charoen Pokphand) were chosen as their daily diet. Before the experiment, those animals were acclimatized for a week. We prepared six treatments i.e., diabetic control (DC); diabetic treated with the extract at a dose of 385 mg/kg BW (DE1); diabetic treated with the extract at a dose of 770 mg/kg BW (DE2); diabetic treated with the extract at a dose of 1540 mg/kg BW (DE3); diabetic treated with glibenclamide at a dose of 10 mg/kg BW as reference group (Ref); and normal non-diabetic control (NC).

2.3 Induction of diabetes and treatment of the extract
Before induction of diabetes by STZ, the animals were fasted overnight. Their baseline fasting glucose level was determined using a glucometer, by collecting their blood via tail cut. Diabetes was induced by intravenous injection of a freshly prepared solution of STZ at dose of 65 mg/kg BW in 10 mM citrate buffer solution (pH 4.5) [14] of five groups, while the negative control rats were injected by the vehicle alone. Then, the animals were fasted overnight for 72 hours after administration of STZ. The
blood was collected via their tail cut for determining of their fasting glucose levels. The animals with glucose level more than 250 mg/dL were categorized as diabetic rats and used for a further experiment. Normal non-diabetic control and diabetic control rats were given 0.5% CMC solution, whereas *A. pauciflorum* extract or glibenclamide was administered orally to diabetic rats using intragastric tube once a day for 14 days.

2.4 Blood sampling and biochemical analysis

For these analyses, on the fifth day, the fasted animals were sacrificed by cervical dislocation. The blood sample for biochemical analysis was prepared from intra-cardiac. The blood serum was collected as described previously [15]. Total cholesterol and triacylglycerol levels were determined using multiCareinTM cholesterol strips and triacylglycerol strips [16] at before (day 1) and after 14 days of treatment (day 15). HDL cholesterol level was assayed enzymatically with Randox Commercial Test Kits CH200 and C203 (Randox Laboratories Ltd., Crumlin, England, UK). HDL cholesterol level was calculated as describe by Pusparaj et al. [17] using spectrophotometry at wavelength of 500 nm with formulae:

\[
\text{HDL cholesterol level} = 219.2 \times (\text{OD}_{500}) \text{ sample (mg/dL)}
\]

Plasma LDL cholesterol level calculated using the equation from Friedewald *et al.* [18] which is:

\[
\text{LDL cholesterol} = \text{Total cholesterol} - \frac{[\text{Triacylglycerol}]}{5} \text{ mg/dL}
\]

The atherogenic indices calculated using the following formulae as describe by Chigozie and Chidinma [16], which are:

\[
\text{Cardiac Risk Ratio (CRR)} = \frac{\text{Total cholesterol}}{\text{HDL cholesterol}}
\]

\[
\text{Atherogenic Coefficient (AC)} = \frac{\text{(Total cholesterol} - \text{HDL cholesterol})}{\text{HDL cholesterol}}
\]

\[
\text{Atherogenic Index of Plasma (AIP)} = \log\frac{\text{Triacylglycerol}}{\text{HDL cholesterol}}
\]

2.5 Data analysis

Results were expressed as mean ± standard deviation (S.D). The differences of parameters (mention of parameters in this study) were tested by SPSS ver. 21.00 (IBM, Armonk, NY, USA). Significant differences between means were calculated by one-way ANOVA followed by Duncan multiple range test. Significance levels were set at *P* < 0.05.

3. Results and Discussion

The effect of *A. pauciflorum* fruit peel extract on the blood total cholesterol and triacylglycerol level of tested animals at before (1st day) and after 14 days (15th day) treatments is presented in Table 1. Our statistical analysis failed to detect the significant different between total cholesterol level in normal non-diabetic control group (NC) and diabetic groups (DC, DE1, DE2, DE3, Ref) at before the treatment period (Table 1). We observed the total cholesterol among diabetic groups at the end of incubation were overall similar, suggesting that *A. pauciflorum* fruit peel extract has a little effect on the total cholesterol of tested animals. Although, the present study detected the triacylglycerol levels in diabetic treated groups (DE1, DE2, D3, Ref) were much higher than that in normal non-diabetic
control (NC) at before treatment, however, our data are presented here show that the triacylglycerol level in diabetic treated groups decreased compared with normal non-diabetic control (NC) at the end of treatment. This finding suggests that *A. pauciflorum* fruit peel extract has effect on the decreasing of the triacylglycerol level.

**Table 1.** Blood total cholesterol and triacylglycerol level of normal and streptozotocin treated rats at before and after 14 days of treatment

| Treatment Group | Total Cholesterol (mg/dL) | Triacylglycerol (mg/dL) |
|-----------------|----------------------------|------------------------|
|                 | Day 1                      | Day 15                 | Day 1                      | Day 15                     |
| Normal non-diabetic control (NC) | 167.00 ± 44.75 | 177.00 ± 37.58 | 285.25 ± 73.70<sup>a</sup> | 251.50 ± 77.71 |
| Diabetic control (DC) | 186.75 ± 3.30 | 189.50 ± 11.82 | 317.00 ± 83.21<sup>b</sup> | 261.00 ± 39.08 |
| Diabetic, treated with *A. pauciflorum* extract dose of 385 mg/kg BW (DE1) | 191.50 ± 10.26 | 187.00 ± 29.64 | 408.00 ± 63.17<sup>c</sup> | 223.25 ± 139.28 |
| Diabetic, treated with *A. pauciflorum* extract dose of 770 mg/kg BW (DE2) | 196.00 ± 22.14 | 191.25 ± 24.11 | 373.25 ± 199.28<sup>d</sup> | 267.25 ± 190.04 |
| Diabetic, treated with *A. pauciflorum* extract dose of 1540 mg/kg BW (DE3) | 179.75 ± 21.71 | 176.25 ± 25.81 | 431.25 ± 58.14<sup>c</sup> | 226.25 ± 118.90 |
| Diabetic, treated with glibenclamide dose of 10 mg/kg BW (Reference) | 168.75 ± 27.68 | 161.25 ± 34.05 | 408.00 ± 134.31<sup>c</sup> | 202.00 ± 122.79 |

Note: Values are expressing as mean ± S.D (n=4). Data was analyzed using ANOVA and Duncan’s post-hoc test. Different alphabet in same column showed P values less than 0.05 and considered as significance.

In this study, intravenous injection of streptozotocin (STZ) by dosage 65 mg/kg BW mimicks type 1 diabetes, because STZ could be enter specifically to β cell pancreas through glucose transporter protein GLUT-2 and triggering apoptosis of β cell pancreas, which results in decreased insulin production [19]. Glucose and lipid metabolism linked to each other in many ways; the most important are diabetic dyslipidemia, and they are characterized by elevated triglycerides, low HDL cholesterol, and the predominance of small-dense LDL particles [20]. In type 1 diabetes occurs less advance dyslipidemia because of insulin deficiency altered cholesterol metabolism, i.e. high absorption and low synthesis of cholesterol, as also shown in streptozotocin-induced diabetic in experimental animals [21]. The higher levels of cholesterol and triacylglycerol in diabetic rats compared with normal non-diabetic rats as mentioned above due to accumulation of lipids and insulin deficiency induced derangements in lipid metabolism.

As mentioned above, the cholesterol level of the tested animals was slightly decrease as effect of *A. pauciflorum* fruit peel extract. An earlier study suggested that metabolism of cholesterol in type 1 diabetes show relatively normal lipid pattern compared with type 2 diabetes [21]. In addition, elevated level of plasma triacylglycerol is often associated with abnormal lipoprotein metabolism, leads to an increased catabolism of HDL (resulting in low HDL cholesterol) and a shift in the LDL form into a small dense LDL which are more “atherogenic”, thus showed a synergistic risk factor for cardiovascular disease [16, 20], as shown by streptozotocin-induced diabetic rats in this study. Therefore, we analysed the effect of *A. pauciflorum* fruit peel extract on LDL and HDL cholesterol levels of the rats (Table 2). We found that LDL cholesterol level in diabetic groups (DC, DE1, DE2, DE3, Ref) was significantly higher (P<0.05) than that in normal non-diabetic control group (NC). In contrary, HDL cholesterol level in diabetic groups (DC, DE1, DE2, DE3, Ref) was significantly lower (P<0.05) than that in normal non-diabetic control group (NC) (Table 2). We also detected the extract treatment group at a dose of 770 mg/kg BW (DE2) was lowest LDL cholesterol level, but was highest HDL cholesterol level compared with the other extract-treated groups. In addition, the cholesterol level in that group was significantly higher than that in the glibenclamide-treated group (Table 2).

The treatments of *A. pauciflorum* fruit peel extract and glibenclamide for 14 days reduced plasma levels of triacylglycerol, although did not show a dose-dependent manner. Reduced level of LDL cholesterol and elevated level of HDL cholesterol compared with diabetic control and reference
groups only showed in the extract treated-diabetic rats by dosage 770 mg/kg BW. The reduction in plasma total cholesterol triacylglycerol, and LDL cholesterol as well as elevated HDL cholesterol level was assumed could reduce the risk of cardiovascular disease in diabetes, as shown by calculated atherogenic indices in this study.

Table 2. LDL and HDL cholesterol level of normal and streptozotocin treated rats after 14 days of treatment

| Treatment group                                      | LDL (mg/dL)   | HDL (mg/dL)   |
|-----------------------------------------------------|---------------|---------------|
| Normal non-diabetic control (NC)                    | 19.40 ± 17.64c| 107.29 ± 33.09d|
| Diabetic control (DC)                               | 72.25 ± 25.35ba| 74.05 ± 14.99bc|
| Diabetic, treated with A. pauciflorum extract dose of 385 mg/kg BW (DE1) | 91.99 ± 13.62a| 50.85 ± 18.21a|
| Diabetic, treated with A. pauciflorum extract dose of 770 mg/kg BW (DE2) | 59.87 ± 39.56b| 77.93 ± 20.14c|
| Diabetic, treated with A. pauciflorum extract dose of 1540 mg/kg BW (DE3) | 94.31 ± 14.20a| 36.69 ± 14.77a|
| Diabetic, treated with glibenclamide dose of 10 mg/kg BW (Reference) | 66.79 ± 23.71b| 54.06 ± 6.37ab|

Note: Values are expressing as mean ± S.D (n=4). Data was analyzed using ANOVA and Duncan’s post-hoc test. Different alphabet in same column showed P values less than 0.05 and considered as significance.

The effect of A. pauciflorum fruit peel extract on atherogenic indices in tested animals after 14 days of treatment is presented in Table 3. Cardiac risk ratio (CCR) and atherogenic coefficient (AC) for diabetic groups (DC, DE1, DE2, DE3, Ref) were significantly higher (P<0.05) than those for non-diabetic control group (NC), whereas atherogenic indexes of plasma (AIP) were overall similar among all the treatment groups, except the extract treated group at a dose of 1540 mg/kg BW (DE3). The extract treatment group at a dose of 770 mg/kg BW (DE2) showed lowest of CCR, AC, and AIP values compared with the other extract-treated groups, including the glibenclamide-treated group. An earlier study suggested that Atherogenic indices are powerful indicators of the risk of cardiocarcular disease, the higher the value, the higher the risk of developing cardiovascular disease and vice versa [24]. In addition, low atherogenic indices are protective against coronary heart disease [16]. It has been well known that therogenic Index of Plasma (AIP) is part of index atherogenic that usually used for patient with type 2 diabetes to predict the risk of cardiovascular disease. A specific data was needed to determine the indication and the complication compared with using formulae, due to the correlation of nitric oxide (NO) as a marker for alkylation that damaging β cell pancreas-related to atherogenic index, which is not considered [25].

Table 3. Atherogenic indices of normal and streptozotocin treated rats after 14 days of treatment

| Treatment group                                      | Cardiac Risk Ratio (CCR) | Atherogenic Coefficient (AC) | Atherogenic Index of Plasma (AIP) |
|-----------------------------------------------------|--------------------------|------------------------------|----------------------------------|
| Normal non-diabetic control (NC)                    | 1.67 ± 0.30a             | 0.67 ± 0.30a                 | 0.37 ± 0.25a                     |
| Diabetic control (DC)                               | 2.59 ± 0.68b             | 1.59 ± 0.68b                 | 0.51 ± 0.29a                     |
| Diabetic, treated with A. pauciflorum extract dose of 385 mg/kg BW (DE1) | 3.82 ± 0.75c             | 2.80 ± 0.57c                 | 0.63 ± 0.26ab                    |
| Diabetic, treated with A. pauciflorum extract dose of 770 mg/kg BW (DE2) | 2.49 ± 0.42b             | 1.49 ± 0.42b                 | 0.47 ± 0.14a                     |
| Diabetic, treated with A. pauciflorum extract dose of 1540 mg/kg BW (DE3) | 4.98 ± 1.24d             | 3.98 ± 1.24d                 | 0.78 ± 0.27b                     |
On the other hand, the present study detected the decreasing of the Cardiac Risk Ratio (CCR), Atherogenic Coefficient (AC), and AIP values on the extract treated-diabetic rats by dosage 770 mg/kg BW. Such finding indicates that *A. pauciflorum* fruit peel extract has a potency as anti-hyperlipidemia, although the effect did not show dose-dependent positive manner. This finding is consistent with previous studies by Singh *et al.* [22], and Ezeigbo and Asuzu [23]. We assume that some chemical components in the extract such as alkaloids, flavonoids, saponins, phenolic, and tannins [22] are responsible for such phenomenon. Supporting this, earlier studies suggested that those chemical components have effect on decreasing of cholesterol [3, 10, 16, 17, 25]. Besides that, those components also showed athero-protective activities or the ability to protect against cardiovascular complications in the diabetic [16, 28, 29, 30].

4. Conclusion

Overall, our data suggest that *A. pauciflorum* fruit peel extract has a potency as anti-hyperlipidemia in streptozotocin-induced diabetes in female Wistar rats following oral administration. It was clearly observed that the extract evidently reduce the level of triacylglycerol, LDL cholesterol, and atherogenic indices (cardiac risk ratio, atherogenic coefficient, and atherogic index of plasma), as well as elevate the level of HDL cholesterol. The results of this study well support its use in traditional health care for the management of diabetes mellitus as well as protecting agent against coronary heart disease. Further biochemical and pharmacological investigations related to anti-diabetes effect of the extract are now in progress.

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