Effects of ciplukan (Physalis angulata l.) juices on lipid profile status and histopathological of liver in rats with streptozotocin diabetes

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Effects of Ciplukan (*Physalis angulata* l.) Juices on Lipid Profile Status and Histopathological of Liver in Rats with Streptozotocin Diabetes

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Abstract. Type 2 diabetes mellitus (T2DM) is associated with an abnormal lipid profile. Several functional foods have therapeutic potential for treating chronic diseases, including diabetes. One plant that has this therapeutic potential is *Physalis angulata* or ciplukan. This study aimed to evaluate the effects of *P. angulata* juice drink (PJ) on the levels of plasma lipid profiles and health of liver in streptozotocin (STZ) induced T2DM Wistar rats. Twenty healthy male Wistar rats were induced to diabetes with a single dose intraperitoneal administration of STZ (40 mg/kg b.w.). Diabetic rats were orally administered with 1 mL/day of ciplukan juice (D-T1) or 2 mL/day of ciplukan juice (D-T2) or 62.5 mg/kg b.w. of metformin every day for 14 days. Rats in all groups were sacrificed on day 14. PJ lowered triglyceride (TGs) significantly ($P<0.05$), but not for total cholesterol (TC) compared to the diabetic group (negative control). Moreover, the administration of PJ significantly increased the levels of HDL-cholesterol (HDL-c) ($P<0.05$). Oral administration of *P. angulata* juices and metformin drug to diabetic rats significantly reversed all these changes to near-normal levels. In conclusion, the active constituents with high antioxidant properties in PJ might be responsible for its anti-hyperlipidaemia and anti-inflammatory effects, as well as the restoration effect on the damaged liver in experimental rats. Hence, these PJ treatments indicated their helpful effects in the amelioration of diabetes-associated complications.

INTRODUCTION

Diabetes is considered as a major health problem in Indonesia, with more than 10 million people living with diabetes (prevalence rate of 6.2%) [1]. Globally, Indonesia was rated as one of the top ten countries with a high number of individuals living with diabetes in 2013 [2]. Pharmacologic therapies such as oral medications and insulin are still considered contemporary interventions [3]. Treatment of type 2 diabetes mellitus (T2DM) can be done with an antioxidant approach. This approach reduces oxidative stress and ROS production in the body by increasing the activity of antioxidants produced by the body and those derived from food intake.

On the other hand, natural products have long been used in traditional systems of medicine to cure diabetes. Among the possible natural product available in Indonesia to treat diabetes is *Physalis angulata* L., an underutilized plant and weed in the paddy field with high nutritional value and exclusive taste of its fruit. *P. angulata* is an annual and herbaceous plant that belongs to the Solanaceae family. It is native to Central America and widely distributed in

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tropical regions of Asia, including South and Southeast Asia [4]. In Indonesia, it is known as Ciplukan and grows widely as a weed in the paddy field area.

Some biological activities of *P. angulata* such as antiallergenic, anti-carcinogenic, anti-inflammatory, antihyperglycemic, antimicrobial, antiseptic, antiviral, and cardio-protective have been reported [5]. For antidiabetic activity several studies on *P. angulata* have been conducted sporadically. Aju and Mamidala [6] assessed antidiabetic activity of *P. angulata* and found isolated compound from this plant reduced blood sugar level in alloxan induced diabetic (hyperglycaemic) rats orally at 25 mg/kg. Mafuyai et al. [7] evaluated anti-diabetic activity of *Physalis angulata* against streptozotocin-induced diabetic wistar albino rats. The results showed that *P. angulata* extract has a significant ($p<0.05$) hypoglycemic effect in diabetic rats. There has been a lot of literature on *P. angulata* as a juice drink or functional drink. Darwish et al. [8] have developed *P. peruviana* juice with pomace as antidiabetic drinks. The development of *P. angulata* as a functional drink also has been carried out by [9] and is labeled "Salata". The study results found that the Ciplukan beverage product that had the best response to acceptability with the highest phenolic and flavonoid content was the fruit:bud composition of 15:1, and the stabiliser concentration was 0.1%. The results showed that the greater the composition of the added fruit juice and the higher the concentration stabilizer, the higher the antioxidant activity.

T2DM disease is closely related to lipid profile. Increased ROS production and decreased activity of antioxidant enzymes compromise the body's defense system in hyperglycemia with the pathogenesis of diabetic dyslipidemia, micro and macrovascular complications [10]. The flavonoids and phenolics content in food products allows stimulation of antioxidant production in the body. It may improve lipid profiles and decrease blood glucose [11] which is also indicated by improvements in liver tissue architecture [12-13]. Ciplukan drink which has been proven to have high antioxidant activity, has a great opportunity to be used as an alternative to DM therapy. Therefore, it is necessary to prove that ciplukan drink can control hyperglycemia by improving the lipid profile and liver histopathology. This study was conducted to evaluate the effects of *P. angulata* juice (PJ) on the levels of plasma lipid profiles and health of the liver in streptozotocin (STZ) induced T2DM Wistar rats.

MATERIALS AND METHODS

Materials

Fresh fruit and bud ciplukan (*Physalis angulata* L.) were obtained from the village area of Dawuan, Dawuan District, Subang City, West Java, Indonesia. Ciplukan plants were obtained from January -June 2019. The botanical identification of these ciplukan plants has been carried out (No. 886/IPH.1.01/If.07/IV/2018). Citric acid, non-calorie sugar (stevia), and CMC were obtained at Setia Guna Chemical Store, Bogor; while honey was bought at CV. Nutrima, Bogor. Methanol, DPPH, quercetin, $AlCl_3$, gallic acid, Folin-Ciocalteu, Na_2CO_3, and NaOH were purchased from Sigma-Aldrich, Singapore.

Sample Preparation

Fresh ciplukan fruits and buds are sorted, weighed, then washed with running water. The washed ciplukan fruit and buds, blended at 70°C, for two minutes. The extraction process of ciplukan juice and buds is carried out by weighing the ingredients and extracting them using a water solvent, each ratio of 1:2 (w/v). Each extract was filtered using filter paper, then collected for the next process. The production of ciplukan juice drinks is processed by mixing ciplukan juice extract and ciplukan bud extracts with a ratio of 20:1 (v/v). The extract that has been mixed was further added with honey, non-calorie sweetener, and stabilize. The mixture was pasteurized at 70°C, for 15 minutes. After that citric acid is added, homogenized, and packaged in sterilized bottles [9].

The total phenolic contents, total flavonoid contents, and antioxidant activity of *P. angulata* juices drink were determined according to the procedures described by [13]. The phenolic contents were expressed as milligram of gallic acid equivalents (GAE) per g of extract. Flavonoid contents were expressed as mg of quercetin equivalents (QE) per g of extract. Antioxidant activity was expressed as inhibition % of the absorbance at 515 nm, using a UV-Vis spectrophotometer (Shimadzu UV-1900, Tokyo, Japan).

Experimental design

Animal test

A total of 25 rats were kept in cages, separated individually, and fed with standard feeding. Five rats were separated and assigned as the normal (N) group, while the remaining rats were injected with Streptozotocin (STZ) with a single dose of 40 mg/kg BW [15]. Verification of a diabetic condition was characterized by Fasting Blood Glucose (FBG) levels above 126 mg/dl [16]. Rats that received STZ induction became hyperglycaemic on the third day after injection. Rats that showed confirmed hyperglycaemia were divided into 5 groups: N (normal rats, 5 rats), D (negative control, hyperglycaemia rats, 5 rats), D-Mt (control of metformin drugs BW, 5 rats), D-T1 (intervention with ciplukan "Salata drink" juice 1 ml/day, 5 rats), and D-T2 (intervention with ciplukan "Salata drink" juice 2 ml/day, 5 rats). Metformin was dissolved with distilled water to facilitate administration [16]. Intervention with ciplukan "Salata drink" juice and control of metformin drugs were administered using a feeding tube 1 ml at the same schedule every day for 14 days [17]. This study was approved by the Animal Ethics Commission, Research and Community Service Institute, Bogor Agricultural University (No. 156/KEH/SKE/XI/2019 IPB).

Blood glucose level.

Blood glucose level data were measured using a glucometer. Blood was taken from the tip of the tail and dropped on a glucometer strip [18].

Necropsy.

On the 15th day after the intervention, rats were anesthetized with a mixture of ketamine (90 mg) and xylazine (10 mg). Blood was taken from the heart and centrifuged at a speed of 3000 rpm for 15 minutes to obtain the serum part.

Lipid profile

Blood was collected by cardiac puncture and immediately transferred into tube containing EDTA. Blood was then centrifuged at 6.000 gx for 8 min recover serum for the estimation contents of total cholesterol (TC), triglycerides (TGs) and HDL-cholesterol level were estimated using commercial diagnostic kits (Rajawali-Nusindo). All estimations were performed according to the kit manufacturer's instruction [19].

Toxicity and histopathological observation of liver

At the end of the experiment, the rats were consequently euthanized to examine the standard histopathology of the liver. The fibrosis consequences of the treatments were studied using a blind scoring technique [20]. The fibrosis effects were evaluated based on the following criteria: 0 (none, very little), +1 (mild), +2 (moderate), +3 (severe).

Statistical analysis.

Data were processed using Microsoft Excel 2013 and *R*-Statistics 4.0.4 for Windows. The differences in lipid profile between treatments were analyzed using analysis of variance (ANOVA). Significant differences between mean values were determined using Duncan's Multiple Range Test (α=5%) [21].

RESULTS AND DISCUSSION

Antioxidant properties of *P. angulata*

Under chronic hyperglycemia, the antioxidant role of polyphenol can protect pancreatic β-cells from the toxic effects of free radicals [22]. Table 1 showed that *P. angulata* fruit juice contained total phenolics content, flavonoid contents, and antioxidant activity of 18.74 mg GAE/L, 0.25 mg QE/L, and 93.79 µg/mL respectively. The results demonstrated that *P. angulata* juice contains antioxidant activity. Silveira et al. [23] revealed that normal-weight

individuals who consumed red orange juice each day for eight weeks decreased low-density lipoprotein (LDL) cholesterol and C-reactive protein, increased antioxidant activity in serum, and insulin resistance, and systolic blood pressure declined.

TABLE 1: Antioxidant properties of *P. angulata* juices

Constituent	Amount (%)
Total phenolic contents (mg GAE/L)	18.74±0.67*
Total flavonoid contents (mg QE/L)	0.25±0.04*
Antioxidant activity (IC_{50}) (µg/mL)	93.79±0.38

Data are expressed as mean ± standard deviation (Std) (n=3).
*source: [8]

The characteristics of rats

The characteristics of rat samples used in interventions are presented in Table 2. Table 2 showed no significant differences between groups of rats sampled from the blood glucose values of basal and after streptozotocin-treatment and the weight of control and diabetic rats ($P>0.05$). This is indicated that the sample of rats used in the intervention was homogeneous.

TABLE 2: The characteristics of rats

Treatment cluster	Blood glucose (mg/dl)		Weight (g)
	Basal values	After *STZ* -treatment	
N	116.20±8.14	111.40±17.18	127.6±14.17
D	116.00±5.39	116.00±260.4	138.40±21.61
D-T1	111.80±11.30	305.25±129.70	130.60±16.13
D-T2	117.40±6.35	223.75±62.26	126.80±.22.65
D-Mt	120.75±6.40	141.25±15.84	135.60±17.56

Data are expressed as mean ± standard deviation (Std); n=5 animals in each group. N: normal; D: diabetic; D-T1: diabetic+*P. angulata* juice doses I; D-T2: diabetic+*P. angulata* juice doses II: D-Mt: diabetic+metformin. STZ: streptozotocin. *Values are statistically significant at $P<0.05$.

Effect of treatment on lipid profile

Diabetic dyslipidaemia shows high levels of plasma cholesterol (TC), triglyceride (TGs), and low HDL-cholesterol (HDL-c) concentrations and alterations in lipid metabolism can cause lipotoxicity, which can further exacerbate diabetic complications. Table 3 shows the levels of plasma cholesterol, triglycerides, and lipoproteins in rats' control and experimental groups.

The levels of plasma cholesterol and triglycerides were significantly increased, whereas HDL–cholesterol (HDL-c) were significantly decreased in diabetic rats compared with corresponding control rats. Oral administration of *P. angulata* juices and metformin drug to diabetic rats significantly reversed all these changes to near normal levels.

In this light, of course the result of the present study (Table 3) revealed that the levels of triglyceride (TGs) were significantly highest, and levels of HDL–cholesterol (HDL-c) was lowest for the negative control (D groups) ($P<0.05$). The lipid triad (elevated triglyceride, cholesterol levels and decreased HDL-cholesterol concentrations) are there major predisposing factors for atherosclerosis in DM. However, *P. angulata* juices treatment significantly enhanced the levels of lipid triad relative to the negative control across all 14 days ($P<0.05$).

Our biochemical results related to lipid metabolism showed that the *P. angulata* juices have reduced blood triglycerides and increased HDL-cholesterol levels ($P<0.05$). These results suggest that the *P. angulata* juice or *P. angulata* plant would have a significant potential also in the treatment of coronary diseases, which are secondary complications of diabetes [6]. They are in a relationship with the transaminases results, which are operated in the balance cardiac as necrosis marker (mainly AST) combined with other assays. According to Ofusori et al [24], serum triglycerides increase is attributed to insulin deficiency. Furthermore, a study confirmed the reduction in serum cholesterol and triglycerides in mice subjected to hyperlipidemia treated to *Physalis peruviana* [25].

TABLE 3: Effects of *P. angulata* juices on lipid profile levels in diabetic rats at 14 days treatment

Treatment cluster	Total cholesterol (mg/dL)	Triglycerides (mg/dL)	HDL- cholesterol (mg/dL)
N	49.75±6.30	52.00±9.87^{b}	21.67±2.04^{bc}
D	61.00±2.55	65.00±15.28^{a}	20.00±1.41^{d}
D-T1	65.33±0.41	47.67±6.01^{bc}	23.67±3.49^{b}
D-T2	62.25±3.90	37.40±9.34^{cd}	24.80±2.59^{b}
D-Mt	60.25±4.82	34.60±8.56^{cd}	26.00±1.87^{a}

Data are expressed as mean ± standard deviation (Std); n=5 animals in each group. N: normal; D: diabetic; D-T1: *P. angulata* juice dose I; D-T2: *P. angulata* juice dose II: D-Mt: diabetic+metformin. a>b>c>d>e, Values followed different upper-case letters in the same column are significantly different according to the Duncan's test ($P< 0.05$).

Toxicity and histopathological observation of the liver

The liver plays a vital role as a guardian of postprandial hyperglycemia through glycogen synthesis. DM is a result of the failure of the liver in performing glycogenesis. In *STZ*-induced rats, DM occurs because of the deactivation of enzyme glycogen synthase phosphatase [26]. The number of glycogen deposits in individuals with DM decreases because of reduced insulin production or sensitivity; thus, glycogenesis is inhibited, and glycogenolysis occurs in the liver, contributing to an increase in blood glucose levels. Therefore, DM therapy is expected to increase insulin production so that glycogenesis occurs properly, and glycogenolysis can be inhibited to attain glucose homeostasis in the body.

In a normal liver, it is known that lobectomy as much as 70% of the liver results in a very rapid proliferation of liver cells so that within two to three weeks, the lost liver can be replaced. Even so, the continuous damage will cause severe damage to the liver [27]. The scoring levels of liver damage are presented in Table 4.

TABLE 4: Scoring levels of liver damage

Treatment Cluster	Liver
N (normal)	0
D (diabetic rats)	+2
D-T2 (diabetic+ *P. angulata* juice)	0
D-Mt (diabetic+metformin)	+1

0 (none, very little), +1 (mild), +2 (moderate) (2-5 focus of mineralization) in the cortex or renal medulla, +3 (severe).

Table 4 showed that in the positive control (N) rats group, there is congestion in most large blood vessels and infiltration of a small number of mononuclear inflammatory cells in the multifocal parenchyma area. Almost completely degenerate hepatocytes. While a 5 mm cyst was seen on the periphery of the parenchyma in the diabetic rat group (D). The cyst contains pieces of the parasite with outer cuticle layer is cellular, eosinophilic; contains two suckers, hooks, muscle strands, and calcareous bodies (cestoda). The majority of large blood vessels were also congested, and many mononuclear inflammatory cells infiltrate around the cyst. In the group of diabetic+treated with ciplukan juice (D-T2) and diabetic+metformin (D-Mt) rats, there was an infiltration of a small number of mononuclear inflammatory cells in the multifocal areas of the parenchyma, and inflammation in the parenchyma contained a large number of inflammatory lymphocytes, neutrophils (intact and degeneration), edema, lytic necrosis, and aggregation of coccus bacteria, respectively.

Fig. 1 showed that group N has normal liver, central vein, and sinusoid (blood capillary vessels) tissue. Meanwhile, group D suffered serious liver damage. Al-Mahmood et al. [28] and Al Faris et al. [13] explain that giving STZ can cause sinusoid dilatation (widening) and congestion (abundance of blood), centrilobular necrosis, inflammatory cell infiltration, deposition of amyloid material, and fibrosis around the area triad portal. Subsequently, it can be seen that administration of D-T2 stimulates improvement in liver architecture. It appears that there has been a degradation of liver tissue, as shown by the increase in nucleated hepatocytes. This indicates that there is an effect of DM treatment from ciplukan juice. Research [12] reported that an increase in hepatocytes due to flaxseed was shown by returning to normal liver cells without signs of swelling, decreasing central vein obstruction, and normal content of glycogen granules.

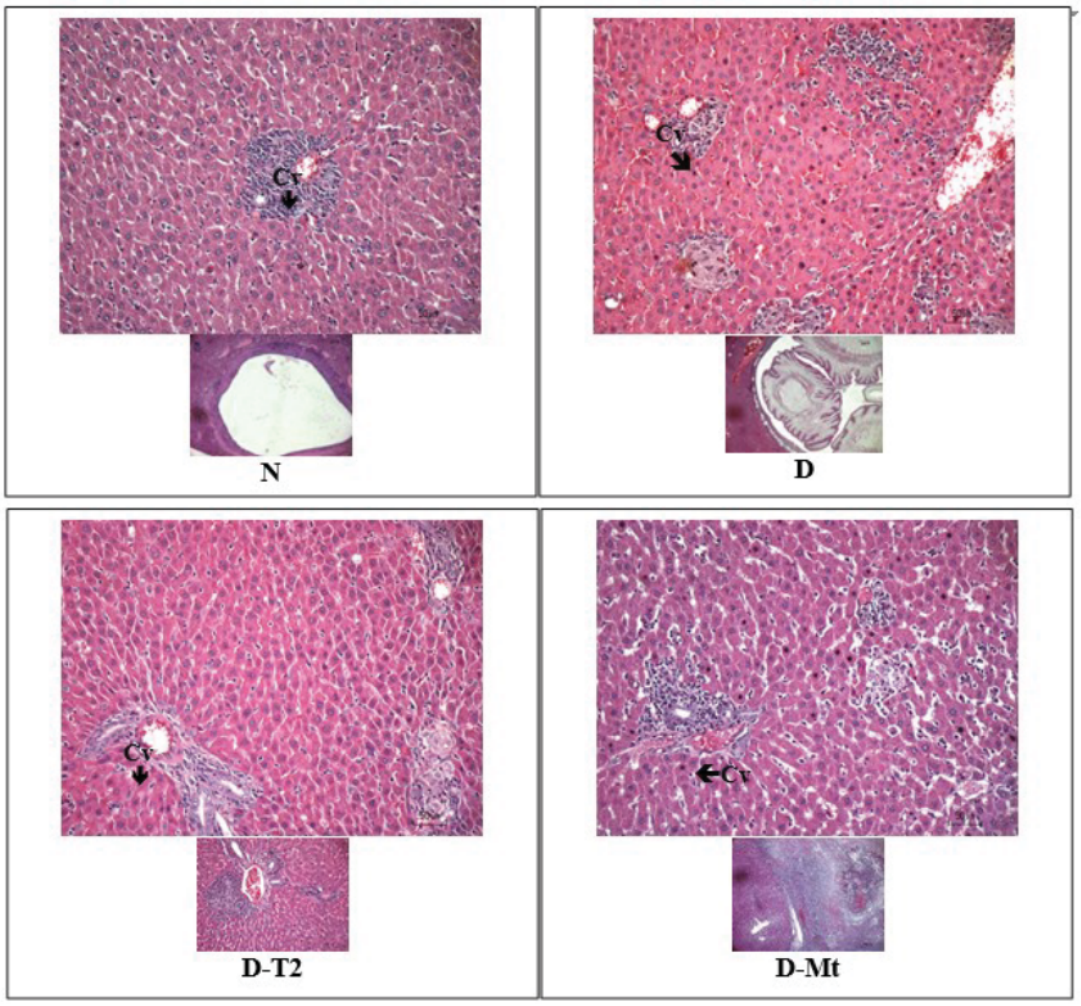

FIGURE 1. Rats' liver histology in all groups by arrows. N: normal; D: diabetic; D-T2: diabetic+ciplukan juice dose II; D-Mt: diabetic+metformin

The mechanism of repair of liver architecture by ciplukan juice has not been clearly explained. However, Kusumaningtyas et al. [29] stated that ciplukan contains phenolic compounds, which are antioxidants. Oliviera et al [30] demonstrated that the antioxidant activity in ciplukan is highest compared to other fruits. The types of phenolic compounds contained in ciplukan are ferulic acid and p-hydroxybenzoic. In addition, there are cinnamic acid derivatives which mostly consist of ferulic acid, synapic acid, p-coumaric, and caffeic acid.

CONCLUSION

In conclusion, *Physalis angulata* juice drink (PJ) has antioxidants to improve the liver's health in diabetic Wistar rats. Therefore, the consumption of PJ would be helpful to control or prevent oxidation, inflammation, and cholesterols in diabetic rats. The results finding support the traditional usage of PJ for controlling blood glucose and hyperlipidemia

in diabetic patients. Hence, these PJ treatments indicated their helpful effects in ameliorating diabetes-associated complications, such as hypercholesterolemia and atherosclerosis.

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AUTHOR'S CONTRIBUTION

A.C.I and R.L. conceptualized, implemented the research, and wrote the manuscript (as main contributor). A.C.I and R.L. contributed equally. N.R. and R.C.E conducted the research. A.C.I, M.D, R.L and Y.A revised the paper.

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