Hypoglycemic effects of *Aloe vera* peel extract on type 2 diabetic rats

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**Abstract.** Aloe vera is one of many medicinal plants used as hypoglycemic. Higher glucose levels are one of the characteristics of diabetes mellitus. This research aimed to study the effectiveness of Aloe vera peel extract on insulin and serum glucose levels of rats with type 2 diabetic. Twenty Wistar rats were induced intraperitoneally using single dose of 65 mg/ kg of streptozotocin (STZ) and 230 mg/ kg of nicotinamide acid (NA). The rats were divided into control and treatment groups, which was supplemented using 100 mg/ kg, 200 mg/ kg and 400 mg/ kg body weight of Aloe vera peel extracts for 28 days, respectively. The serum glucose levels were measured after three days of induction, 2 and 4 weeks after treatment, while the insulin levels were measured after three days of induction and at the end of treatment. In the control groups, the serum glucose levels in the second and fourth weeks remained significantly higher (p<0.05) compared to the treatment group. The insulin levels of the groups with Aloe vera peel extract was significantly higher than control group. Aloe vera peel extract exerts hypoglycemic effects by reducing the blood glucose level and improving insulin secretion on the type 2 diabetic rats.

1. **Introduction**

Diabetes mellitus is a metabolic disorder or chronic disease that is generally indicated by high blood glucose levels caused by disrupted insulin production and its action [1]. Type 2 diabetes mellitus (T2DM) is a common disease. If not handled properly and correctly it will lead to microvascular, macrovascular and other complications [2]. Clinical studies have shown that complications of diabetes take a long time since the disease appears. Complications can cause functional disorders and structural abnormalities in the kidneys, retina, and blood vessels. Furthermore, the severity of complications is related to monitoring of glucose levels and the duration of the incidence of diabetes [3].

T2DM characterizes by insensitive receptors triggering insulin resistance, insufficient insulin production and pancreatic β cell destruction which causes impaired glucose transport to adipose, muscle and liver cells [4]. The main insulin resistance is a contributor to the pathogenesis of T2DM and further consequent rises incidence of dyslipidemia. The release of free fatty acids can inhibit the insulin signaling pathway and cause insulin resistance. During insulin resistance, the combination of failure of
pancreatic β cells in the production of insulin triggered by glucose and impaired glucose tolerance can cause hyperglycemia [5].

Lifestyle, food, and exercise remain the main points in the management of metabolic syndrome and diabetes conditions. Nutritional approaches are needed to improve the occurrence of insulin resistance such as the use of supplements from plants [6]. Previous studies have proven that many plants and their products have hypoglycemia action. Currently herbal products are increasingly in demand for alternative medicine which is believed to have minimal side effects [7,8]. In addition, antidiabetic plants provide new oral hypoglycemia compounds at affordable prices, easily obtained and available especially for people in developing countries [9].

*Aloe vera* is one of antidiabetic plants. Clinical evaluation has revealed that the active components which are pharmacological are mainly found on the peel and the inside / gel of *Aloe vera* leaves [10]. Green leaves are the thickest outer layer of A. vera leaves functioning as a protector which contain carbohydrates and proteins [11]. Research on the structural component of leaf parts show that the skin is 20-30% and pulp is 70-80% of the total dry weight of the leaves. The lipid and protein content of leaf peel was 2.7% and 6.3%, while gel 4.2% and 7.3% [12]. Many effects of the drug have been associated with polysaccharides found in deep gels, and the synergistic action of the active compounds responsible for various plant benefits [13]. Therefore, this study was conducted to study the influence of various doses of *Aloe vera* extract on serum glucose levels and insulin in streptozotocin-induced diabetic rats.

## 2. Methods

### 2.1 Preparation of *Aloe vera* peel extract

*Aloe vera* leaves were washed, cut into pieces and sliced longitudinally to separate the thick peel with the center of the gel. The peel was wiped off in a cabinet dryer and was made into a slurry using a blender with 95% ethanol. The filtrate was filtered using paper and evaporated ethanol until a viscous ethanolic extract was obtained in a rotary evaporator at 60°C.

### 2.2 Animals treatment

The twenty two-months-old male-Wistar rats weighing 170-200 gr were grouped into four groups, which consisted five rats each groups. The rats were given standard feed and water ad libitum. Before initiating the experiments, the rats had been acclimatized for 7 days in normal laboratory conditions of temperature, humidity, dark and light cycles. All experimental animals were treated based on animal care and used guidelines in the food and nutrition laboratories in the Center for Food and Nutrition Studies of Pusat Antar Universitas (PAU) Universitas Gadjah Mada. This study was performed in accordance with the ethical norms approved by the Commission of Health Research Ethics Faculty of Medicine Diponegoro University/RSUP Dr. Kariadi Semarang (Approval no. 75/EC/H/FK-SDK/X/2017).

The experimental groups are illustrated as follows: for the first group, all rats were received placebo (distilled water). Then, for the test groups were received *Aloe vera* peel extract every day orally, which 100 mg/ kg were given for Group II, 200 mg/ kg for Group III and 400 mg/ kg for Group IV. The treatment was conducted for 28 days.

After 28 days, the rats’ blood was collected from the orbitalis vein, then sacrificed by cervical decapitation after completing the treatment on day 29th. The blood was collected and placed inside microtubes, the centrifuged for 15 minutes at 5000 rpm to separate serum from blood. The serum glucose were carried out using Glucose GOD FS (DiaSys Diagnostic Systems GmbH Germany) and insulin levels were analysis using an enzyme-linked immunosorbent assay (ELISA) kit (Rats insulin ELISA Kit, Wuhan Fine Biotech Co., China).

### 2.3 Induction of diabetes

Experimental animals were fasted overnight before being induced by injection single dose of 65 mg /kg of streptozotocin and 230 mg/kg body weight of Nicotinamide acid, intraperitoneally. Hyperglycemia
condition was observed after three days after injection to determine T2DM condition. The rats with a serum glucose levels ≥200 mg/dl were selected [14].

2.4 Statistical Analysis

The serum glucose and insulin data were analyzed statistically using one way analysis of variance (ANOVA), the different mean scores among group were follow tested by least significant difference (LSD); p < 0.05. All of the data analysis were conducted in SPSS 20 for Windows.

3. Results and Discussion

Glucose levels of rats on day 3 after induction of STZ and NA produced an average of more than 200 mg/dl. These results showed that on day 0 the treatment of all rats was hyperglycemia. The administration of Aloe vera peel extract in groups II, III and IV were given significant results in reducing serum glucose levels. In the second and fourth week measurements, compared to the control group, the serum glucose levels in the treatment groups were significantly decreased. Variations in extract doses also showed a significant difference in reducing glucose levels. The greater the dose given there was a tendency to decreased glucose levels (Table 1).

| Group | Blood Glucose (mg/dl) | 2nd week | 4th week |
|-------|------------------------|----------|----------|
| I     | 254.5±1.9              | 255.9±1.6 | 256.7±2.1 |
| II    | 257.4±3.1              | 223.7a,b,c,d±2.8 | 140.0a,b,c,d±2.8 |
| III   | 253.4±1.8              | 192.1a,b,c,d±3.9 | 101.2a,b,c,d±3.6 |
| IV    | 257.7±3.8              | 174.6a,b,c±3.6 | 88.7a,b,c±5.7 |

Significant difference p<0.05, superscript alphabetic font (a,b,c,d) representing significant differences among groups, ns = non significant

All groups insulin levels measured on day 0 were no different. Oral administration Aloe vera peel extract for 28 days was able to increase the insulin level of the treatment group, significantly. The significantly different was presented both in among treatment group (the groups were supplemented with 100 mg, 200 mg and 400 mg / kg) and with control group (Table 2).

| Group | Insulin (pg/ml) | 4th week |
|-------|-----------------|----------|
| I     | 438.7±2.2       | 405.8±3.5 |
| II    | 442.7±4.7       | 467.7a,b,c,d±2.1 |
| III   | 435.7w±3.8      | 503.1a,b,c,d±4.3 |
| IV    | 425.9±4.4       | 527.3a,b,c±6.7 |

Significant difference p<0.05, superscript alphabetic font (a,b,c,d) representing significant differences among groups, nw = non significant

Blood glucose levels in group I (control) still showed hyperglycemia both on day 0, after the second and fourth weeks. Meanwhile, the group that received various doses of peel extract showed a significant decreased (p <0.05) (Figure 1). This decreased was indicated by the results of the second week's measurement until the fourth week (Figure 1). The serum insulin levels in Group I at the fourth week was 405.8 pg/ml lower than on day 0 438.7 pg/ml. There was an increased in insulin levels in the group received Aloe vera peel extract, group II from 442.7 pg/ml to 467.7 pg/ml, 435.7 pg/ml to 503.1 pg/ml (group III) and group IV from 425.9 pg/ml to 527.3 pg/ml (Figure 1).
In 28th day after treatment, the serum glucose levels significantly decreased in the rats of treatment groups. It was indicating that Aloe vera’s supplementation has positive effect in reducing diabetes. The injection of Streptozotocin in rats caused a significant increase in the serum glucose levels of the controlled rats. Oral supplementation of Aloe vera peel extract was reduced serum glucose concentration. The hypoglycemic action of the Aloe vera peel extract was established by this study as has been demonstrated by other research. Peniati et. al., [15] reported that Aloe vera administration for 28 days was significantly able to decrease serum glucose in fasting alloxan-treated albino rats. The hyperglycemia condition as a result of free radical oxygen species overproduction contributes to the progression of T2DM. The further complications that followed during T2DM are also associated to the oxidative stress condition. Aloe vera leaf peel extract was found more effective than the known hypoglycemic drug glibenclamide in both types of diabetes[16].

In addition to lipids and proteins, Aloe vera also contains a lot of magnesium, calcium, sodium, zinc and iron [17,18]. Minerals such as Cr, Zn, and Mn are responsible for co-factor, induction, and insulin secretion. These elements are widely known as hypoglycemic elements because they have a large role in glucose metabolism. Chromium facilitates a further increase in insulin and glucose absorption to cells [19, 20]. Other researchers stated that Aloe vera can reduce hyperglycemia because of increase levels of calcium that can stimulate beta cells to secrete insulin and in turn increase liver glycogen levels, stimulate metabolism which increases glycogenesis and glycolysis [21].

Aloe vera peel has a high content for phenolic and flavonoid compounds indicating that the skin is a potent antioxidant agent sources [22]. Aloe vera extract could act directly to collect reactive oxygen metabolites as various antioxidant principles such as flavonoids are there [23]. A recent study of oxidative stress condition in pancreatic β-cell damage, clarifying that the presence of oxidative stress is a major factor correlates to pathogenesis of diabetes. Therefore, Aloe vera is potential to ameliorate the β cells [24].

The increase of liver glycogen levels which reduced in type 2 diabetes rats due to the Aloe vera peel extract showed an increase in liver glycogenesis [25]. The anthraquinone component in Aloe vera peel is found to stimulate glycogen synthesis by inhibiting glycogen synthase kinase-3β which thereby boost the glucose transport and transformation into glycogen [26]. After that, low serum glucose condition
and increased glycogen content in liver may be the results of pancreatic β cell activity which leads to the stimulation of insulin biosynthesis and secretion that increases the glycogen and glycolysis [27].

The results of this research was in accordance with the results previous studies showed that Aloe vera extract was also effective in reducing hyperglycemia in rats induced by alloxan [28, 29]. In another study it was also mentioned that Aloe vera extract can also reduce cholesterol levels, triglycerides and fats in diabetic induction alloxan [30]. In the final words, this research result indicates that Aloe vera is a promising antidiabetic especially for T2DM, Furthermore, it needs further clinical trials concerning the clinical use of the Aloe vera extract as antidiabetic to treat T2DM.

4. Conclusion

This study concluded that Aloe vera peel extract was able to reduce glucose levels and increase insulin concentration in T2DM rats. Further research was needed to determining the optimal dose and identify the mechanism of action of the components of Aloe vera peel which specifically have hypoglycemic efficacy.

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