

Aloe Vera Peel Extract Administration Increased Antioxidant Enzyme Levels of Serum and Seminal Plasma in Type 2 Diabetic Rats

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ABSTRACT

Background: Diabetes mellitus (DM) is considered as a complex metabolic disorder characterized by hyperglycemia. **Aim:** The present study aimed to evaluate the effect of *Aloe vera* peel extract on the antioxidant levels of serum and seminal plasma of type 2 diabetic rats. **Materials and Methods:** Male Wistar rat was injected by 65 mg/kg streptozotocin (STZ) combined with 230 mg/kg of Nicotinamide acid (NA) intraperitoneally. The rats were declared to have diabetic with fasting blood glucose level > 200 mg/dl 72 hours after induction. Diabetic rat samples were divided into four groups, control group (diabetes without treatment) and three groups were treated by *Aloe vera* peel extracts orally: 100 mg (P.1), 200 mg (P.2), and 400 mg/kg body weight (P.3), respectively. Antioxidant levels of serum and seminal plasma, including superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH) were examined after 28 days of treatment. **Results:** The levels of SOD, CAT, and GSH in the group receiving *Aloe vera* peel extract were statistically significant ($p < 0.05$) higher than the control. There were also significant differences between the dose variations group. **Conclusion:** *Aloe vera* peel extract can significantly increase antioxidant levels in serum and seminal plasma of type 2 diabetic mice.

Key words: *Aloe vera* peel extract, Antioxidants, Diabetes, Seminal Plasma, Serum.

INTRODUCTION

Diabetes mellitus (DM) is a heterogeneous and complex metabolic disorder characterized by high blood glucose levels (hyperglycemia). Insufficient or ineffective insulin contributes to the etiology of diabetes. Type 1 diabetes is an autoimmune disease that causes pancreas β cell damage resulting in insulin deficiency, whereas type 2 diabetes develops due to inefficient use of insulin or insufficient insulin production.¹ Prevalence of diabetes in the world in the adult age range 20 - 79 year by 6.4% affecting 285 million (2010). It will increase to 7.7% and 439 million people by 2030.² In addition, between 2010 and 2030, there will be a 69% increase in developing countries and 20% in developed countries.³

Hyperglycaemia in diabetes leads to oxidative stress conditions with increased free radical formation derived from non-enzymatic protein glycation, glucose oxidation, and increased lipid peroxidation. This results can damage the enzymes, cellular machinery, and increased insulin resistance; therefore, the oxidative stress becomes an essential factor in the pathophysiology of diabetes complications.^{4,5} In addition, oxidative stress in diabetes is also caused by decreased antioxidant mechanisms with reduced catalase production (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GSH).⁶ The mechanisms of antioxidant protection in helping diabetes treatment and its complications have

been demonstrated in experimental, clinical, and epidemiological studies.⁷ Antioxidants can inhibit the activity of free radicals through several ways such as acting as an enzyme, the ability to bind metals that stimulate the production of free radicals and act as free radical scavengers.⁸ Various types of antioxidants, especially from natural sources such as enzymes (SOD, CAT, and GSH), tocopherol, carotenoids, ascorbic acid, polyphenols can inhibit cell damage from free radicals.⁹

In recent decades, WHO has supported traditional treatment programs with medicinal plants.¹⁰ Medicinal plants are plants that in one or more parts such as leaves, roots, rhizomes, stems, bark, flowers, fruits, grains contain substances that can be used for therapeutic purposes.¹¹ Research on plants containing glycosides, alkaloids, terpenoids, anthocyanins, tocopherols, flavonoids, carotenoids, polyphenols, peptidoglycan, steroids, coumarin and other constituents are often involved as an antidiabetic activity.¹²

The gel and peel of *Aloe vera* are common in use as alternative medicines. There is the fact that *Aloe vera* peel has a higher content of phenol and flavonoid compounds than in the gel¹³ and it is widely employed in the study of antioxidant activity.^{14,15} Moreover, *Aloe vera* peel extract has been examined for its antimicrobial effect against *Staphylococcus aureus*, *Bacillus spp.*, *Enterococcus spp.*, and *Aspergillus niger* which was characterized by a significantly reduced number of bacterial and fungal colonies after treatment using peel extract.^{16,17} *Aloe vera* peel

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also has strong scavenging activity against radical superoxide and is moderate for lipid peroxidation.¹⁸ Other researchers state that peel extracts can significantly reduce serum 8-oxo-dG levels compared to the gel.¹⁹

MATERIALS AND METHODS

Animal samples and experimental design

An experimental study with post test only control group design was employed. Thirty-two Wistar rats weighing 175 - 200 g were acclimated for one week before treatment. Rats were placed in individual cages with a standard feed of pellets and *ad libitum* drinking. They were maintained indoors with temperatures at ± 24 °C, humidity and light-dark cycles of 12 h: 12 h by laboratory protocol of Food and Nutrition, Inter-University Food and Nutrition Studies Center, Gadjah Mada University, Yogyakarta. The Commission of Health Research Ethics Faculty of Medicine Diponegoro University/RSUP dr. Kariadi Semarang has approved this research.

Chemicals

Streptozotocin (No: 32238-91) and nicotinamide acid (No: 24303-84) were obtained from Nacalai Tesque, Inc. Kits from bioVision Inc., USA were used for examining the serum and seminal plasma antioxidant; i.e., superoxide dismutase (Catalog #K335-100), catalase (Catalog # K773-100) and glutathione (Catalog # K264-100).

Extraction of *Aloe vera*

Aloe vera plants were obtained from Sleman, Special Region of Yogyakarta Province, Indonesia. The plants were subsequently identified in the Laboratory of Plant Taxonomy, Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Negeri Semarang (No. 800/UN/37.1.4.5/LT/2017). *Aloe vera* leaf peel was cut into small pieces ± 2 cm. It was dried in a cabinet dryer at 40 °C and mashed into flour. The flour was dissolved in 70% ethanol with a ratio of 1:10, macerated for 48 h to get the macerate which was further concentrated with the rotary evaporator to obtain the viscous extract.

Induction of type 2 diabetes mellitus and treatment

Thirty-two rats were injected with a single dose of streptozotocin at 65 mg/kg and nicotinamide acid at 230 mg/kg body weight intraperitoneally. Diabetic rats were characterized by blood glucose levels of ≥ 200 mg/dl at 72 h after induction.²⁰ Then, it was divided into 4 groups with 8 rats on each group, i.e., the first group is control group (C) that treated using placebo, second group was received 100 mg/kg (P.1), then for third 200 mg/kg (P.2) and fourth group were received 400 mg/kg of *Aloe vera* peel extract (P.3). *Aloe vera* leaf peel extract was given for 28 days.

At the end of the study, blood was taken from an orbital vein with microhematocrit and collected in the microtubes with EDTA as an anticoagulant. Microtubes were centrifuged at 4000 rpm for 15 min to get the serum. Rats were decapitated and dissected in the

abdominal section. Then, testes and its ducts were taken. Next, the caudal epididymis section was cut into pieces and mixed with 2 ml PBS (phosphate buffer saline) solution. Homogenate was centrifuged at 4000 rpm for 15 min to obtain the supernatant used for examination of superoxide dismutase, catalase, and glutathione.²¹ Superoxide dismutase (SOD) serum and seminal plasma were measured using the xanthine oxidase activity.²² Catalase (CAT) was measured based on the reduction of the hydrogen peroxide bond (H_2O_2).²³ Glutathione (GSH) was examined based on the 5,5-dithiobis (2-nitrobenzoic acid) (DTNB) reaction.²⁴

Data analysis

Data were presented as the mean \pm standard deviation (SD). The significant difference between the control group and treatment groups was analyzed statistically by one-way ANOVA followed by LSD (*Least Significance Different*) test. The result is significant with the p-value at < 0.05 .

RESULTS

The results of the antioxidant of the serum are presented in Table 1. The mean SOD of the control group (21.81 ± 5.97) showed a significant difference ($p < 0.05$) compared with P.1 (39.21 ± 7.49), P.2 (52.20 ± 6.28) and P.3 (59.56 ± 5.34). P.1 was significantly different ($p < 0.05$) with P.2 and P.3; P.2 was also significantly different from P.3. *Aloe vera* peel extract of each dose 100, 200 and 400 mg/kg gave a significant difference in the levels of CAT and GSH P.1 (2.48 ± 0.07 and 46.01 ± 3.27), P.2 (5.07 ± 0.12 and 66.17 ± 2.97) and P.3 (5.65 ± 0.29 and 76.01 ± 2.06) compared to the control group (1.89 ± 0.15 and 27.88 ± 3.26). Catalase and GSH between treatment groups also showed a significant difference ($p < 0.05$).

Aloe vera leaf peel extract was able to significantly increased SOD, CAT, and GSH of the serum. Figure 1 shows that the control group is lower for SOD, CAT, and GSH than the treatment group and will increase consecutively according to the dose of *Aloe vera* peel extract given at 100, 200 and 400 mg/kg.

The superoxide dismutase of seminal plasma in the control group (14.22 ± 7.09) was significantly lower with P.1 (27.94 ± 6.93), P.2 (46.32 ± 5.64) and P.3 (49.02 ± 6.79), as well as P.1, compared to P.2 and P.3 group; while P.2 was no different from P.3. The control group CAT levels (1.83 ± 0.15) showed significant different ($p < 0.05$) with the treatment group, also for P.1 (2.40 ± 0.09), P.2 (5.04 ± 0.09) and P.3 (5.56 ± 0.19), which was significantly different one with others. Glutathione of seminal plasma of control group (26.91 ± 2.96), P.1 (43.89 ± 4.09), P.2 (63.28 ± 3.85) and P.3 (73.02 ± 2.33) showed significant differences in each group (Table 2).

The superoxide dismutase level of seminal plasma (14.22 U/ml), CAT (1.83 nmol/ml) and GSH (26.91 μ g/ml) were the lowest control group which would then increased according to the dose of *Aloe vera* extract given successively P.1 (27.94 , 2.40 , 43.89), P.2 (46.32 ; 5.04 ; 63.28) and P.3 (49.02 ; 5.56 ; 73 ; 02) (Figure 2).

Table 1: Superoxide dismutase, catalase and glutathione of type 2 diabetic rat serum on control and treatment group of *Aloe vera* peel extract.

Group	Superoxide dismutase (SOD) (U/ml)	Catalase (CAT) (nmol/ml)	Glutathione (GSH) (μ g/ml)
DM + Distilled water	21.81 ± 5.97	1.89 ± 0.15	27.88 ± 3.26
DM + 100 mg/kg/day	$39.21 \pm 7.49^*$	$2.48 \pm 0.07^*$	$46.01 \pm 3.27^*$
DM + 200 mg/kg/day	$52.20 \pm 6.28^*$	$5.07 \pm 0.12^*$	$66.17 \pm 2.97^*$
DM + 400 mg/kg/day	$59.56 \pm 5.34^*$	$5.65 \pm 0.29^*$	$76.01 \pm 2.06^*$

Data is presented as mean \pm Sd. * $p < 0.05$ compared to control # $p < 0.05$ between treatments

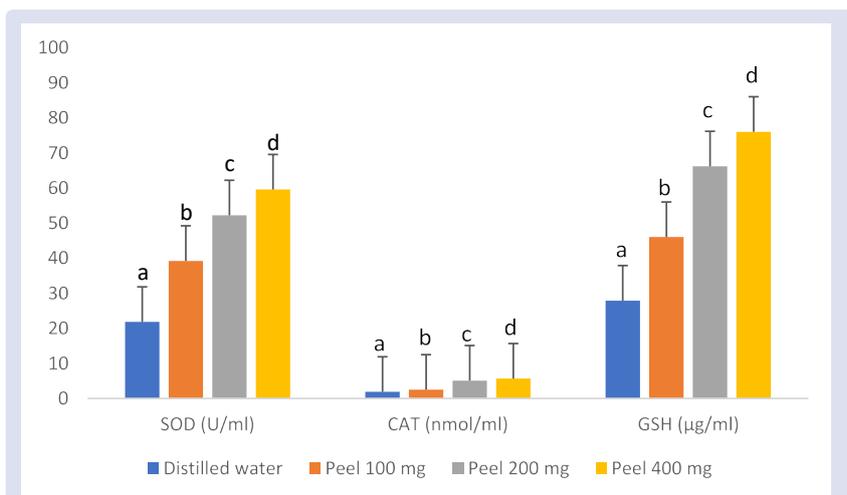


Figure 1: Comparison of superoxide dismutase, catalase, and glutathione of rat serum of control and treatment group. Bars with the same letters are not significantly different ($p < 0.05$).

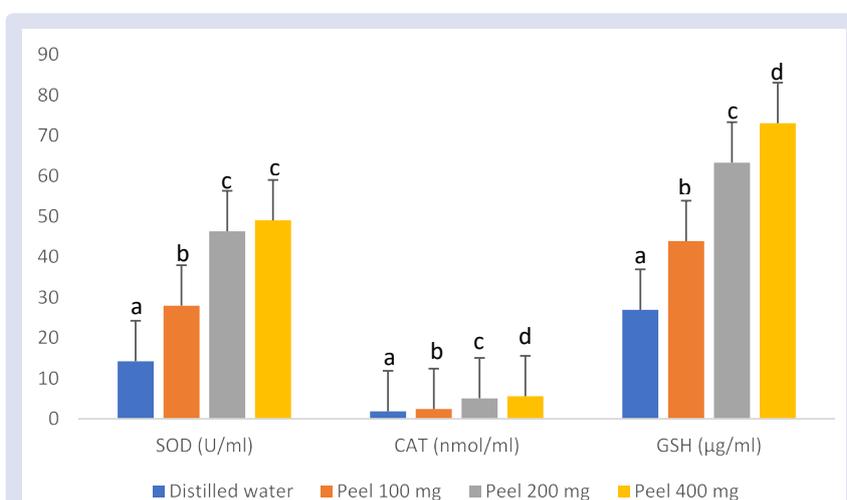


Figure 2: Comparison of superoxide dismutase, catalase, and glutathione of rat seminal plasma of control and treatment group. Bars with the same letters are not significantly different ($p < 0.05$).

Table 2: Superoxide dismutase, catalase, and glutathione of type 2 diabetic rats seminal plasma on control and treatment group of *Aloe vera* peel extract.

Group	Superoxide dismutase (SOD) (U/ml)	Catalase (CAT) (nmol/ml)	Gluthatione (GSH) (µg/ml)
DM + Distilled water	14.22 ± 7.09	1.83 ± 0.15	26.91 ± 2.96
DM + 100 mg/kg/day	27.94 ± 6.93 [#]	2.40 ± 0.09 [#]	43.89 ± 4.09 [#]
DM + 200 mg/kg/day	46.32 ± 5.64 [#]	5.04 ± 0.09 [#]	63.28 ± 3.85 [#]
DM + 400 mg/kg/day	49.02 ± 6.79 [#]	5.56 ± 0.19 [#]	73.02 ± 2.33 [#]

Data is presented as mean ± SD. * $p < 0.05$ compared to control, [#] $p < 0.05$ between treatments

DISCUSSION

The level of blood glucose was found to be higher than the normal level. It indicates that there was oxidative stress by the elevation of free radicals and the mechanism of antioxidants alleviation. The results showed that serum SOD, CAT, and GSH levels in the diabetic group were significantly the lowest (Table 1, Figure 1). This result is the same as the results of the study of the Abo-Youssef *et al.*²⁵, which stated that the group of diabetic rats induced by streptozotocin had decreased levels of SOD and GSH. The administration of *Aloe vera* skin extract at a dose of 100, 200, and 400 mg/kg in diabetic rats could significantly increase serum SOD, CAT, and GSH. This result is supported by a study

that was resulting in the levels of the antioxidant enzymes (SOD and GSH) increase, and the malondialdehyde (MDA) levels decrease with the administration of aqueous extract of *Aloe vera* doses at 150 and 300 mg/kg.²⁶

The presence of free radicals can be reduced by involving endogenous and exogenous antioxidants. Food is the best source of various exogenous antioxidants.²⁷ For example, vegetables and fruits are rich in vitamins (E, C) and polyphenol compounds, which are included as important antioxidants.²⁸ In this case, *Aloe vera* peel contains organic and bioactive compounds that have great potential as antioxidants such as flavonoids, ascorbate acid, β -carotene, and α -tocopherol.²⁹

Aloe vera is one of the popular plants with its feature of active substances. Many previous studies used *Aloe vera* gel as antidiabetic agent^{30,31} and to accelerate spermatogenesis.^{32,33} In this research, *Aloe vera* peel was proved that it has several constituents better than the gel part. Peel extract with ethanol solvent has free radical scavenger activity 39.7% greater than 14.2%.³⁴ Antioxidant activity with 2,2-Azobis(3-ethylbenzthiazoline-6-sulphonic acid) ABTS method at 10.4 ± 0.5 mg/ml, total phenol 7.99 ± 0.26 mg gallic acid equivalent (GAE)/g, 9.17 ± 0.19 mg quercetin equivalent (QE)/g flavonoids were also higher than gel extracts.¹³

Antioxidant enzymes in seminal plasma also increased significantly in the group that received *Aloe vera* peel extract compared to the diabetes group (Table 2, Figure 2). Antioxidants in seminal plasma play an important role in protecting sperm because of the limitations of intracellular antioxidants.³⁵ Seminal plasma has a rich source of antioxidants such as SOD, GSH, catalase, vitamin C, and vitamin E as a defense mechanism to protect sperm from oxidative stress.³⁶

Enzymatic antioxidants are natural antioxidants to neutralize excess free radicals and to prevent cell damage. The SOD enzyme is the earliest defense against free radicals in all cells and converts O_2^- to H_2O_2 .³⁷ Glutathione peroxidase plays the role of its catalyst by reducing hydrogen peroxide and organic peroxide including phospholipid peroxide^{38,39}, whereas catalase breaks down hydrogen peroxide into oxygen and water.⁹

Aloe vera is one of the recognized medicinal plants in diabetes management and is beneficially protective acting as free radical scavengers and other antioxidant properties in diabetic patients.³¹ *Aloe vera* has antioxidant potential through mechanisms to inhibit the free radical formation and increase cellular thiol status.²⁵ Presence of various antioxidants such as flavonoids can act directly to scavenge for reactive oxygen metabolites.²⁶ Phenolic compounds and flavonoids contribute by donating hydrogen atoms.⁴⁰ In addition, they also inhibit enzymes and elements involved in the formation of free radicals, reduce hydrogen peroxide, and produce highly reactive hydroxyl radicals.⁴¹ These antioxidant components can directly look for reactive oxidants, protect membranes lipids from lipid peroxidation which can ultimately reduce the total or partial clinical abnormality of diabetes.⁴²

CONCLUSION

Aloe vera peel extract has a potency of reducing the oxidative in the diabetic rat by increasing the serum and seminal plasma antioxidant levels. Data from the study showed that administration of a peel extract dose of 400 mg/kg was able to provide the highest levels for SOD, CAT, and GSH.

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CONFLICTS OF INTEREST

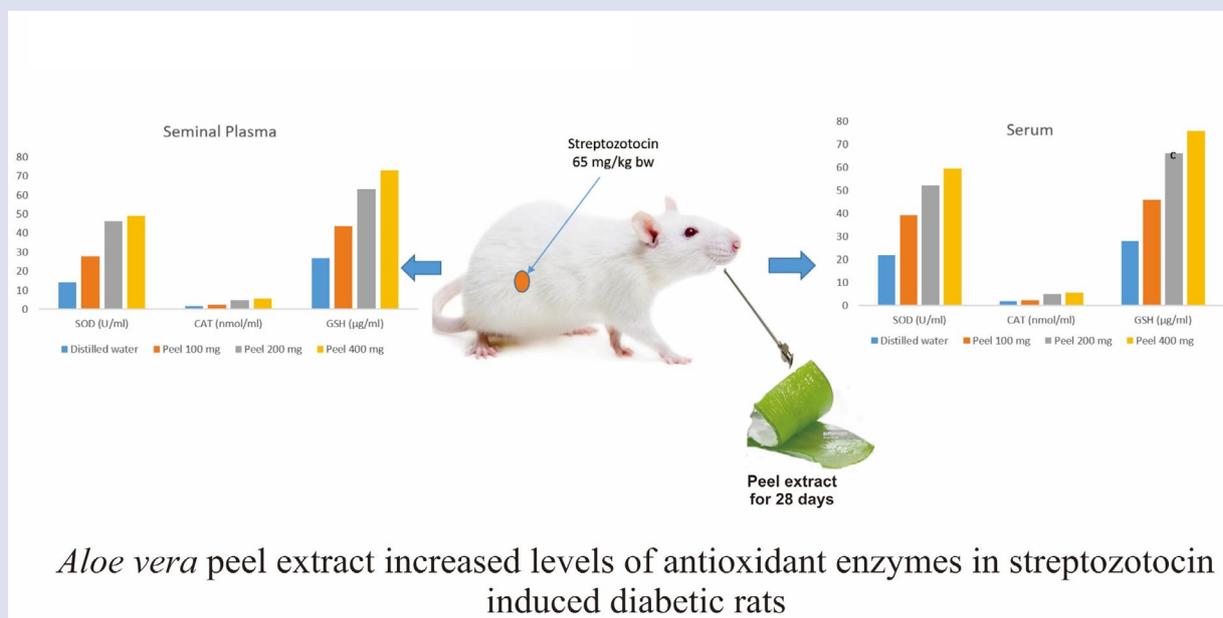
All authors declare that there is no conflict of interest in this research content and its components of the process (sample, preparation, research, and publication).

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GRAPHICAL ABSTRACT



ABOUT AUTHORS



Wulan Christijanti since 1996 worked as a lecturer in Animal Physiology, Department of Biology, Faculty of Mathematics and Natural Sciences, Semarang State University. She is currently completing a doctoral program in the Doctoral Program in Medical / Health Sciences, Faculty of Medicine, Diponegoro University. Her research interest is the use of medicinal plants for the reproduction of male animals.



Dr. Achmad Zulfa is an Andrology specialist who received his PhD in 2014 from Erasmus Universiteit Rotterdam.



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