Protective Effect of White-Skinned Sweet Potato (*Ipomoea batatas* L.) against Renal Damage in Streptozotocin-Induced Diabetic Rats

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White-skinned sweet potato (*Ipomoea batatas* L.) has been traditionally used for diabetes treatment and management in many countries. In this experiment, methanol extract of white-skinned sweet potato (WSPMe) at a dose of 100 or 200 mg/kg body weight was tested to evaluate its effect on renal damage in streptozotocin (STZ)-induced diabetic rats. Its efficacy was compared with that of insulin secretogogue, glimepiride (50 μg/kg body weight). Experimental diabetes was induced by a single dose of STZ (45 mg/kg, i.p.) injection. The WSPMe and glimepiride were administered orally for 14 days and the effects on glucose, renal markers including blood urea nitrogen (BUN), creatinine and lactate dehydrogenase (LDH), lipid peroxide (LPO) level, antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathion-S-transferase (GST) activities in kidney were studied. An increase in BUN, creatinine, LDH, glucose, LPO levels and decrease in SOD, CAT, GPx and GST features were observed in diabetic control rats. Administration of WSPMe at a dose of 200 mg/kg body weight caused a significant improvement in blood glucose, LPO level, renal markers, lipid peroxidation markers and increased antioxidant levels in diabetic kidney. In conclusion, the WSPMe was found to be effective in reducing oxidative stress, thus confirming the ethnopharmacological use of *I. batatas* L. in protecting diabetes and its complications.

Key words : White-skinned sweet potato, diabetes, streptozotocin, oxidative stress, antioxidant

Introduction

Diabetes is a complex metabolic disorder, involving characteristic alterations of glucose metabolism. In diabetic patients, insulin is not produced or is insufficiently produced (diabetes type 1) or peripheral receptors to insulin lack the normal sensitivity (diabetes type 2), which in both case cause hyperglycemia and severe alterations of glucose and lipid metabolism. This abnormal metabolism leads to an increased generation of reactive oxygen species (ROS) [34]. Therefore, maintenance of glucose level is a key strategy in treating patients with type 2 diabetes [27].

Imbalance between ROS production and ROS elimination in the biological system cause oxidative stress. It leads to oxidative damage to cell and tissue paralleled by modifications in the morphology and function, resulting in aging and premature cell death [12,41].

Oxidative stress had been reported play a role in the pathogenesis and progression of diabetic tissue damage [19,23,47]. Numerous evidences suggesting that the hyperglycemia associated oxidative stress are the central event for the development of diabetes and its complications [4,7]. However, chronic diabetes is shown to disturb antioxidant defence systems in diabetes ; alteration in antioxidant enzymes [3], impaired glutathione metabolism [29] and decreased ascorbic acid levels [22]. Some natural defence mechanism exists against oxidative stress through endogenous or exogenous antioxidant substances. Supplementation with exogenous antioxidants has been proved as a complementary treatment of diabetes.

Recently, there has been a considerable interest in finding natural antioxidants. The plant kingdom has become a target for the search for new drugs and biologically active compounds [37,39]. Some plants have been used in traditional medicines as antidiabetic medicine [2,12,15], but a few have received scientific scrutiny.

Antioxidant activity of plant materials was attributed to well-known phytochemicals such as α-tocopherol, ascorbic acid, and β-carotene. Recent researches have focused on pol-

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yphenolic compounds as major antioxidant [24]. Oki et al. [31] identified several phenolic compounds present in sweet potato and had oxygen radical absorbance capacity. Kano et al. [26] reported that anthocyanin from purple sweet potato had better radical scavenging activity than that of red cabbage, grape skin elderberry and purple corn.

Several studies have reported on the antioxidant activity [21,44,45] and anti-diabetic activity [5,38,45] of sweet potato extracts. Purple sweet potato has been reported to attenuate the oxidative stress and inflammatory response [49].

White-skinned sweet potato (*Ipomoea batatas* L. WSP) has been used in Indonesia, Japan as a traditional medicine for the treatment of diabetes and other diseases. Shuichi et. al. [38] reported that WSP shows unique antidiabetic effects in both insuline defficient diabetic models and insuline-resistant diabetic models. In addition, antidiabetic components from WSP was an acidic glycoprotein (M_r 22,000). However, It has not been studied for its effect on the oxidative stress much.

Streptozotocin (STZ) is widely used to induce diabetes mellitus in research used animal, diabetogenic effect of STZ is due to excess production of ROS leading to toxicity in pancreatic cells which reduces the synthesis and the release of insulin [42] while affecting organs such as liver, kidney, and hematopoietic system [23].

The present study was designed to evaluate the reno-protective property of an traditional antidiabetic plant, WSP in STZ-induced diabetic rat and the efficacy was compared with insulin secretogogue, glimepiride.

Materials and Methods

Animals

Male Sprague Dawley (200±10 g) rats aged 6 weeks were purchased from Hyochang Science, Daegu, Korea. All animals were maintained in the institutional animal facility and handled according to the guidelines of the pharmacology department, college of pharmacy, Kyungsung University, Republic of Korea. Animals were adapted with condition for a week with a light/dark cycle: 12 hr, humidity: 46-60%, temperature 22±0.5°C in university animal room and given with free access to rodent food and water *ad libitum* throughout the experimental period.

Preparation of the extract

Fresh storage roots of white-skinned sweet potato (*Ipomoea batatas* L) were purchased from a local market in Yogyakarta Indonesia. Samples were processed into extract in Biology Pharmacy, Ahmad Dahlan University, Yogyakarta, Indonesia. The samples were sliced, dried and ground into powder. The powder was dissolved three times in 3 volumes of methanol for 3 days, filtered and evaporated to obtain the crude methanol extract. The crude methanol extracts were lyophilized for 3 days to get dried powder and was kept at 4°C before use.

Experimental design and induction of diabetes mellitus

Animals were divided into five groups with five animals in each group as follows; Group I, normal (nondiabetic) rats treated with the vehicle (tween : saline) only; Group II, control (diabetic) rats treated with the vehicle and a single dose of STZ (Sigma Chemical Co. St. Louis, MO, USA. 45 mg/kg); Group III, rats treated with WSPMe 100 mg/kg and a single dose of STZ 45 mg/kg; Group IV, rats treated with WSPMe 200 mg/kg and a single dose of STZ 45 mg/kg; Group V, rats treated with glimepiride 0.5 mg/kg and a single dose of STZ 45 mg/kg. Both normal and control groups were orally administered an equivalent volume of the vehicle for the two weeks of the treatment (pre-experiment). And then normal rats were injected with saline alone, control rats were injected with STZ 45 mg/kg prepared in 2 ml citrate buffer pH 4.5 by a single intraperitonial injection to make diabetes rats. After oral administration with WSPMe and glimepiride as pre-experiment for 2 weeks, rats were injected with STZ 45 mg/kg. On three days after the STZ treatment, development of diabetes was confirmed by measuring the blood glucose levels using glucose reagent strips (Glucometer 4 Ames, Bayer Diagnostics). Rats with a fasting blood glucose levels above 250 mg/dl were considered to be diabetic. The WSPMe and glimepiride continue administered orally during the 2 weeks after STZ injection (post experiment). After completion of the treatments, the animals were sacrificed using carbon dioxide as anesthesia. Blood was collected directly from the abdominal vein and separated to obtain serum. The kidney were dissected and rinsed with ice-cold normal saline. Kidney tissue was minced and a 10% (w/v) homogenate was prepared with phosphate-buffered saline (0.1 M, pH 7.4) using a homogenizer at 4°C for biochemical study.

Determination of serum enzyme and components

For the blood glucose analysis, a drop of blood was col-

lected from the tail vein of animals. The blood glucose level was determined using a one touch glucometer (Roche). Serum was extracted from the blood collected directly from the abdominal vein after the rats had been subjected to anesthesia. Serum was separated for the estimation of the blood urea nitrogen (BUN), creatinine, lactate dehydrogenase. BUN was determined by the method of Chaney et al. [9], creatinine content was determined by the method of Slot [40], lactate dehydrogenase activity was assayed by the Cabaud and Wroblewski method [10].

Determination of renal antioxidant enzyme activity of WSP

The level of lipid peroxidation was measured as the amount of malondialdehyde (MDA), a thiobarbituric acid reactive substance (TBARS), using 1'1'3'3'-tetramethoxypropane as the standard [30]. Superoxide Dismustase (SOD) activity was assayed by the method of Marklund and Marklund [28]. This assay procedure involved the inhibition of epinephrine auto-oxidation to adenochrome in alkaline medium (pH 10.2) which is markedly inhibited by the presence of SOD. Epinephrine was added to the assay mixture, containing tissue supernatant with the change in the extinction coefficient observed at 480 nm using spectrophotometer. The catalase activity in tissue was measured at 240 nm spectrophotometrically by calculating the degradation of H_2O_2, the substrate of enzyme [1]. The glutathion peroxidase (GPx) activity was measured according to the method of Paglia and Valentine [32]. The assay was determined by measuring the decrease in the glutathione (GSH) content after incubation the sample in the presence of H_2O_2 and NaN_3. The glutathione S-transferase (GST) was determined according to the method of Habig [17]. This assay was determined by the amount of p-nitrobenzylchloride as the substrate. The absorbance was measured UV-Vis spectrophotometrically at 310 nm.

Statistical analysis

All data were expressed as mean±SD. Total variation present in a set of data was estimated by one-way analysis of variance (ANOVA) followed by Duncan's multiple range tests. $p<0.05$ was considered significant.

Results

Blood glucose level and renal profiles

Table 1 exhibited the effect of WSPMe on the blood glucose level. As expected and shown, blood glucose level was increased in STZ-treated rats as compared to nomal group. The mean blood glucose level in normal group (group I) was stable throughout the experimental period. 2 weeks administration before STZ-induced (pre experiment), all groups showed no significant difference ($p>0.05$) in blood glucose level. 7 days after STZ-induced, treatments of WSPMe showed no significant ($p>0.05$) reduction in blood glucose compared to diabetic control group. Glimepiride showed significant ($p<0.05$) reduction in blood glucose level as compared to diabetic control group. After 14 days treatment (post experiment), diabetic animal had significant responses of WSPMe compared to control group. Also glimepiride showed significant ($p<0.05$) reduction in blood glucose level compared to control group and WSPMe group. Oral administration of WSPMe dose 200 mg/kg revealed more reduction in blood glucose level compared to WSPMe dose 100 mg/kg, but statistically no significant difference ($p>0.05$).

In diabetic rats, serum levels of all three tested renal markers: urea, creatinine and lactate dehydrogenase were significantly increased compared to the normal rats (Table 2). The elevation of these indicated impaired kidney function. Administration of WSPMe to diabetic rats at 200 mg/kg body weight significantly decreased the levels of BUN, creatinine and LDH. However it was not noteworthy

Table 1. Effect of MeOH extract of WSP on the blood glucose levels in STZ-induced diabetic rats

Group	Dose (mg/kg)	Blood glucose level (mg/dl)				
		0 wk	1 wk	2 wk	3 wk	4 wk
Normal		101.6±8.53^a	96.3±7.26^a	100.6±8.25^a	103.4±5.26^c	103.9±11.4^d
Control		97.3±7.26^a	103.6±5.48^a	98.7±7.12^a	530.4±46.7^a	580.2±37.8^a
MeOH ext.	100	99.8±8.17^a	98.5±7.46^a	101.4±8.16^a	500.2±39.2^a	531.8±57.2^b
	200	106.3±10.4^a	99.3±8.53^a	106.4±9.43^a	498.7±40.3^a	487.8±31.4^b
Glimepiride	0.5	103.7±9.43^a	101.7±7.46^a	95.6±8.46^a	390.9±33.5^b	321.4±25.8^c

Values are the means±SD (n=5). Values within a column with different superscripts are significantly different at <0.05 by the Duncan's test

Table 2. Effect of MeOH extract of WSP on urea, creatinine and lactate dehydrogenase levels in STZ-induced diabetic rats

Group	Dose (mg/kg)	BUN	Creatinine	LDH
Normal		18.4±3.25^{d}	4.97±0.96^{e}	22.5±3.17^{e}
Control		76.9±9.43^{a}	12.60±1.15^{a}	89.4±7.45^{a}
MeOH extract	100	73.2±8.16^{a}	10.30±0.77^{b}	80.5±9.16^{b}
	200	62.4±9.10^{b}	8.42±0.63^{c}	65.2±5.49^{c}
Glimepiride	0.5	50.7±7.16^{c}	6.17±0.81^{d}	51.7±6.11^{d}

Values are the means±SD (n=5). Values within a column with different superscripts are significantly different at <0.05 by the Duncan's test
BUN: blood urea nitrogen, LDH: lactate dehydrogenase

difference compared to the glimepiride treated groups.

Lipid oxidation activity in kidney

Lipid oxidation has been established as a major mechanism of cellular injury in many biological systems of plant and animal origin. Polyunsaturated fatty acid peroxides further react to form MDA, which has become one of the most widely reported analytes for the purpose of estimating oxidative stress effects on lipids [23]. Table 3 showed the level of MDA, a secondary product of lipid peroxidation in the kidney tissue homogenate of control and experimental rats. STZ-induced diabetic group resulting in a significant ($p<0.05$) increased in MDA levels compared to normal group, whereas oral administration of WSPMe at dose 100; 200 mg/kg and glimepiride to diabetic rats exhibited significant ($p<0.05$) reduction in compared with control group.

Antioxidant enzyme activity in kidney

As shown in Table 4, a significant ($p<0.05$) decrease in the activities of SOD, CAT and GPx compared to normal

Table 3. Effect of MeOH extract of WSP on lipid peroxide in STZ-induced diabetic rats

Group	Dose (mg/kg)	MDA (TBARS)
Normal		20.6±4.25^{d}
Control		39.2±5.17^{a}
MeOH extract	100	35.6±5.26^{ab}
	200	30.7±4.10^{bc}
Glimepiride	0.5	27.6±3.19^{c}

Values are the means±SD (n=5). Values within a column with different superscripts are significantly different at <0.05 by the Duncan's test
MDA: malondialdehyde, TBARS: thiobarbituric acid reactive substance

Table 4. Effect of MeOH extract of WSP on antioxidant enzyme levels in STZ-induced diabetic rats

Group	Dose (mg/kg)	SOD	Catalase	GPx
Normal		18.7±0.86^{a}	1.98±0.27^{a}	2.96±0.37^{a}
Control		4.3±0.25^{e}	0.92±0.11^{d}	1.60±0.14^{c}
MeOH extract	100	5.7±0.30^{d}	1.06±0.12^{cd}	1.83±0.23^{c}
	200	8.5±0.28^{c}	1.21±0.17^{c}	2.16±0.16^{b}
Glimepiride	0.5	11.4±0.65^{b}	1.45±0.18^{b}	2.37±0.13^{b}

Superoxide Dismustase (SOD, U/mg protein); Glutathione Peroxidase (GPx, NADPH oxidized/min/mg protein); Catalase (CAT, nmol of H_2O_2 consumed/min/mg protein)
Values are the means±SD (n=5). Values within a column with different superscripts are significantly different at <0.05 by the Duncan's test

Table 5. Effect of MeOH extract of WSSP on glutathion-S-transferase in STZ-induced diabetic rats

Group	Dose (mg/kg)	Glutathion-S-Transferase
Normal		141.7±11.4^{a}
Control		93.2±11.4^{d}
MeOH extract	100	100.6±13.4^{cd}
	200	110.8±10.6^{bc}
Glimepiride	0.5	121.2±11.8^{b}

Values are the means±SD (n=5). Values within a column with different superscripts are significantly different at <0.05 by the Duncan's test

group was a notable manifestation of STZ toxicity. The activity of these enzymes was improved significantly ($p<0.05$) by the administration of WSPMe dose 200 mg/kg when compared with control diabetic group. Also administration of glimepiride, an insulin releaser improved these enzymes activities. While, oral administration of WSPMe dose 100 mg/kg showed no significant difference ($p>0.05$) reduction in antioxidant enzyme activities compared with control group.

Table 5 showed the concentration of GST in animals treated with STZ which were significantly ($p>0.05$) decreased in kidney compared to normal group. Whereas Oral administration of WSPMe and glimepiride were significant difference ($p>0.05$) compared with control group.

Discussion

Diabetes mellitus is a wide-spread disease characterized by high blood glucose levels which, in turn, induce damages to cell membranes and generate ROS [41]. Vascular complications and diabetic nephropathy which are generally asso-

ciated to diabetes are known to be largely related to the oxidative stress [16].

Oxidative stress results from an imbalance between the generations of oxygen derived radicals and antioxidant potential.

The pathogenesis of type 2 diabetes involves insulin resistance, increased hepatic glucose output, and impaired insulin secretion [27]. These features are potential targets for pharmacologic intervention in addition to diet and increased physical activity [14].

The non-insulin dependent diabetic has a less severe form of the disease but nevertheless develops the same complications as the insulin dependent diabetic, that is, neuropathy, retinopathy, kidney disease, and coronary artery disease.

In the present study, as expected, the elevation of blood glucose levels during the experimental period clearly indicates the persistent hyperglycemia in the STZ-induced diabetic rats (Table 1). However, administration with WSPMe markedly reduced the blood glucose concentration in diabetic rats. The WSPMe can decrease blood glucose levels implies WSPMe can block free radical production and prevent the production of ROS during diabetes. This result indicates that WSPMe acts as an antihyperglycemic agent and significantly reduce the blood glucose level. ROS and advanced glycation end products are known to have a wide range of chemical, cellular and tissue effects implicated in the development and progression diabetic nephropathy including accelerating uremic glomerulopathy with tubulointestinal damage [6].

In experiment, diabetic rats showed symptoms of renal nephropathy. The level of blood urea nitrogen is determined by the amount of protein intake, the production and the excretion of the urea. The most common cause of the elevation of blood urea nitrogen is poor kidney function. Creatinine is one of the main nitrogen compounds in normal urine. The creatinine concentration in blood and body fluids is normally very low, and reaches higher values only if the kidneys are damaged. The diabetic hyperglycemia induces elevation of the plasma levels of urea, creatinine and LDH which are significant markers of renal dysfunction and reflecting a decline in the glomerular filtration rate. In diabetic rats, serum levels of all three tested renal markers; urea, creatinine and lactate dehydrogenase were significantly increased when compared to the normal rats (Table 2). Administration of WSPMe to diabetic rats significantly reversed these changes to near normal levels. However, no noteworthy changes were observed in the normal rats treated with WSPMe.

The results of the present study showed significant ($p < 0.05$) increase in the level of these parameters in the diabetic rats when compared with control rats, while, after the treatment with WSPMe, the levels of urea, creatinine and LDH were significantly ($p < 0.05$) decreased. These results are in agreement with other previous studies [2,25,33].

Chronic hyperglycemia was found to produce oxidative stress and increased lipid peroxidation in kidneys, as shown by the increased level of renal MDA, as a lipid peroxidation marker [4]. This increased level of lipid peroxidation could be associated to increase in free radicals generation in diabetes caused primarily due to high blood glucose levels, which upon autoxidation generates free radicals and secondarily due to the effects of diabetogenic agents.

Elevated levels of lipid peroxidation in tissues and plasma is one of the characteristic features of chronic diabetes [3]. Therefore inhibition of free radical generation and oxidative damage could be considered as an important strategy in the management of diabetes.

In analysis of TBARS, our study clearly showed that MDA level was decreased in WSPMe treated diabetic rats and may have role in scavenging hydroxyl and peroxyl radicals generated by STZ (Table 3). Lipid peroxidation in diabetes mellitus can be considered with overproduction of oxidants or a decrease in antioxidant defenses [46]. Such a decrease of MDA level in kidney of diabetic rats was also observed by Sukalski et al. [33]. Three antioxidant enzymes which has important function are SOD (scavenges superoxide anions), GPx (removes H_2O_2 and lipid peroxides), also CAT that are considered primary antioxidant enzymes involved in the direct elimination of reactive oxygen species. Associated with changes in lipid peroxidation, the diabetic kidney showed decreased activity of the key antioxidant enzymes SOD, CAT, GPx and GST, which are important in scavenging the toxic intermediates. According to our results, WSPMe treatment showed significant improved free radical scavenging enzymes (SOD, CAT, GPx) in the kidney of STZ treated rats (Table 4). SOD, CAT, and GPx are enzymes that break the peroxides and play an important role in supplying antioxidant substances to an organism. SOD reduces superoxide to H_2O_2 that can be readily reduced to water principally by CAT and GPx [35]. The functions of all three enzymes are interconnected with the lowering of their activities resulting in the accumulation of lipid peroxides and an associated in-

crease in oxidative stress in diabetic rats [11]. Oral administration of WSPMe improved the activities of these enzymes and thus may help protect the generation of free radicals during diabetes mellitus. The decreased activities of SOD and CAT in tissue are due to excess availability of superoxide ($O_2^{\cdot-}$) and hydrogen peroxide (H_2O_2) in the biological systems, which in turn generate hydroxyl and peroxyl radicals, resulting in the initiation and propagation of lipid peroxides [43].

Meanwhile WSPMe treatment has similar effect with glimepiride produced no significant ($p > 0.05$) reduction in kidney GST compared with control group. Based on the results, protective effect of WSPMe is may be due to the counteraction of free radicals throughout three antioxidant enzymes, increasing antioxidant free radical formation, leads to reduces LPO and a significant lowering in blood glucose level. These results suggest that WSPMe administration has protective effect in STZ-induced oxidative stress in rats. However, the precise molecular mechanism by which WSPMe exerts its protective effect against oxidative damage remains to be established.

The present study demonstrated that WSP ameliorates diabetes-induced oxidative stress by reducing the blood glucose level and prevent diabetes-induced renal damage. Further, Our results provided scientific evidence of the preventive and therapeutic potential of WSP from Indonesia against renal damage associated with diabetic oxidative stress.

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초록 : Streptozotocin으로 유발된 당뇨쥐의 신장 손상에 대한 white-skinned sweet potato (*Ipomoea batatas* L.) 추출물의 보호효과

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White-skinned sweet potato (WSP, *Ipomoea batatas* L.)는 일본, 인도네시아 등에서 당뇨병과 그 치료에 민간에서 사용되고 있다. 본 실험에서는 WSP의 메탄올 추출물을 체중 1 kg 당 Dose 100, 200 mg을 투여하여 streptozotocin으로 유발된 당뇨쥐에서 손상된 신장 보호효과를 평가하였고 그 효능을 인슐린 분비촉진제인 glimepiride (45 mg/kg 체중)와 비교해 보았다. WSP 메탄올 추출물과 glimepiride를 2주 투여 한 후 혈당, 혈중 요소성 질소 (BUN), 크레아티닌, 젖산 탈수소효소(LDH), 지질 과산화물(LPO) 함량, 그리고 항산화효소들인 superoxide dismutase (SOD), 카탈라아제(CAT), 글루타치온 과산화물 분해효소(GPx), 글루타치온 S-전이효소(GST) 등의 활성도를 측정하였다. BUN, 크레아티닌, LDH, 혈당, LPO 함량 등은 대조군에 비하여 그 값이 증가하였고, SOD, CAT, GPx, GST 값은 감소하였다. WSP 메탄올 추출물(200 mg/kg)을 투여한 후 측정한 값은 혈당, LPO, 신장병 표지인자인 BUN, 크레아티닌, LDH, 그리고 지질 과산화물 함량에서 의미있는 개선효과를 볼 수 있었고 항산화효소, 항산화물질의 증가도 나타났다. 따라서 WSP 메탄올 추출물은 당뇨쥐의 혈당을 낮추며 산화적 스트레스를 약화시키고 당뇨로 유발된 신장 손상을 보호해 주는 효과가 있다는 결과를 얻었다. 또한 민간에서 사용하고 있는 WSP가 실제로 당뇨 치료에 효과가 있음을 과학적 증거로 제공해 주었다고 판단된다.