

In vitro and *In vivo* Anti-Diabetic Activity of Extracts From *Actinidia kolomikta*

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Abstract

Diabetes is a chronic disease, which occurs when the pancreas not produces enough insulin, or when the body cannot effectively utilise the insulin it produced. The anti-diabetic activities of both roots and leaves extracted by water and ethanol from *Actinidia kolomikta* (*A. kolomikta*) have been corroborated by this research by *in vitro* and *in vivo* tests. In the alpha-glucosidase inhibitory activity test, ethanol extract of roots showed the best inhibitory activity (74.2%, 6 mg/ml). Aqueous extracts from leaves prevented the increase in blood glucose level without causing a hypoglycemic state in the oral glucose tolerance test (120 min, 0.8 mg/g, 85.2 mg/dl) which performed *in vivo* and the maximum effect of the extract showed in 60 and 90 min after the administration of glucose. In the long term anti-diabetic test, the activities of regulation for the blood indicators demonstrated ethanol extracts of the roots from *A. kolomikta* has the effect to prevent and regulate the issue dysfunctions cause by complications of diabetes. The results reveal that roots and leaves of *A. kolomikta*, as forestry waste before, possess a high potential for the development of novel anti-diabetic drugs.

Keywords: *Actinidia kolomikta*, anti-diabetic activity, alpha-glucosidase

1. Introduction

Diabetes mellitus, which was considered as a disease of minor significance to world health, now is taking its place as one of the main threats to human health in the 21st century (Zimmet, 2000). The number of people afflicted with diabetes experienced an explosive increase in the past 20 years worldwide (Amos et al., 1997; King, Aubert, & Herman, 1998). In 2004, about 3.4 million people died from consequences of abnormal fasting blood glucose (Yen-Chang, Trần Dương, Shu-Yin, & Pung-Ling, 2014). More than 80% of deaths caused by diabetes occur in low and mid income countries (Mathers & Loncar, 2006). WHO estimated that diabetes would be the 7th major cause of death in 2030 (Lopez & Mathers, 2006). Diabetes mellitus is a metabolic disorder of multiple etiologies characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulted from defects in insulin secretion, insulin action, or both (Geert et al., 2006). Diabetes mellitus may present with characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss (Intekhab & Barry, 2006). The long term effects of diabetes mellitus include progressive development of the specific complications of retinopathy with potential blindness, nephropathy that may lead to renal failure, and/or neuropathy with risk of foot ulcers, amputation, Charcot joints, and features of autonomic dysfunction, including sexual dysfunction (Intekhab & Barry, 2006).

Diabetes mellitus was divided into two major types, Type 1 (Insulin Dependent Diabetes Mellitus) and Type 2 (Non-Insulin Dependent Diabetes Mellitus), and about 90% of diabetes patients in the world are Type 2 diabetes (Lilliooja et al., 1993). Daily injection of insulin, the main treatment method employed to management of Type 1 diabetes, is administered and also brings great pain to patients. Alpha-glucosidase inhibitors focusing on reducing the digestion of carbohydrate are the most common and efficacious agents utilized for the treatment of Type 2 diabetes. Since alpha-glucosidase inhibitors prevent the hydrolyzation of carbohydrates into glucose, a large amount of carbohydrates remain in the intestine. Therefore the bacteria will digest the carbohydrates, which may cause gastrointestinal side effects such as flatulence and diarrhea.

In recent years, more and more researches are focused on anti-diabetic effect brought by natural plants. For

example, American Ginseng (Xie et al., 2004), green tea (Chen, Zhang, & Xie, 2005), astragalus (Zhou, Wu, & Ouyang, 2005) are reportedly used as anti-diabetic agent. *Actinidia kolomikta* (*A. kolomikta*), belong to genus *Actinidia* (over fifty-eight species) which is a locally renowned traditional medicine for diabetes (Guan et al., 2011). Anti-tumor activity, immunomodulatory activity (Guan et al., 2011), anti-proliferative activity (Liu et al., 2010), anti-oxidant activity (Sun et al., 2013) have been also evaluated gradually. Moreover, anti-diabetic activity of aqueous extracts from *A. kolomikta* roots was investigated. However, in this study, ethanol extracts and aqueous extracts from roots and leaves were further executed *in vitro* and *in vivo* through alpha-glucosidase inhibitory activity, oral glucose tolerance test and long term hypoglycemic activity.

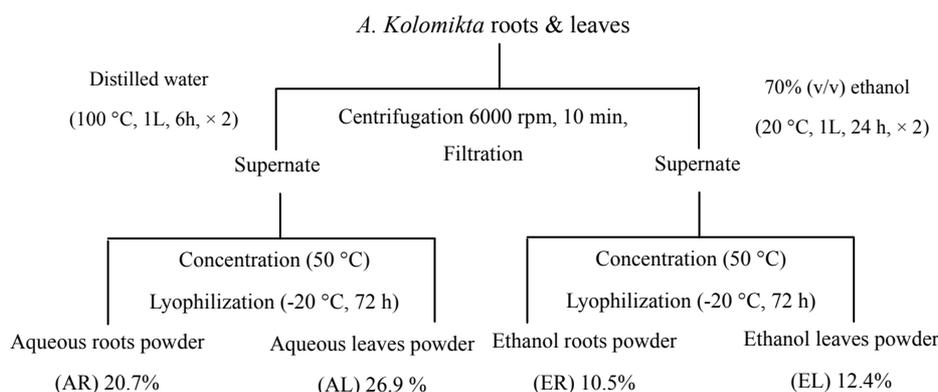
2. Materials and Methods

2.1 Materials and Reagents

Glucose, sucrose, maltose, acarbose, glucose assay kit, dimethyl sulfoxide and ethanol (99.5%) were purchased from Wako Pure Chemical Industries. (Osaka, Japan). α -glucosidase from intestine of rat was provided from Oriental yeast Co., LTD. (Tokyo, Japan). Streptozotocin and glibenclamide were purchased from Sigma-Aldrich Co., LTD. (St. Louis, MO, USA). All other chemicals and solvents were analytical grade and used without further purification.

2.2 Preparation of Different Extracts

Roots (200 g) and leaves (200 g) of *A. kolomikta* were used in this experiment. Raw materials were washed with distilled water and dried in a conventional oven (50 °C, 72 h). Dried roots and leaves were well powdered by a dry pulverizer (National MX-152S, National, Co., Ltd., Japan).



2.3 Animals and Experimental Design

10 weeks old of Sprague Dawley rats weighting about 250 g were obtained from Laboratory Animal Resource Center, University of Tsukuba (Japan). All mice were randomly separated into 5 groups consisting of six per cage and fed standard laboratory chow with 12-h dark/light cycle conditions for 1 week before the start of the experiments with a constant temperature of 20 ± 2 °C and humidity, $60 \pm 5\%$. All laboratory feed pellets and bedding was autoclaved and supported by Laboratory Animal Resource Center, University of Tsukuba (Japan).

Type 2 diabetes was induced (Masiello et al., 1998) with slight modifications, by using standardized dose of STZ. Intraperitoneal injection of freshly prepared STZ (55 mg/kg) in 0.1 M citrate buffer (pH 4.5) in a volume of 1 mL/kg was injected to overnight-fasted normal rats, 15 min after intraperitoneally injected administration of nicotinamide (210 mg/kg). Hyperglycemia was confirmed by elevation in blood glucose levels, determined at 96 h after the STZ-nicotinamide administration. Rats with a fasting blood glucose range of 11-14 mmol/L were considered DM2 and subsequently used for the study.

2.4 Assay for Alpha-Glucosidase Inhibitory Activity of Extracts From *A. kolomikta*

Alpha-glucosidase inhibitory activity was determined using the method introduced a literature (Brain et al., 1997). Alpha-glucosidase solution (1.52 UI/ml) obtained by mixing 1 mg powder (76 UI) with 50 ml phosphate buffer (pH 6.9) was stored at -20 °C. 0.1 mL of gradient concentrations (0.094, 0.187, 0.375, 0.75, 1.5 and 3 mg/ml) of extracts then was mixed with 0.35 ml of sucrose (65 mM) and maltose solution (65 mM), respectively. After preheated (37 °C, 5 min), 0.2 mL of alpha-glucosidase solution was added into the preheated system and

then reacted at 37 °C for 15 min. The reaction was arrested by heating the system in 100 °C water bath for 2 min. Acarbose was used in this experiment as the positive control and a group without an addition of extracts was served as negative control. The treatment of control was same as the treatment of extracts.

The activity of alpha-glucosidase was expressed as the glucose production level in the experiment. 0.2 ml of testing solution was combined with the solution got from alpha-glucosidase inhibitory test then 3 ml color reagent was added into the reactive system. Later the system was heated at 37 °C for 5 min and the absorption of the solution was checked at 505 nm. One test without the addition of the sample was served as blank control in this determination. The inhibitory activity of each sample was calculated as follows:

$$I = \left[1 - \frac{(As - Ab)}{(An - Ab)}\right] \times 100\% \quad (1)$$

Where I is the inhibitory activity, As is the absorbance of samples, An is the absorbance of negative control and Ab is the absorbance of blank control. All the data were expressed as mean \pm S.D.

2.5 Oral Glucose Tolerance Test in Non-Diabetic Rats

The oral glucose tolerance test was performed in non-diabetic rats by using the similar method in literature (Barik et al., 2008). The rats were fasted overnight (16 h) before the test. Fasting blood glucose level in each rat was tested before the test. Rats were divided into five groups, and each group contained 6 animals. Control group was provided with an equal volume of distilled water. Group 2, 3 and 4 rats were administered aqueous extracts from the leaves of *A. kolomikta* orally at doses of 0.2, 0.4 and 0.8 mg/kg body weight. Group 5 were fed with acarbose at a dose of 5 mg/kg body weight. Glucose (2 g/kg body weight) was fed 30 min after the administration of extracts. Blood was withdrawn from the retro barbital plexus at 30, 60, 90 and 120 min of extracts administration and plasma glucose level was determined by blood glucose meter. All the data were expressed as the average level in 6 experimental animals in one group.

2.6 Long Term Anti-Diabetic Activities of Extracts From *A. kolomikta*

Group I was diabetic control. Group II and III were the extracts treated group with ethanol extracts from roots of *A. kolomikta* at the concentration of 0.2 and 0.4 mg/g body weight, respectively, and Group IV was treated with glibenclamide. The final group (Group V) was the normal control. Each group included 6 animals.

Extracts and glibenclamide were intragastric administered continuously daily for 28 days. The groups of diabetic and normal controls were administered with the same amount of distilled water. All the animals were free for feed and tap water during the experimental period. After the last dose of the extracts of the drugs, rats were fasted overnight for 16 h and the blood samples were obtained from the heart of animals into plain centrifuge tubes.

Blood samples were permitted to stand for 1 h and centrifuged at 3000 rpm for 15 min to obtain serum. The clear serum was used to biochemical assays.

Blood glucose level, plasma uric acid level, blood urea nitrogen, high-density lipoprotein, total cholesterol, triglyceride and the activities of alanine and aspartate aminotransferases in serum were analyzed by using the Fuji Dri-Chem 7000 (Fujifilm Corporation, Tokyo, Japan) blood automatic analyzing system.

2.7 Statistical Analysis

All values are means of at least three replicates \pm S.D. Differences in mean values between groups were analyzed by a one-way analysis of variance (ANOVA) and Duncan's multiple range test using SPSS statistical software (version 16.0 for Windows, SPSS Inc., Chicago, IL, USA) to identify significant differences among means ($P < 0.05$).

3. Results and Discussion

3.1 Alpha-Glucosidase Inhibitory Activities of Ethanol and Aqueousextracts From *A. kolomikta*

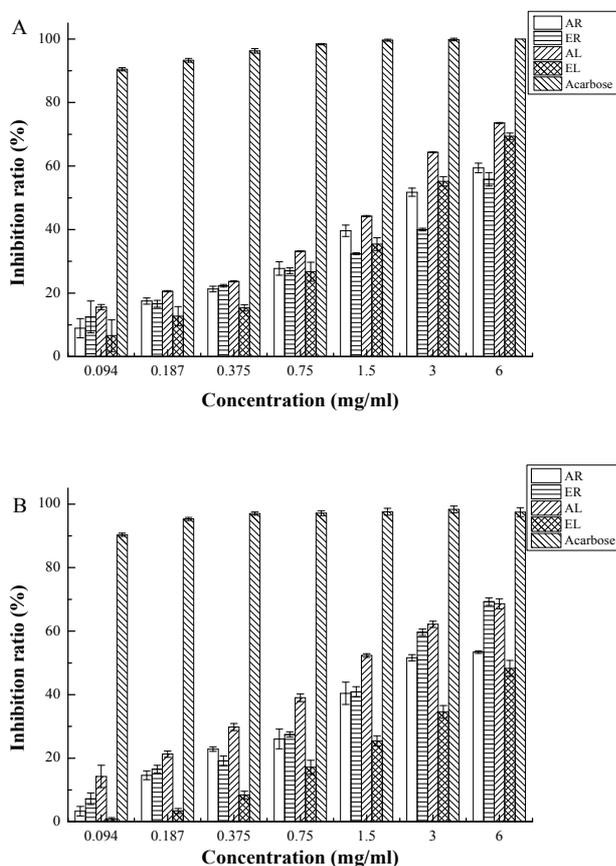


Figure 1. Alpha-glucosidase inhibitory activity of extracts from *A. kolomikta*. (A): Sucrose was the substrate. (B) : Maltose was as the substrate. AR: Aqueous extracts of roots; ER: Ethanol extracts of roots; AL: Aqueous extracts of leaves; EL: Ethanol extracts of leaves. Acarbose was invoked as negative control. Data are expressed as means \pm S.D. of three independent experiments. ($p < 0.05$ in comparison with control)

Alpha-glucosidase inhibitory activities of aqueous and ethanol extracts with geometric gradient concentrations from both roots and leaves of *A. kolomikta* were illustrated in Figure 1. Besides, sucrose as the substrate was presented in Figure 1A and maltose as the substrate was displayed in Figure 1B. Acarbose, the alpha-glucosidase inhibitor can reduce the digestion of carbohydrate in the upper part of the small intestine, thus ameliorating postprandial hyperglycemia and enabling the beta-cells to make up the first phase insulin secretory defect in Type 2 diabetes mellitus (Furnary, Wu, & Bookin, 2004).

According to Figure 1A, it was demonstrated that each extract showed alpha-glucosidase inhibitory activity, which was in a dose-dependent manner. Moreover when treated with the concentration of 6 mg/ml, AL had the highest inhibitory activity (73.5%) among four extracts, which was in accordance with the previous results (Shai et al., 2010). Referred to Figure 1B, results including alpha-glucosidase inhibitory activity of each extract and AL possessing the higher inhibitory activity at each concentration were almost same with Figure 1B, however a slight difference of that was the ER manifested a similar inhibitory activity with aqueous extracts from leaves in higher concentrations, whose best inhibitory activity was 74.2% at the concentration of 6 mg/ml. Nevertheless, compared with the commercial drug acarbose, no precedence of extracts possessed higher inhibitory activities than acarbose in this test. Although the consequence that lower activities of both aqueous and ethanol extracts from *A. kolomikta* were obtained. It could be implicated that a high potential of medicine utilization and a novel alpha-glucosidase indicator instead of acarbose extracted from *A. kolomikta* after purification was completed feasibility.

3.2 Oral Glucose Tolerance Test in Non-Diabetic Rats

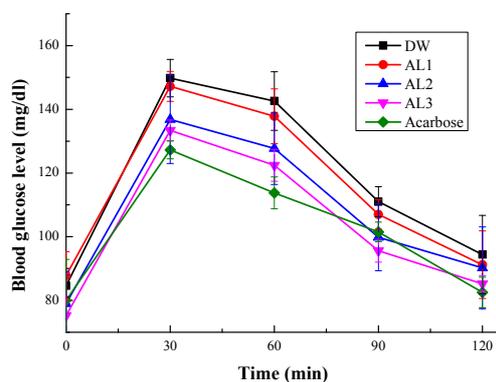


Figure 2. Effect of aqueous extracts from leaves of *A. kolomikta* on oral glucose tolerance test in normal rats. DW: distilled water. AL1: Aqueous extracts, 0.2 mg/g; AL2: Aqueous extracts, 0.4 mg/g; AL3: Aqueous extracts, 0.8 mg/g; Acarbose: 5 mg/kg. n = 6 for all groups. Data are expressed as means \pm S.D. of three independent experiments. ($p < 0.05$ in comparison with control)

A long term hyperglycemia was a major factor in the development of the complications of diabetes mellitus (Luzi et al., 1998). The oral glucose tolerance test was to investigate the effect of AL on glucose metabolism (Ariful et al., 2009). Distilled water and acarbose were invoked as the negative and positive control, respectively. The effect of aqueous extracts from the leaves of *A. kolomikta* on oral glucose tolerance test was administered (Figure 2). Animals treated with extracts (0.8 mg/g, 133.4 mg/dl) and acarbose (127.3 mg/dl) showed a decrease in blood glucose level when compared with the control group (149.8 mg/dl) in 30 min after the administration of glucose, which was to simulate huge amounts of carbohydrates, proteins and lipid were transferred into glucose through gastrointestinal digestion and entered into the blood circulation. At the time of 60 minutes, a perceptible decrease was appeared in five groups which meant insulin and drugs had played a role in converting glucose into glycogen stored in the liver and muscles. During 60 min to 90 min, it is noteworthy that more effective hypoglycemic capability was performed in aqueous extracts which certificated itself efficacy possessed persistence. After 120 min, blood glucose level was back to the starting point (84.6 mg/dl) with treatment of either acarbose (82.5 mg/dl) or AL (AK1, 91.2 mg/dl; AK2, 90.2 mg/dl; AK3, 85.2 mg/dl) without causing a hypoglycemic state, which further proved that *A. kolomikta* had an ability of lowering blood glucose for the treatment of Type 2 diabetes mellitus, especially in normoglycemic rats.

3.3 Effects of Ethanol Extracts From Roots of *A. kolomikta* on Blood Glucose Level

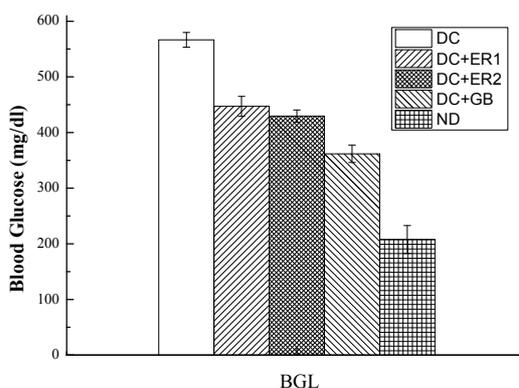


Figure 3. Effects of ethanol extracts from roots of *A. kolomikta* on blood glucose level in diabetic rats after 28 days of administrations. DC: Diabetic control; ER1: 0.2 mg/g; ER2: 0.4 mg/g; GB: Glibenclamide; ND: Non-diabetic control; BGL: blood glucose level. n = 6 for all groups. Data are expressed as means \pm S.D. of three independent experiments. ($p < 0.05$ in comparison with control)

For the sake of evaluation of the long term anti-hyperglycemic activity of the extracts from *A. kolomikta* in streptozotocin-induced diabetic rats, a repeated oral glucose tolerance test for extracts from roots of *A. kolomikta*

in diabetic rats was carried out. Streptozotocin, which is a nitrosourea compound produced by *Streptomyces achromogenes* that induces DNA strand breakage in beta-cells causing diabetes mellitus (Kumar & Prakash, 2010; Arunachalam & Parimelazhagan, 2012; Kumar et al., 2011) by high doses of intraperitoneal injection was to produce Type 1 diabetes and a low level of streptozotocin injection can be used for the induction of Type 2 diabetes (Palsamya, Subramanian, & Veratrol, 2008). As described in the Figure 3, there was no doubt that the highest BGL appeared on the diabetic rats and the lowest BGL emerged from normal rats. After 28 days of administration, a decrease of blood glucose level was discovered in the group administrated with extracts (ER1, 447.0 mg/dl; ER2, 429.5 mg/dl) and glibenclamide (361.8 mg/dl). The group with a higher concentration (0.4mg/g) of extracts showed more effective on decreasing of the blood glucose level after 28 days of administration notwithstanding not as good as the reference drug, which may be ascribed to the crude nature of the plant extracts.

3.4 Effects of Ethanol Extracts From Roots of *A. kolomikta* on Protein Metabolism

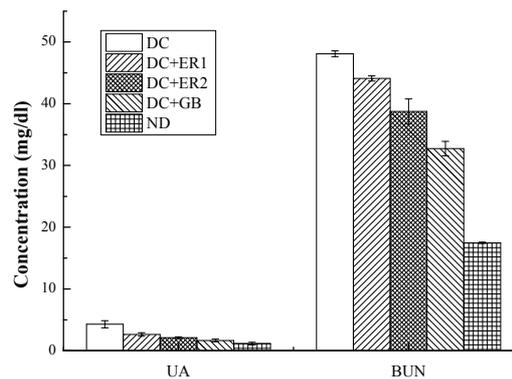


Figure 4. Effects of ethanol extracts from roots of *A. kolomikta* on protein metabolism in diabetic rats after 28 days of administrations. DC: Diabetic control; ER1: 0.2 mg/g; ER2: 0.4 mg/g; GB: Glibenclamide; ND: Non-diabetic control; UA: uric acid; BUN: blood urea nitrogen. n = 6 for all groups. Data are expressed as means \pm S.D. of three independent experiments. ($p < 0.05$ in comparison with control)

It was manifest from Figure 4 that ethanol extracts from roots of *A. kolomikta* impacted protein metabolism by means of reduction of serum uric acid and blood urea nitrogen which was provided a theoretical basis for the possible protective effect of *A. kolomikta* against diabetes-induced renal dysfunction in the animals. More precisely, after 28 days administrations, uric acid (4.27 mg/dl) and blood urea nitrogen (48.1 mg/dl) was raised in the diabetic control group when compared with normal control (UA, 1.15 mg/dl; BUN, 17.47 mg/dl). The extracts reduced the level of uric acid (ER1, 2.62 mg/dl; ER2, 2.10 mg/dl) and blood urea nitrogen (ER1, 44.10 mg/dl; ER2, 38.75 mg/dl) in a dose-dependent manner after 28 days of administration and the treatment with glibenclamide reduced the uric acid (1.65 mg/dl) and blood urea nitrogen (32.75 mg/dl) level as well.

3.5 Effects of Ethanol Extracts From Roots of *A. kolomikta* on Lipid Profile

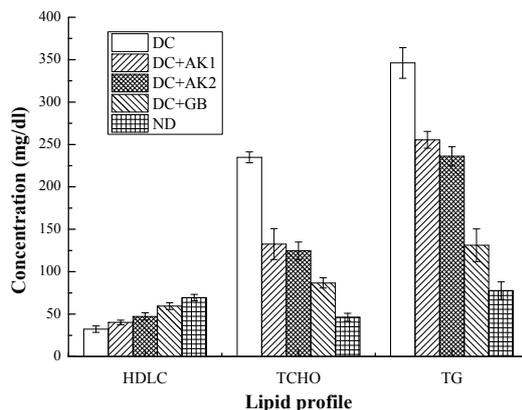


Figure 5. Effects of ethanol extracts from roots of *A. kolomikta* on the lipid profile in diabetic rats after 28 days of administrations. DC: Diabetic control; AK1: 0.2 mg/g; AK2: 0.4 mg/g; GB: Glibenclamide; ND: Non-diabetic control; HDLC: High-density lipoprotein; TCHO: total cholesterol; TG: triglycerides. $n = 6$ for all groups. Data are expressed as means \pm S.D. of three independent experiments. ($p < 0.05$ in comparison with control)

Diabetes poses a risk factor for coronary heart disease and the chance of coronary heart disease in diabetic patients is as four times as non-diabetic patients which may be one of the elements of coronary heart disease diabetes heart disease. In other words, patients who suffered diabetes can further complicated by coronary heart disease. Abnormal levels of total cholesterol and triglyceride are major important coronary risk factors (Temme et al., 1990), whereas previous studies showed that an increase in high-density lipoprotein is associated with a decrease in coronary risk. Most of the drugs that reduce total cholesterol also reduce high-density lipoprotein (Wilson, 1990). As can be observed in Figure 5, plasma lipid profile including total cholesterol, triglycerides and high-density lipoproteins were influenced entirely that the administration of extracts not only lowered the total cholesterol and triglyceride but also enhanced the level of high-density lipoprotein which indicated that the application of extracts from *A. kolomikta* may definitely reduce the incidence of coronary events occurred in the patient with diabetes.

3.6 Effects of Ethanol Extracts From Roots of *A. kolomikta* on Liver Indicators

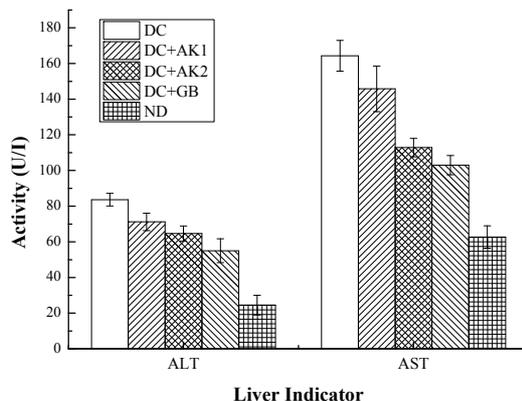


Figure 6. Effects of ethanol extracts from roots of *A. kolomikta* on liver indicators in diabetic rats after 28 days of administration. DC: Diabetic control; AK1: 0.2 mg/g; AK2: 0.4 mg/g; GB: Glibenclamide; ND: Non-diabetic control; ALT: alanine aminotransferase; AST: aspartate aminotransferase. $n = 6$ for all groups. Data are expressed as means \pm S.D. of three independent experiments. ($p < 0.05$ in comparison with control)

Aspartate aminotransferase and alanine aminotransferase are reliable marker enzymes for liver function in animals. These two enzymes can be detected in the liver, cardiac muscle, skeletal muscle, kidney, brain, pancreas, lungs leukocytes and erythrocytes (Breitling, Arndt, & Drath, 2011). The increased activities of these two enzymes in blood indicate an increased permeability and damage or necrosis of hepatocytes (Adjroud, 2011). The effects of ethanol extracts from roots of *A. kolomikta* on liver indicators are shown in Figure 4. Diabetic rats showed increases in the liver indicators such as aspartate aminotransferase and alanine aminotransferase. On the contrary, a dose-dependent decrease of ethanol extracts after the treatment was detected in the rats and when treated with 0.4 mg/g per day, ethanol extract 2 had a similar regulatory effect (112.83 U/I) on aspartate aminotransferase as glibenclamide (103 U/I) after 28 days. This observation indicates the extracts from roots of *A. kolomikta* can protect the liver from oxidative pressure due to the high level of blood glucose in diabetic rats.

4. Conclusions

Anti-Diabetic activity of extracts from *A. kolomikta* was explored *in vitro* and *in vivo*. High inhibitory activity of aqueous extracts was exhibited in the alpha-glucosidase inhibitory activity test. In addition, blood glucose level was also reduced without causing a hypoglycemic state in the blood tolerance test *in vivo*. Moreover, some blood indicators such as protein metabolism, lipid profile and liver indicators caused by complications of diabetes were controlled effectively. These consequences indicated that *A. kolomikta* could be a potential and sustainable bio-resource to utilization for therapy of diabetic. However, further studies are in progress on isolation, purification, characterization and toxicity detection of the extracts.

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