# Anti-diabetic activities of *Paecilomyces tenuipes* N45 extract in alloxan-induced diabetic mice

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**Abstract.** Due to the limitations of existing anti-diabetic drugs, the treatment of diabetes mellitus remains a significant challenge. The present study aimed to investigate the hypoglycemic, hypolipidemic and antioxidant effects of *Paecilomyces tenuipes* N45 extracts on alloxan-induced type I diabetes mellitus in mice. Diabetic Kunming mice were orally administered with water extract (WE) at doses of 2.50, 0.25 and 0.05 g/kg) or alcohol extract (AE) at doses of 2.00, 0.20 and 0.04 g/kg, for 3 weeks, following which the levels of factors associated with blood glucose, lipids and free radicals were determined. The anti-diabetic activities of AE and WE were further confirmed via an oral glucose tolerance test. Similar to the effects of metformin, *Paecilomyces tenuipes* N45 extracts led to a significant reduction in blood glucose levels, increase in serum insulin concentration and normalization in the densities of low-density lipoprotein cholesterol and high density lipoprotein cholesterol. The *Paecilomyces tenuipes* N45 extracts exerted antioxidative effects, indicated by regulation in the levels of superoxide dismutase, malondialdehyde and glutathione peroxidase. Taken together, the results of the present study demonstrated that *Paecilomyces tenuipes* N45 extract, a safe pharmaceutical agent, exerted anti-diabetic and anti-nephropathic activities and, thus, offers potential as a novel therapeutic agent in the treatment of diabetes.

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## Introduction

In addition to cancer, cardiovascular disease and cerebrovascular disease, diabetes mellitus is the third leading contributor to mortality rates, and produces significant pressure on society and public health (1). As previously reported, diabetes-associated mortality rates represent almost 2.2% of the total morality rates worldwide, and its prevalence in China has increased rapidly (2-4). Complex metabolic disorders in three major nutrients, including lipids, carbohydrates and proteins, are observed in patients with diabetes (5). Insulin secretion deficiency in diabetes further results in an increase of blood glucose levels and organ damage (6). Additionally, various complications, including nephropathy, neuropathy, retinopathy and hyperlipemia, are observed in the majority of patients with diabetes (7).

As a widespread problem, traditional therapy for diabetes has focused on blood glucose regulation, which does not control the associated complications (8). At present, there remains no suitable therapeutic regimen that can cure diabetes. Insulin injection and commonly prescribed drugs, including metformin and pioglitzone, have undesirable averse effects, including insulin resistance, hypoglycemia and gastrointestinal disturbances (9). Therefore, the identification of alternative treatment strategies for the treatment of diabetes is in high demand.

Due to their reduced adverse effects and favorable economic characteristics, herbal medicine is considered a valuable reservoir of novel drugs (10). It has been revealed that natural products exhibit anti-diabetic activities and have auxiliary therapeutic effects on complications (11). Our previous study successfully demonstrated that *Cordyceps militaris* exhibits anti-diabetic and anti-nephropathic activities (12). *Paecilomyces tenuipes*, a well-known Chinese medicinal entomopathogenic fungi, has been traditionally used in folk medicine in Japan, Korea and China for years (13). *Paecilomyces tenuipes,* containing polysaccharides, adenosine, cordycepin, sterol and cyclopeptide, is increasingly notable for its antidepressant, antitumor and immunomodulatory effects (14,15). However, the regulatory effects of a polysaccharide-enriched fraction of *Paecilomyces tenuipes* on diabetic mice has not been reported previously.

In our previous study, through chemical mutagenesis, an improved mutant *Paecilomyces tenuipes*, termed N45, was developed, which is preserved at the China Center for Type Culture Collection (no. M2011145).

Based on our previous study, the present study hypothesized that *Paecilomyces tenuipes* N45 may possess anti-diabetic and hypolipidemic activities (12). The present study was designed to confirm this hypothesis in an alloxan-induced diabetic animal model. Following treatment with polysaccharide-enriched fractions of *Paecilomyces tenuipes* N45, indices associated with oxidation resistance, and hypoglycemic and hypolipidemic activities were detected. These data aimed to provide experimental evidence to support the clinical use of *Paecilomyces tenuipes* as an effective agent for the treatment of diabetes.

## Materials and methods

*Submerged fermentation of Paecilomyces tenuipes N45.* The *Paecilomyces tenuipes* N45 mutant was established from *Paecilomyces tenuipes* Pt196 (RCEF 4339; Anhui Agricultural University, Anhui, China) via nitrosoguanidine treatment. The wild strain (RCEF4339) was cultured at 30˚C in a potato dextrose agar (PDA) slant medium for 5 days and washed with 10 ml of sterilized normal saline. The cell concentration was adjusted to $10^8$/ml. The fungal suspension was treated with nitrosoguanidine (1 mg/ml; Sinopharm Chemical Reagent Co., Ltd., Shanghai, China) for 15 min at room temperature. Then, the fungal suspension was cultured in PDA medium, in a rotary shaker incubator (10 l; Biostat B; Germany) at 150 rpm for 5 days. The culture medium comprised glucose (40 g/l; Sinopharm Chemical Reagent Co., Ltd.), peptone (10 g/l; Aoboxing Biotechnology Co., Ltd., Beijing, China) and yeast extract powder (10 g/l; Aoboxing Biotechnology Co., Ltd.). The culture temperature was 26˚C. The mycelium pellets were harvested and lyophilized for further use.

*Paecilomyces tenuipes N45 extract preparation.* Similar to our previous study (12), water extract from *Paecilomyces tenuipes* N45 (WE) was prepared, as follows: 100 g mycelial powder was extracted twice in 5 liters of distilled water at 80˚C for 3 h. Following centrifugation at 3,550 x g for 10 min at 4˚C, the supernatant was evaporated under reduced pressure of 0.09 mPa and 80˚C using a rotary evaporator R1002B obtained from Shanghai SENCO Technology Co., Ltd. (Shanghai, China) and was dissolved in physiological saline prior to use. The concentration of the WE was 0.44 g/ml and the concentration for the alcohol extract (AE) was 0.35 g/ml. The AE was prepared using an alcohol distillation-extractor, the heating mantle used was obtained from Zhongxingweiye Instrument Co., Ltd, Beijing, China. Following removal of the existing proteins, the extracts were lyophilized by being dried using a Genesis Pilot Lyophilizer SQ 25ES (SP Industries, Inc., Warminster, PA, USA) and stored at -20˚C.

*Chemical compositions analyzed.* As reported previously (16), the present study examined the levels of amino acids, polypeptides, proteins, sugars, phenolics, tannin, alkaloids, sterols, terpenes, organic acid, essential oil, anthraquinone, flavonoids, coumarin and lactone, were analyzed in the WE and AE from *Paecilomyces tenuipes* N45.

*In vivo experiments using an animal model of diabetes.* The current study was approved by the ethics committee of the Jilin University (Changchun, China). The experimental protocol was approved by the Lab Animal Centre of Jilin University. A total of 90 Kunming male mice (weight, 18-22 g; age, 6 weeks; Norman Bethune University of Medical Science Jilin University (Jilin, China) were maintained under a constant 12:12 h light-dark cycle (8:00 am-8:00 pm) at an environmental temperature of 22±1˚C and a humidity of 60±2%. The mice were fed standard chow and had access to water *ad libitum* prior to and following the experimental period, unless stated otherwise. All mice were fed adaptively for 1 week prior to experiments.

As shown in Fig. 1, the overnight fasted mice fed with 2 g/kg sucrose solution for 72 h were used for diabetic mouse model establishment. Diabetes was induced by intraperitoneal injection with a freshly prepared solution of alloxan (Sigma-Aldrich, St Louis, MO, USA) in physiological saline at a dose of 150 mg/kg bodyweight. After 4 h, the mice were orally administered with 25% glucose solution (0.3-0.4 ml) to prevent fetal hypoglycemia. The same procedure was repeated on the second day. After 72 h, mice with persistent fasting blood glucose levels >11.1 mmol/l were identified as a severe diabetic group (17). Another 10 mice were fed with normal water and injected with physiological saline, and served as a control group (CTRL).

The alloxan-induced diabetic mice were separated randomly into eight groups, as follows, and received drug administration for 3 weeks (once a day):

Diabetic model group (model group; n=10): administrated with physiological saline orally; metformin group (DH group; n=10): administrated with 125 mg/kg metformin (Sino-American Shanghai Squibb Pharmaceuticals Ltd, Shanghai, China) orally,

AE group: administrated orally with 2.5 g/kg (n=10; equal to 5 g/kg of dried mycelial powder), 250 mg/kg (n=10; equal to 0.5 g/kg of dried mycelial powder) and 50 mg/kg (n=10; equal to 0.1 g/kg of dried mycelial powder) of alcohol extract orally;

WE group: administrated with 2 g/kg (n=10; equal to 5 g/kg of dried mycelial powder), 200 mg/kg (n=10; equal to 0.5 g/kg of dried mycelial powder) and 40 mg/kg (n=10; equal to 0.1 g/kg of dried mycelial powder) of WE.

Bodyweight was recorded during the course of the experiment. Fasting blood glucose levels were recorded on the 21st day following 18 h of food deprivation. Blood samples (0.2 ml) were collected from the caudal vein of the mice 60 min after the final treatment, and the levels of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), malondialdehyde (MDA), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were analyzed using commercial assay kits (Nanjing Jiancheng Bioengineering Institute, Nanjing, China). Serum insulin was measured using a mouse insulin enzyme-linked immunosorbent assay kit (R&D Systems, Inc., Minneapolis, MN, USA). Following an oral glucose tolerance test, the animals were sacrificed via administration with 200 mg/kg pentobarbital (Sinopharm Chemical Reagent Co., Ltd); following which organs (heart, liver, lungs, spleen and kidneys) were excised out, washed with ice cold saline and weighed immediately. The relative organ weights were

Table I. Summary of the chemical constituents in crude extracts of *Paecilomyces tenuipes* N45.

| Test | Reaction/test | AE | WE |
|---|---|---|---|
| Amino acid/polypeptides/protein | Biuret reaction/ninhydrin reaction | - | - |
| Soluble reducing sugar | Fehling reagents reaction | + | + |
| Sugars | Open-loop reaction | + | + |
| Phenolics/tannin | Ferric chloride test | - | - |
| Alkaloids | Mercuric potassium iodide/silicotungstic acid test | - | - |
| Sterols | Acetic anhydride-concentrated sulfuric acid | - | - |
| Terpenes | Foam test | - | - |
| Organic acid | Bromophenol blue test | + | + |
| Essential oil/oil | Phospho-molybdic acid-ethanol test | - | - |
| Anthraquinone | Magnesium acetate test | - | - |
| Flavonoids | HCL-Mg powder test/HCL-Zn powder test | - | - |
| Coumarin/lactone | Open-loop reaction | - | - |

AE, alcohol extract; WE, water extract; +, presence of compound; -, absence of compound.

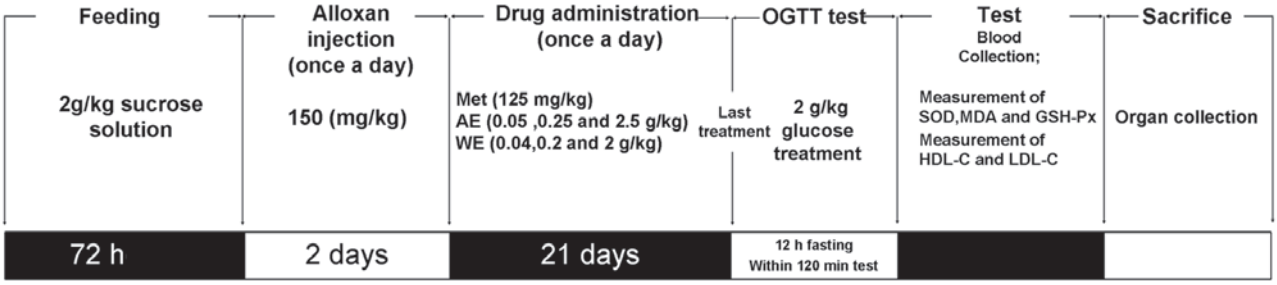


Figure 1. Experimental protocol for establishment of the alloxan-induced diabetic mouse model and drug administration. Met, metformin; AE, alcohol extract; WE, water extract; OGTT, oral glucose tolerance test; SOD, superoxide dismutase; MDA, malondialdehyde; GSH-Px, glutathione peroxidase; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

calculated by dividing the weight of each organ by the weight of the mouse. The levels of SOD, GSH-Px and MDA in the liver were determined using associated commercial kits (Nanjing Biotechnology Co. Ltd., Nanjing, China).

*Oral glucose tolerance test*. In order to investigate glucose homeostasis in the experimental diabetic mice, an oral glucose tolerance test was performed at the end of the experiment using a previously described method with a modification (18). Following overnight, but with provision of water *ad libitum* for >12 h, the mice in all groups were administrated with the relevant extracts. After 30 min, 2.0 g/kg glucose was administered orally to all mice. Blood samples were collected 0, 0.5, 1 and 2 h following the glucose load, and plasma glucose concentrations were measured using a Glucose Assay kit (Nanjing Jiancheng Bioengineering Institute). Calculation of the area under the blood glucose curve (AUC) was made according to the following equation (19): AUC = (basal glycemia + glycemia at 0.5 h) x 0.25 + (glycaemia at 0.5 h + glycaemia at 1 h) x 0.25 + (glycemia at 1 h + glycemia at 2 h) x 0.5.

*Statistical analysis*. All data are was expressed as the mean ± standard deviation. Statistical significance was determined using one-way analysis of variance, followed by post-hoc multiple comparisons (Dunn's test) using SPSS 16.0 software (SPSS, Inc., Chicago, IL, USA). $P \leq 0.05$ was considered to indicate a statistically significant difference.

## Results

*Identification of active ingredients*. The screening assessment of the active ingredients revealed that soluble reducing sugar, sugars and organic acid were found in the WE and AE of *Paecilomyces tenuipes* N45 (Table I).

*Effect of Paecilomyces tenuipes N45 extracts on bodyweight and organs*. A decrease in bodyweight was found in the alloxan-induced diabetic mice during the experimental period. The suppressive effect of alloxan on bodyweight was reversed following treatment with metformin hydrochloride, and with all doses of *Paecilomyces tenuipes* N45 extract, with the exception of 0.05 g/kg AE and 2 g/kg WE (Fig. 2A; $P<0.01$).

In all drug treatment groups, no significant differences were identified when relative organ weights of mice in the control group were compared with mice in the exposure groups (Table II). Compared with the control mice, the lung index was significantly increased in the alloxan-induced diabetic mice

Table II. Effect of extracts on organ indices in alloxan-induced diabetic mice.

| Group | Dose (g/kg) | Heart index (g/g) | Liver index (g/g) | Spleen index (g/g) | Lung index (g/g) | Kidney index (g/g) |
|---|---|---|---|---|---|---|
| CTRL | - | 5.70±0.74 | 52.68±5.34 | 7.27±1.66 | 7.21±0.58 | 7.06±0.60 |
| Model | - | 6.12±0.79 | 53.62±7.74 | 7.51±2.10 | 9.06±2.36[a] | 7.37±1.24 |
| DH | 0.125 | 7.20±2.80 | 49.65±7.61 | 8.52±1.03 | 7.14±1.38[b] | 7.69±0.71 |
| | 0.05 | 5.89±0.44 | 52.43±8.85 | 6.67±2.26 | 8.40±1.44 | 8.07±1.36 |
| AE | 0.25 | 5.69±1.51 | 50.27±11.13 | 6.67±2.46 | 7.36±3.42[b] | 7.41±0.95 |
| | 2.50 | 5.37±0.66 | 51.69±4.32 | 7.18±2.13 | 7.42±1.08[b] | 7.57±0.61 |
| | 0.04 | 6.40±1.07 | 53.42±14.05 | 8.23±1.05 | 7.84±2.32 | 7.90±2.09 |
| WE | 0.20 | 6.20±1.01 | 48.84±3.84 | 7.09±1.27 | 7.56±1.14[b] | 7.24±0.98 |
| | 2.00 | 6.23±1.06 | 49.98±11.23 | 8.30±1.92 | 8.61±1.66 | 7.84±1.04 |

Data are expressed as organ tissue weight (g) / body weight (g), and are presented as the mean ± standard deviation (n=10). [a]P<0.05, compared with the CTRL group; [b]P<0.05, compared with the model group. CTRL, untreated control; Model, diabetes model; DH, metformin; AE, alcohol extract; WE, water extract.

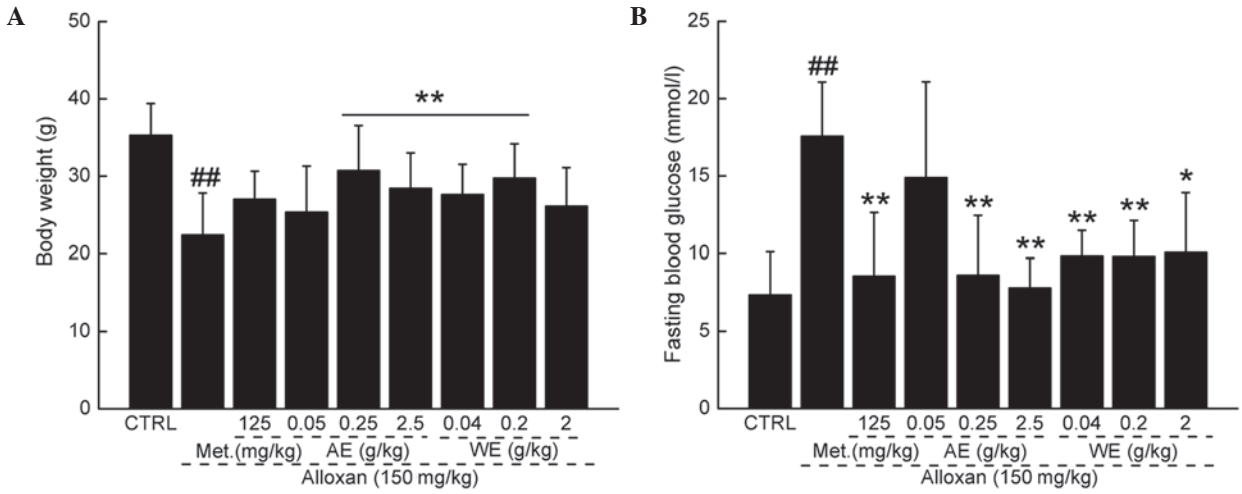


Figure 2. A mouse model of diabetes was established by 72 h sucrose administration and 48 h alloxan injection. Untreated mice served as control group. The diabetic mice were treated with or without 125 mg/kg metformin and *Paecilomyces tenuipes N45* extracts at various doses for another 3 weeks. The changes in (A) bodyweights and (B) fasting plasma glucose were detected. Data are expressed as the mean ± standard deviation (n=10) and were analyzed using one-way analysis of variance, followed by Dunn's test. [##]P<0.01, vs. CTRL; [*]P<0.05 and [**]P<0.01, vs. alloxin-induced model group. CTRL, untreated control; AE, alcohol extract; WE, water extract; Met, metformin.

(P<0.05). Treatment for 21 days with metformin hydrochloride, AE and WE suppressed lung hyperplasia (Table II).

*Paecilomyces tenuipes N45 extracts exert hypoglycemic effects*. Fasting blood glucose levels were measured to evaluate the hypoglycemic effects of *Paecilomyces tenuipes* N45 extracts. The fasting blood glucose concentration in the alloxan-induced diabetic mice was 11.1 mmol/l higher than that of the normal control animal group; whereas treatment with 125 mg/kg metformin hydrochloride resulted in a 51.24% reduction in fasting blood glucose concentration (P<0.01; Fig. 2B). The administration of 0.25 and 2.5 g/kg AE reduced fasting blood glucose levels by almost 44.29 and 50.53%, respectively (P<0.01; Fig. 2B), compared with the model group. Similarly, administration of 0.04, 0.2 and 2 g/kg WE suppressed fasting blood glucose levels by 40.70, 56.72 and 37.31%, respectively, compared with the model group (P<0.01; Fig. 2B).

The oral glucose tolerance test served as a second diagnostic indices to further confirm the hypoglycemic effects of *Paecilomyces tenuipes* N45 extracts (20). Significantly higher fasting blood glucose levels were observed in the alloxan-induced diabetic mice between 0.5 and 2 h, compared with the normal mice (P<0.05; Fig. 3A). Similar to the results following exposure to metformin hydrochloride, AE and WE significantly prevented the rapid increase in blood glucose levels, particularly at 60 min (P<0.05; Fig. 3A). High AUC values in the model group revealed a state of impaired glucose tolerance in the diabetic mice (P<0.01; Fig. 3B). Treatment with metformin hydrochloride, AE and WE significantly reduced the AUC during the oral glucose tolerance test (P<0.05; Fig. 3B).

*Paecilomyces tenuipes N45 extracts increase plasma levels of insulin and hepatic glycogen*. Compared with the

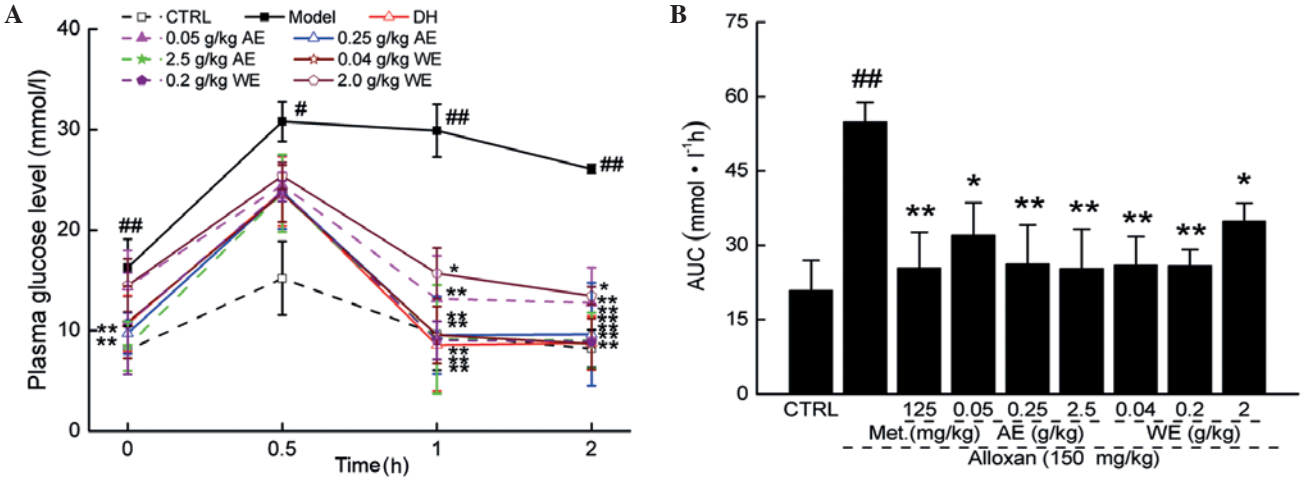


Figure 3. (A) Blood glucose levels and the (B) AUC of the OGTT in normal and diabetic mice in the OGTT. Data are expressed as the mean ± standard deviation (n=10). $^{\#}$P<0.05 and $^{\#\#}$P<0.01, vs. CTRL; $^{*}$P<0.05 and $^{**}$P<0.01, vs. alloxin-induced model group. AUC, area under curve; CTRL, untreated control; AE, alcohol extract; WE, water extract; Met, metformin; DH, metformin group.

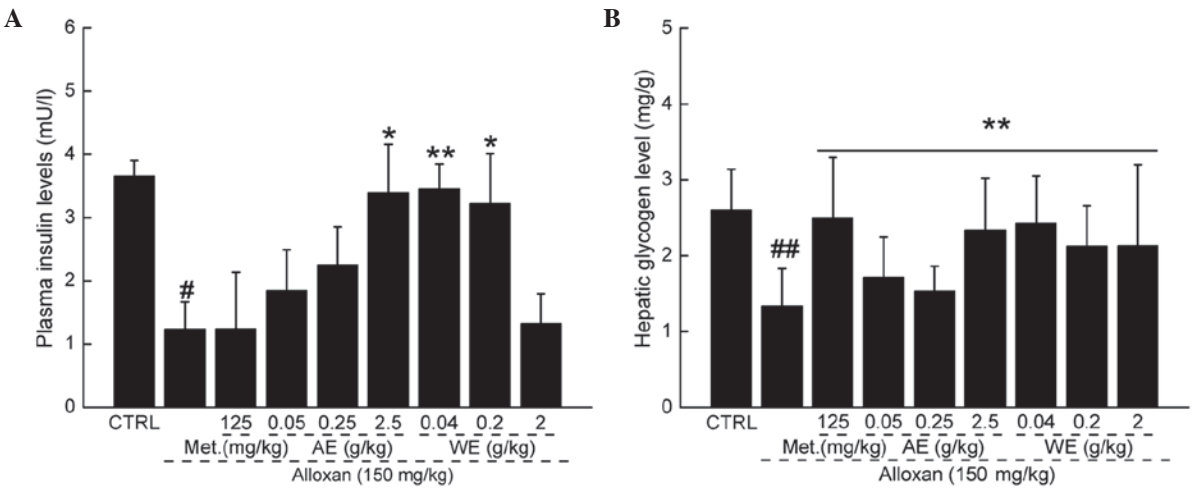


Figure 4. Administration of AE and WE for 3 weeks significantly enhanced the levels of (A) serum insulin and (B) hepatic glycogen in diabetic mice. Data are expressed as the mean ± standard deviation (n=10). $^{\#}$P<0.05 and $^{\#\#}$P<0.01, vs. CTRL; $^{*}$P<0.05 and $^{**}$P<0.01, vs. alloxin-induced model group. CTRL, untreated control; AE, alcohol extract; WE, water extract; Met, metformin.

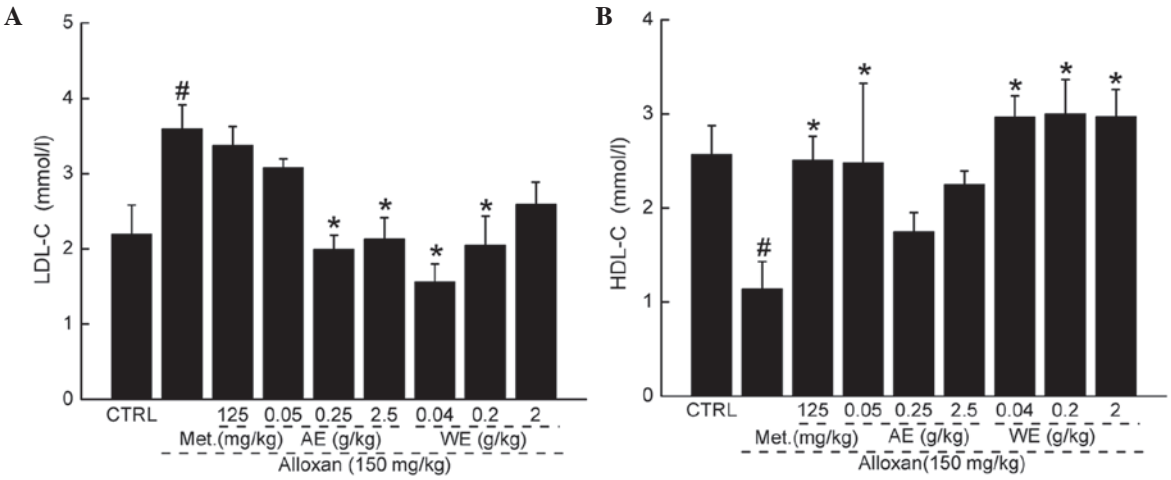


Figure 5. Hypolipidemic effects of *Paecilomyces tenuipes* N45 extracts on alloxan-induced diabetic mice. Administration of AE and WE for 3 weeks resulted in a reduction in (A) LDL-C (A) and an increase in (B) HDL-C in the serum, compared with the diabetic model mice. Data are expressed as the mean ± standard deviation (n=10) and were analyzed using one-way analysis of variance, followed by Dunn's test. $^{\#}$P<0.05, vs. CTRL; $^{*}$P<0.05, vs. alloxin-induced model group. CTRL, untreated control; AE, alcohol extract; WE, water extract; Met, metformin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

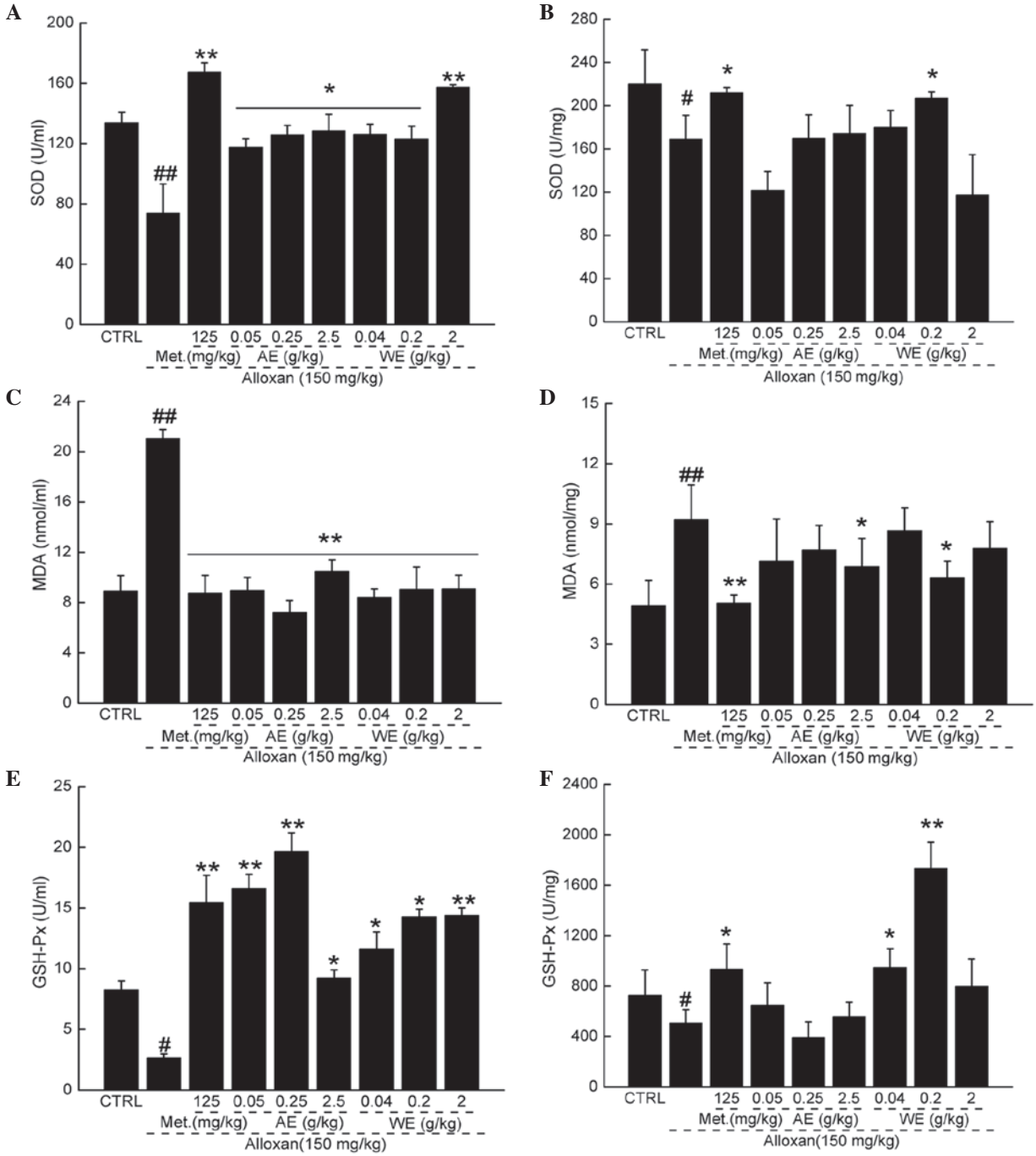


Figure 6. Antioxidative effects of *Paecilomyces tenuipes* N45 extracts on alloxan-induced diabetic mice. The levels of (A and B) SOD, (C and D) MDA and (E and F) GSH-Px in the plasma and liver, respectively, were detected. Data are expressed as the mean ± standard deviation (n=10) and were analyzed using one-way analysis of variance, followed by Dunn's test. $^{\#}$P<0.05 and $^{\#\#}$P<0.01, vs. CTRL; $^{*}$P<0.05 and $^{**}$P<0.01, vs. alloxin-induced model group.

untreated group, a significant decrease in plasma insulin levels was observed following alloxan treatment. AE and WE treatment resulted in the elevation of plasma insulin levels (Fig. 4A; P<0.01). The synthesis and degradation of glycogen in the liver are important mechanisms in the control of blood glucose homeostasis (21). Hepatic glycogen levels were measured to determine whether elevation of hepatic glycogen is involved in the hypoglycemic effects of the extracts. The levels of hepatic glycogen measured at the termination of the various treatments are shown in Fig. 4B. Significant decreases in hepatic glycogen were observed in the diabetic mice. As expected, repeated oral treatment with metformin hydrochloride, and all extract doses caused a marked increase in the levels of hepatic glycogen, compared with the diabetic model group (Fig. 4B; P<0.01).

*Paecilomyces tenuipes N45 extracts exert hypolipidemic effects.* In diabetic mice, significantly high levels of low-density lipoprotein cholesterol (LDL-C) were observed. AE and WE administration reduced the concentrations of LDL-C to normal levels (Fig. 5A; P<0.05). By contrast, compared with the untreated mice, alloxan injection reduced the concentrations of high density lipoprotein cholesterol (HDL-C). AE administration at 0.05 g/kg, and WE at all doses, increased

the low level of HDL after 4-week treatment (Fig. 5B; P<0.05). The therapeutic effect on HDL was noted in metformin hydrochloride-treated mice (Fig. 5B; P<0.05).

*Paecilomyces tenuipes N45 extracts exert antioxidant effects.* Hyperglycemia-induced oxidative stress leads to excessive production of reactive oxygen species (ROS), which may be responsible for the pathogenesis of diabetes-associated complications (22). SOD and GSH-Px, important antioxidant enzymes in mammalian cells, have critical roles against oxidative stress-induced cell damage (23). In the present study, following alloxan injection, the levels of SOD and GSH-Px in the plasma and liver were reduced significantly; whereas the concentration of MDA was significantly enhanced (Fig. 6A-F; P<0.05). Similar to metformin hydrochloride, AE and WE administration normalized the levels of SOD, GSH-Px and MDA to healthy levels in the plasma and liver (Fig. 6; P<0.05).

## Discussion

Due to various pathologic changes, diabetes has become the third leading contributor to mortality rates worldwide (24). As reported previously, natural products, which possess antidiabetic activity offer a valuable reservoir of potential diabetes medications (25). Fungi have received increasing attention, as they have comprehensive hypoglycemic effects (25,26). *Paecilomyces tenuipes* has been considered to be a valuable source of medicinal remedies and health promotion. (27,28). The immune-stimulating and antifatigue activities of *Paecilomyces tenuipes* have been investigated in animal models (14,29). In the present study, based on fermentation culture, the hypoglycemic effects associated with fasting blood glucose levels of *Paecilomyces tenuipes* N45 extracts were successfully investigated in an alloxan-induced diabetic mouse model. In addition, the hypolipidemic and antioxidative activities of *Paecilomyces tenuipes* N45 extracts were confirmed. Through bodyweight and monitoring of visceral indices, *Paecilomyces tenuipes* N45 was confirmed as a safe pharmacological agent.

Various methods of chemical analysis were applied to detect the composition of *Paecilomyces tenuipes* N45 crude extracts. Soluble reducing sugar, sugars and organic acids were found in WEs and AEs. Although natural products are generally accepted as safe and efficacious for clinical use, pharmacological and toxicological evaluations are necessary (30). In our previous investigations, through histopathological detection, and hematological and biochemical analyses, *Paecilomyces tenuipes* N45 was found to have no adverse effects in terms of acute oral toxicity or 90-day subchronic inhalation toxicity (31). In the present study, compared with the untreated mice, minimal change in organ indices were noted, which further confirmed the safety of *Paecilomyces tenuipes* N45.

The pancreas is responsible for the regulation of glucose concentrations in the plasma. Alloxan, an uncommon substance used for diabetes mellitus establishment, possesses a destructive activity on the β-cells of the pancreas (32,33). Through damage of β-cells, alloxan causes a reduction in insulin release, thereby inducing hyperglycemia (34). As reported, the antihyperglycemic activity of natural products is predominantly due to their activity in restoring pancreatic function by increasing insulin output (11). Similarly, the data in the present study confirmed that the WEs and AEs of *Paecilomyces tenuipes* N45 suppressed the alloxan-elevated levels of serum insulin. However, whether *Paecilomyces tenuipes* N45 reverses increasing insulin secretion through the regeneration of damaged β-cells requires further investigation.

Due to the increase in free fatty acid mobilization, abnormally high serum lipid concentrations are were observed in the diabetic animals. Compared with the alloxan-induced diabetic mice, *Paecilomyces tenuipes* N45 extracts reduced serum LDL-C concentrations, whereas the serum levels of HDL-C were markedly enhanced 21 days following extract administration. The above effects may be beneficial in preventing various complications, including coronary heart diseases (35) and atherosclerosis (36).

The levels of liver glycogen, an important reserve of glucose, were also measured in the present study. Administration of the extracts, at all doses, enhanced the abnormally low levels of liver glycogen in the diabetic mice, indicating that it may be a target involved in *Paecilomyces tenuipes* N45-mediated hypoglycemic activities.

ROS accumulate in diabetic patients due to disequilibrium in the production and the scavenging effects on free radicals (37,38). Abnormal high glucose concentrations causes the autooxidation and autooxidative glycosylation of proteins (20), which leads to damage of proteins, lipids and nucleic acids (39,40). The use of antioxidant compounds are considered an effective method to prevent or inhibit pancreatic β-cell destruction caused by alloxan (41). The data obtained in the present study confirmed that the antioxidant activity of SOD and GSH-Px in diabetes mellitus is associated with higher concentrations of peroxide (42). *Paecilomyces tenuipes* N45-mediated hypoglycemic activities may be associated with its normalization effects on the levels of SOD, MDA and GSH-Px in the plasma and liver.

In conclusion, the results of the present study indicated that the extracts of *Paecilomyces tenuipes* N45 prevented the increased fasting plasma glucose levels induced by alloxan. The plasma glucose lowering effects of the extracts may be explained by improving blood glucose and insulin homeostasis, enhancing the levels of liver glycogen and improving antioxidant levels. This primary investigation on the antihyperglycemic, antihyperlipidemic and antioxidant efficacy of *Paecilomyces tenuipes* N45 extracts may assist in isolating the active principles responsible for antidiabetic effects.

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