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Renoprotective Effects of Xanthone Derivatives from *Garcinia mangostana* Against High Fat Diet and Streptozotocin-Induced Type II Diabetes in Mice

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Abstract

Diabetes mellitus is described as a metabolic disorder with multiple etiology, characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolisms. Recently, obesity has been identified as a risk factor of developing type II diabetes, at about 80 - 85 %. 1 out of 3 people with type II diabetes develop kidney disease. *Garcinia mangostana* is used as a traditional medicine in various types of disease, such as abdominal pain, dysentery, wound infections, suppuration, and chronic ulcers. Previous studies have revealed that *G. mangostana* has good antioxidant, antitumoral, antiallergic, anti-inflammatory, antibacterial, and antiviral activities. In this study, an aqueous extract of xanthone derivative from *G. mangostana* was used, and the total phenolic content and total antioxidant capacity was assessed. Mice body weight, plasma glucose level, kidney hypertrophy (KI, kidney damage indicator), kidney function test (BUN, CREA), plasma, and kidney tissue melondialdehyde level (MDA, as oxidative damage marker) were evaluated in a high fat diet/streptozotocin (HFD/STZ)-induced type II diabetes mouse model. The results showed that the total phenolic compound in xanthone was 272.62±2.26 µg GAE/mg extract and, in the case of the total antioxidant capacity, % of inhibition of xanthone was 88.40±0.25 µmol TEAC/mg extract, respectively. This has significant correlation (R^2 = 0.9777) to the total phenolic content. In the *in vivo* study, increased body weight, plasma glucose level, kidney hypertrophy, plasma kidney profile, plasma, and kidney tissue melondialdehyde levels were significantly increased ($P < 0.05$) in the HFD/STZ-induced type II diabetes mouse model. Co-treatment with xanthone significantly ($P < 0.05$) improved all of the biochemical parameters and body weight in the mouse model. Taken together, the results indicate that xanthone possesses a potent renoprotective effect in type II diabetes mice.

Keywords: Xanthone, *Garcinia mangostana*, type II diabetes, renoprotection, oxidative stress

Introduction

Recently, diabetes mellitus (DM) has been a major concern around the world, and its prevalence is increasing epidemically. The global prevalence of diabetes is about 171 million, and is assumed to reach 366 million in a World Health Organization (WHO) report [1]. Intake of high fat diet is the most likely method of producing obesity-induced type II diabetes [2]. Around 90 % of the cases of type II diabetic patients show abnormal insulin secretion caused by impaired beta cell function and insulin resistance in the liver, fat, and muscle tissue [3]. Excessive intake of high fat and insulin-resistance produced hyperglycemia and dyslipidemia induces progressive tissue damage in type II diabetes. Chronic hyperglycemia and dyslipidemia form oxidative stress and inflammatory responses through the formation of advanced glycation end products (AGEs) [4], accelerated generation of reactive oxygen species (ROS)

[5], increased glucose flux through the polyol pathway [6], and activation of the protein kinase C pathway [7]. As a result, the subsequent increase of glycative, oxidative stress, glycoxidative, and carbonyl lipotoxicity play an important role in the pathogenesis of diabetes [8-11]. Therefore, reducing oxidative damage and blood glucose is the key to improving and reversing diabetic complications.

Xanthone, the polyphenolic compound, is isolated from the pericarp of mangosteen (*Garcinia mangostana*) fruits. It has shown potent anti-oxidant, anti-inflammatory, cardio-protective, and neuro-protective effects in previous studies [12-15]. Natural plants such as *Tabernaemontana heyneana*, *Curcuma longa*, *Physalis peruviana*, etc., are polyphenolic in nature, and shows a renoprotective effect on animal models [16-18]. α-mangostin, a xanthone from *G. mangostana*, improved cisplatin-induced nephrotoxicity by attenuating oxidative/nitrosative stress and inflammatory and fibrotic markers in rat models [19]. However, the renoprotective effect of xanthone derivatives from *G. mangostana* has not yet been studied, and the mechanism used is unclear. In this study, we have used an experimental model of ICR mice, chronically treated with high fat followed by a single low dose of streptozotocin (IP), to establish the type II diabetic phenotype. The purpose of this current study was to evaluate the renoprotective effect of xanthone on type II diabetes induced by a high-fat diet (HFD) following low-dose STZ treatment in mice.

Materials and methods

Chemicals and reagents

Xanthone derivatives from *G. mangostana* were purchased from the Thiptipa Company Limited, 13/5 Rangsit-Nakhonnayok Rd., Bungnumrak, Thanyaburi, Pathumthani 12110, Thailand. Streptozotocin was purchased from Merck & Co. (Germany). 2,2'-azino-bis(3-ethyl-benzothiazoline-6-sulphonic acid) (ABTS), Trolox, and gallic acid were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA). Folin-Ciocalteu's phenol reagent was purchased from the Millipore Corporation (Billerica, MA, USA). Glibenclamide was purchased from the Government Pharmaceutical Organization (GPO, Thailand).

Animal

Fifty four six-week-old male IRC mice, weighing 25 - 30 g, from the National Laboratory Animal Center, Mahidol University, Salaya district, Nakhon Pathom, were used. The animals were kept for one week before the start of the trial to receive consistently adequate food and drinking water. The animal control room temperature was 23 ± 2 °C, with a relative humidity of 55±10 % ventilation, and lighting was at 15 - 20 cycles per hour, 12 hours/day [20]. All animal experimental procedures were approved by the Animal Care and Use Committee of Walailak University. The animal ethics code was No.002/2015.

Animal treatment

Mice were treated with a high fat diet (HFD) consisting of a normal diet 60 %, lard oil 12 %, sugar 12 %, peanut powder 6 %, yolk powder 8 %, and milk powder 1 %, for up to 5 weeks, except those kept under a normal control. After 5 weeks, high fat mice were fasted overnight and an intraperitoneal injection of streptozotocin (STZ, 30 mg/kg) given. Xanthone (*G. mangostana* derived aqueous extract) at doses of 100, 200, and 400 mg/kgBW, and Glibenclamide, 60 mg/kgBW, were orally administered between 8:30 am and 9:30 am once a day. Mice body weights were recorded. The experiments were conducted in independent groups (n = 6 per group), as follows:

Group 1: Untreated normal control (received normal chew)
Group 2: Diabetic control (received HFD 8 g/day).
Group 3: DM+ Xanthone (100 mg/kgBW).
Group 4: DM + Xanthone (200 mg/kgBW).
Group 5: DM + Xanthone (400 mg/kgBW).
Group 6: DM+ Glibenclamide (60 mg/kgBW).

Sample collection

Animals were anesthetized using sodium nembutal (65 mg/kgBW). Blood was obtained via left ventricle puncture, and perfusion was followed with the use of cold phosphate buffer saline at pH 7.4. The kidney and liver were removed and kept in −30 °C for further analysis. The kidney was homogenized in cold 0.1 % TCA solution, pH 7.4, containing a mixture of protease inhibitors (leupeptin, pepstatin, and aprotinin), prior to centrifugation at 15,000 g for 15 min. The resulting supernatant was collected for further analysis.

Total phenolic content

The total phenolic content of the xanthone extract was determined using Folin-Ciocalteu's method [21], and gallic acid was used as a standard. The phenolic compound content in xanthone was expressed as a unit of Gallic Acid Equivalents (GAEs). Concisely, 12.5 µl of extract of different concentrations (0.06, 0.12, 0.25, 0.50, and 1 mg/ml) and control (DW) were added in a 96 well microplate. Then, 12.5 µl of Folin-Ciocalteu's reagent was added to each well. 5 min later, 125 µl of sodium carbonate (Na_2CO_3) (7.5 %) solution was added to the well. The reaction mixtures were incubated at room temperature for 30 min. The absorbance was determined at 765 nm using a microplate reader. Distilled water (as a blank) and gallic acid (as a standard) solutions were used in concentrations ranging from 0 to 100 µg/ml to allow plotting of a calibration curve. From the absorbance of the Gallic acid standard, the phenolic content of xanthone was calculated and expressed as Gallic Acid Equivalents (µg of GAEs/mg extract).

Total antioxidant capacity

ABTS scavenging activity was determined according to the method of Re *et al*. [22]. In this assay, $ABTS^{o+}$ was produced by adding 7 mM ABTS in H_2O with 4.9 mM potassium persulfate ($K_2S_2O_8$), and stored in the dark at room temperature for 12 - 18 h. The $ABTS^{o+}$ solution was diluted to give an absorbance of 0.750 ± 0.025 at 734 nm. Then, 20 µl xanthone of concentrations (0.06, 0.12, 0.25, 0.50, and 1 mg/ml) and control (DW) was added to 180 µl $ABTS^{o+}$ solution. After approximately 3 minutes, it produced a colorless solution, dependent on the antioxidant capacity of the extract. The extent of decolonization was calculated as a percentage reduction of absorbance at 734 nm using a microplate reader. For the standard curve, Trolox concentration (0.1 - 0.5 µmol/l) was used and expressed as (µmol TEAC/mg extract).

The correlation coefficient of the total antioxidant capacity and the total phenolic content of xanthone were calculated.

Biochemical estimations

The plasma glucose, Creatine (CREA), and blood urea nitrogen (BUN) levels were examined by an automatic analyzer, KoneLab20 (Tokyo, Japan). The kidney hypertrophy index was assessed by comparing the weight of the kidney to the body weight (KI - kidney weight/body weight) [23].

Determination of lipid peroxide (malondialdehyde (MDA) assay)

The MDA of the plasma and kidney tissue were measured as described previously by Ceci *et al.* 2013 and Goulart *et al.* 2005 [24,25]. For plasma, briefly, 150 µl plasma was added to 25 µl of BHT (0.2 %). Then, 600 µl 0.1 %TCA was added to this mixture, which was vortexed and centrifuged at 4 °C, 4000 g, for 15 min. 300 µl aliquoted supernatant was added to 600 µl 0.5 % TBA in 20 % TCA. Then, it was incubated at 80 °C for 30 min in a water bath. After that, it was immediately cooled and centrifuged at 13,500 rpm for 5 min (4 °C) to separate TBA precipitate. The absorbance of aliquoted supernatant was measured at 532 nm and at 600 nm using a microplate reader.

For kidney tissue, 400 µl kidney homogenate in 0.1 % TCA was added to 1 ml TBA 0.5 % in TCA 20 %, and incubated at 80 °C for 30 min in a water bath. Then, it was cooled and centrifuged at 13,500 rpm for 5 min (4 °C) to separate pellet and TBA precipitate. The absorbance of aliquoted supernatant was

measured at 532 nm and at 600 nm using a microplate reader. The MDA equivalents were calculated as follows;

nmol MDA/ml or g protein= (ΔA corrected*D*1000) / (ε*b*y) (1)

where ΔA corrected = {(A532–A600) – blank}; D = dilution factor; x (ml) = TCA 0.1 % used for extraction (for 1 ml); 1000 = conversion factor (nmol from µmol); ε = millimolar extinction coefficient (155 mM^{-1} cm^{-1}); b = light path length (0.56 cm for 200 µl), and y = (ml/g) of protein used.

Statistical Analysis

All the values were expressed as mean ± standard error of the mean (SEM) and were analyzed by one-way analysis of variance (ANOVA), followed by Tukey's post hoc test using a commercially available software package (SPSS for Windows, V. 17.0 Chicago, USA). $P < 0.05$ was considered statistically significant.

Results

Total phenolic content and antioxidant of xanthone

Xanthone contained high quantities of total phenolic content and anti-oxidant activities, as shown in **Table 1**. Foremost, the antioxidant capacity of xanthone were proportionally correlated ($R^2 = 0.9777$) with the total phenolic content, shown in **Figure 1**.

Table 1 Total phenolic content and total antioxidant capacity of xanthone.

Concentration of xanthone (mg/ml)	Total phenolic content (µgGAE/mg extract)	Total antioxidant capacity (µmolTEAC/mg extract)
0.06	36.22±1.79	19.20±2.82
0.12	56.31±2.49	28.40±1.31
0.25	113.04±2.15	41.17±1.24
0.50	179.82±3.33	71.19±0.99
1.00	272.62±2.26	88.40±0.25

Values are expressed as mean ± SEM.

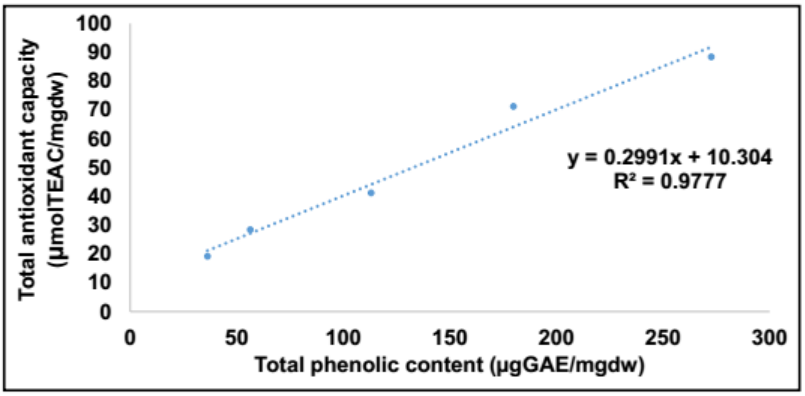

Figure 1 Correlation of total phenolic content (µg GAE/mg dw, X) vs Trolox equivalent antioxidant capacity (µmolTEAC/mg dw, Y) of isolated xanthone extract.

Mice body weight and food consumption

Feeding high fat to mice for 5 weeks significantly increased body weight (from 41.82±0.27 to 49.59±0.64 g), compared to normal controls on a basal diet (from 39.84±0.33 to 40.92±0.68 g), as shown in **Figure 2**.

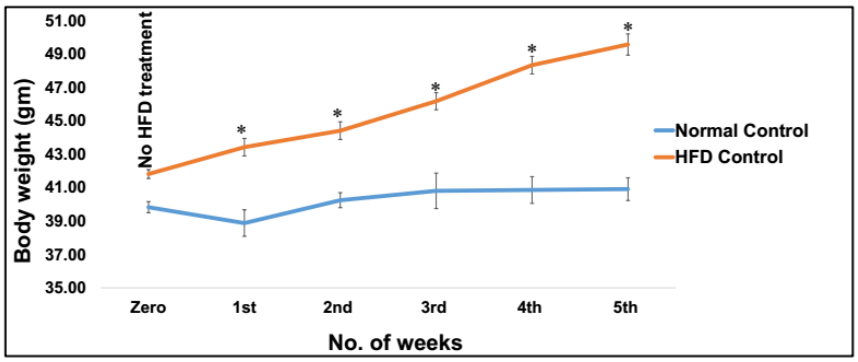

Figure 2 Mice body weight in high dietary fat fed for 5 weeks. All the values are expressed as mean ± SEM (n = 6); the values were analyzed by one-way analysis of variance (ANOVA) followed by the Tukey's post hoc test. *$P < 0.05$ versus normal control.

Effect of xanthone on mice body weight and plasma glucose levels

A high fat diet and a single dose of Streptozotocin 60 mg/kgBW were used to induce type II diabetes one week before following xanthone treatment. All diabetic and xanthone treated high fat fed mice were able to maintain significantly higher body weights, compared to normal control group, before and after treatment. However, in all the treatment groups except diabetic control, mice body weight was decreased after one week of xanthone treatment, whereas body weight increased in the normal control group, as shown in **Table 2**. On the other hand, the plasma blood glucose level in the HFD/STZ-induced diabetic control group was significantly higher (220±5 mg/dL), compared to the normal group ($P < 0.05$). However, xanthone would have been able to reduce elevated plasma glucose levels significantly in the treatment group, as shown in **Figure 3**.

Table 2 Effect of xanthone and Glibenclamide treatment on body weight in high fat diet and low dose streptozotocin-induced type II diabetes mice.

Group	Before treatment	After treatment	Weight gain (%)
Untreated Normal Control	40.92±0.68	41.82±0.74	2.20
DM Control	50.59±2.93[a]	51.35±1.71[a]	1.50
DM+Xanthone 100 mg/kgBW	50.75±0.76[a]	50.33±0.55[a]	-0.83
DM+Xanthone 200 mg/kgBW	49.19±1.27[a]	48.04±0.83[a]	-2.34
DM+Xanthone 400 mg/kgBW	49.12±1.47[a]	47.55±1.22[a]	-3.20
DM+Glibenclamide 60 mg/kgBW	49.98±2.09[a]	47.67±1.77[a]	-4.62

Values are expressed as mean ± SEM (n = 6); the values were analyzed by one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. [a]$P < 0.05$ versus normal control.

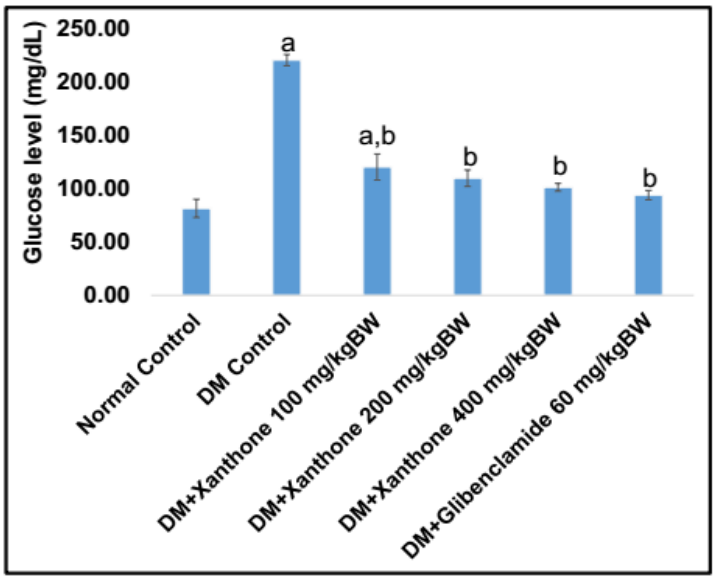

Figure 3 All the values are expressed as mean ± SEM (n = 6); the values were analyzed by one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. [a]$P < 0.05$ versus normal control; [b]$P < 0.05$ versus diabetic control.

Effect of xanthone on KI, BUN and CREA

Compared to the normal control group, the kidney hypertrophy (KI), plasma levels of BUN, and CREA were markedly increased in the diabetic control group. However, the findings on renal function were significantly reduced following the treatment of diabetic mice with xanthone (100, 200, and 400 mg/kgBW and Glibenclamide 60 mg/kgBW) as shown in **Table 3**.

Table 3 Effect of xanthone and Glibenclamide treatment on kidney function in high fat diet and low dose streptozotocin-induced type II diabetes in mice.

Group	KI (10^{-3})	BUN (mg/dL)	CREA (mg/dL)
Normal Control	5.45±0.12	17.75±0.85	0.396±0.01
DM Control	7.23±0.35[a]	25.50±2.21[a]	0.500±0.03[a]
DM+Xanthone 100 mg/kgBW	6.08±0.50[a]	18.50±0.50[b]	0.450±0.03[a]
DM+Xanthone 200 mg/kgBW	5.89±0.10[a,b]	18.00±1.15[b]	0.430±0.01[a,b]
DM+Xanthone 400 mg/kgBW	5.47±0.05[a,b]	18.00±0.50[b]	0.425±0.03[a,b]
DM+Glibenclamide 60 mg/kgBW	5.54±1.12[a,b]	17.60±0.97[b]	0.425±0.01[a,b]

Values are expressed as mean ± SEM (n = 6); the values were analyzed by one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. [a]$P < 0.05$ versus normal control; [b]$P < 0.05$ versus DM control; [c]$P < 0.05$ versus xanthone 100 mg/kgBW.

Effect of xanthone on oxidative stress parameter in plasma and kidney tissues

Oxidative stress was assessed by determining the MDA level in plasma and kidney tissues. The diabetic mice exhibited significantly higher MDA levels, compared to the normal control group ($P < 0.05$). However, treatment with xanthone and Glibenclamide was able to reduce MDA significantly in a dose dependent manner, as shown in **Table 4**.

Table 4 Effect of xanthone and Glibenclamide treatment on plasma and renal markers of oxidative stress in high fat diet and low dose streptozotocin-induced type II diabetes in mice.

Group	Plasma MDA (nmol/ml)	Kidney tissue MDA (nmol/ g protein)
Normal Control	1.91±0.08	94.87±7.30
DM Control	6.78±0.33[a]	481.16±2.80[a]
DM+Xanthone 100 mg/kgBW	4.11±0.68[a,b]	319.8±9.60[a,b]
DM+Xanthone 200 mg/kgBW	2.66±0.17[a,b,c]	262.8±17.60[a,b]
DM+Xanthone 400 mg/kgBW	2.40±0.23[a,b,c]	224.8±24.30[a,b,c]
DM+Glibenclamide 60 mg/kgBW	2.04±0.15[b]	181.1±22.06[a,b,c]

Values are expressed as mean ± SEM ($n = 6$); the values were analyzed by one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. [a]$P < 0.05$ versus normal control; [b]$P < 0.05$ versus DM control; [c]$P < 0.05$ versus xanthone 100 mg/kgBW.

Discussion

In this study, the protective effect of xanthone against HFD/STZ-induced type II diabetes mice was noticeably demonstrated by improving glucose level, oxidative damage, kidney function, and KI. Our finding was similar to previous studies demonstrating that HFD and a low dose intraperitoneal injection STZ showed significantly increased bodyweight and hyperglycemia, which may be due to insulin resistance similar to type II diabetic phenotype [26]. Therefore, BUN and CREA, the kidney injury markers, were significantly increased in HFD/STZ DM type II mice, which was related to the increase of malondialdehyde, the oxidative damage marker, and which leads to kidney hypertrophy.

Xanthone is a potent polyphenolic compound, derived from *G. mangostana* [15]. Isolated xanthone from *G. mangostana* carries a unique tricyclic aromatic structure (C6–C3–C6), containing Isoprene, methoxyl, and hydroxyl groups [27]. These functional groups possess anti-obesity and antidiabetic effects by inhibiting protein tyrosine phosphatase 1B (PTP1B) enzymes, and plays a role in the regulation of insulin signaling and the development of obesity [28]. Mangosteen xanthones contain about 59.9 % alpha mangosteen [29]. Previous studies reported that, alpha mangosteen reduced obesity by improving glucose uptake and inhibiting adipocyte differentiation of 3T3-L1 cells [30] and Cisplatin-induced kidney toxicity by improving oxidative stress and inflammatory markers [19]. Green tea polyphenols, such as (−)-epigallocatechin 3-O-gallate, improved kidney damage by reducing hyperglycemia, AGEs, oxidative stress, and inflammatory cytokine etc. [31]. High extracellular glucose levels rapidly produce reactive oxygen species (ROS) through initiating podocyte apoptosis and podocyte depletion, leading to diabetic nephropathy [32]. In this study, we found that glucose level was higher in the HFD/STZ diabetic model, compared to normal control mice. However, co-treatment with xanthone and Glibenclamide was able to reduce elevated plasma glucose significantly (**Figure 3**). Similarly, the study by Ouassila *et al*. (2015) on 59 diabetic and 48 healthy volunteers found that the MDA levels of diabetic volunteers were higher than those of healthy volunteers [33]. So, MDA is an oxidative stress indicator which works sequentially by lipid peroxidation by ROS generated in the condition of hyperglycemia, leading to kidney injury [34]. However, kidney injury induced by HFD/STZ-induced hyperglycemia could be protected by treatment with xanthone extract derivative from *G. mangostana.* Antioxidants of this extract would be capable of

reducing elevated plasma and kidney tissue MDA levels in HFD/STZ-induced type II diabetic mice (**Table 4**). KI is an abnormal enlargement of the kidney by oxidative stress, such as glomerular enlargement, glomerular basement membrane thickening, mesangial expansion, tubular atrophy, interstitial fibrosis, and arteriolar thickening etc. [35]. Consequently, the kidney is damaged, indicated by abnormal kidney function and increased BUN and CREA levels in the circulation [36]. Moreover, xanthone extract significantly reduced kidney hypertrophy and improved the kidney function of type II diabetic mice, as found in the Glibenclamide-treated group. HFD treatment of normal mice increased glucose and free fatty acid levels, which generated free radicals and initiated oxidative stress-induced cell damage, such as diabetic nephropathy [27,37]. A single STZ treatment produced beta cell dysfunction and reduced insulin level to regulate blood glucose [38]. So, HFD and STZ produced hyperglycemia and obesity-induced type II diabetes, whereas xanthones extract would be able to reduce type II diabetic nephropathy by scavenging free radicals.

Conclusions

The present study demonstrated for the first time that xanthone derived from *G. mangostana* exert renoprotective effects, and can attenuate oxidative stress in high fat diet and low dose streptozotocin-induced type II diabetic mice. Additionally, further study is needed to clarify the mechanism of and identify bioactive compounds against type II diabetes-induced kidney injury.

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