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*Original Article*

# JiangTangSanHuang Tablets ameliorate high-fat diet induced kidney injuries by suppressing galectin-3 expression

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**Abstract:** JiangTangSanHuang Tablets (JTSHT) are a patented compound drug. These tablets have been widely used in China for clinical treatment of type-2 diabetes mellitus. However, the effects of JTSHT on renal injuries, as well as the mechanisms, have not yet been reported. The current study explored the protective effects of JTSHT against renal injuries induced by a high-fat diet in a rat model, examined the mechanisms. Sprague-Dawley (SD) rats were fed with a high-fat diet (HFD group), a high-fat diet and JTSHT (JTSHT group), and a standard diet (Control group), respectively. Six months later, in the HFD group, serum total cholesterol, total triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, glucose, insulin, ten cytokines (TIPM-1, ICAM-1, Gas 1, TWEAK R, Neuropilin-2, LIX, Activin A, eotaxin, galectin-3, and decorin), and body weights were markedly increased. More protein casts were observed in the renal tubules, compared to the control group. Interestingly, administration of JTSHT decreased these blood biochemical indexes and body weights, improving histological damage with fewer renal tubular casts. Furthermore, of the differential cytokines, only galectin-3 was significantly decreased with JTSHT treatment. In summary, in a rat model, JTSHT ameliorated renal injuries caused by a high-fat diet via reducing galectin-3 expression.

**Keywords:** JiangTangSanHuang Tablet, high-fat diet, renal injury, antibody array, galectin-3

## Introduction

Chronic kidney diseases (CKDs) have become increasingly common, worldwide, and are characterized by a progressive decline in renal function. This contributes to severe cardiovascular damage [1, 2]. Therefore, it is necessary to seek more effective medicines for treatment of CKDs. Evidence has shown that ingestion of high levels of saturated fats and sugars is a major risk factor for metabolic disturbances, including type 2 diabetes, cardiovascular disease, and kidney disease. Additionally, studies in animal models have shown that lipids promote progression of CKDs [3, 4].

JiangTangSanhuang Tablets (JTSHT) are a patented compound drug. These tablets are prepared with Traditional Chinese Medicine ingredients, including *Astragalus membranaceus*, *Radix Rehmanniae*, *Ophiopogon japonicas*, *Radix Scrophulariae*, licorice, peach kernel, cassia twig, *Rheum officinale,* and a sulfate mineral mirabilite. JTSHT was developed from a decoction invented by Chief Professor Xiong Manqi, of Guangzhou University of Chinese Medicine in China in the 1980s, after decades of teaching, diagnosis, and treatment of diabetes.

In recent years, JTSHT has been widely used in China for clinical treatment of type-2 diabetes mellitus. In addition, it has been found that JTSHT could effectively treat diabetic nephropathy, suggesting that JTSHT may have strong protective effects against kidney disease [5]. The present study aimed to explore the protective effects of JTSHT on a high-fat diet-induced renal injury rat model, clarify molecular mechanisms behind the roles of JTSHT in lipid nephrotoxicity using a high-throughput amenable

advanced antibody array technology for the rapid detection of proteins.

## Materials and methods

### *Animals*

All animal procedures were reviewed and approved by the Institutional Animal Care and Ethics Committee of Guangdong Medical Laboratory Animal Center (the certification number: B201608-2). A total of 30 male Sprague-Dawley (SD) rats, weighing 180-200 g and aged 13-15 weeks, were purchased from Guangdong Laboratory Animal Testing Institute (China). The rats were housed in well-ventilated cages at 22-25°C and 60% humidity. Water was provided *ad libitum*. For acclimation, these animals were fed with a standard diet (23% crude protein, 5% lipids, 53% carbohydrates, w/w) for one week. They were then randomly divided into three groups, with 10 animals each group. The control group was continually fed with a standard diet. The high-fat diet (HFD) group was fed with a high-fat diet (52.6% standard diet, 1.2% cholesterol, 15% yolk powder, 10% lard, 0.2% sodium deoxycholate, 3% casein, 0.6% calcium hydrophosphate, 0.4% mountain flour, w/w). The JTSHT group was fed with the same high-fat diet as the HFD group but augmented with JTSHT at a dose of 787.5 mg/kg q.d by intragastric administration [6]. The animals remained on these diets for 6 months. Body weights of each animal were recorded once per week. After six months, the rats were fasted for 12 hours. Blood was collected from the tail veins. Next, the animals were sacrificed. The serum was isolated. Serum total cholesterol (TC), total triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and glucose levels were determined using colorimetric enzyme kits (Sigma-Aldrich, St. Louis, MO, USA), according to manufacturer protocol. The study was approved by Ethics Committee of Guangzhou University of Chinese Medicine (the certification number: GUTCM BL20160012).

### *Kidney histology*

The left kidneys were excised, rinsed with saline, and longitudinally sectioned. These sections were immersion-fixed in 10% neutral formalin and paraffin-embedded. The kidney sections were cut into 4 μm slices and de-paraffinized, re-hydrated, and stained with hematoxylin and eosin (HE). Histological analyses of the renal collecting duct, tubular casts, and kidney tubules in the HE stained slides were performed using an Olympus BX43 microscope under 400× magnification.

### *Antibody array assays*

Sera from the three groups of rats were measured using a semiquantitative rat cytokine antibody array (RayBio Rat Cytokine Antibody Array G series 67, RayBiotech, Norcross GA, USA) that detected 67 cytokines in one experiment, according to manufacturer instructions. Briefly, after dilution (1:1) with a blocking buffer, serum was incubated in these assay pools for 2 hours. After washing, a biotin-conjugated anti-cytokine mix was added into the pools for incubation for another 2 hours. The slides were washed again and developed for another 2 hours with Cy3-conjugated streptavidin. Fluorescent signals of the microarrays were detected with an InnoScan 300 Microarray Scanner (Innopsys). Signal values were normalized by an internal control using the RayBiotech analysis tool, specifically designed to analyze the data of rat Cytokine Antibody Array G series 67.

### *ELISA identification*

To validate the results of antibody array analysis, serum cytokine levels were measured using ELISA kits (Raybiotech, Norcross GA, USA), according to manufacturer instructions. After appropriate dilution for the different serum biomarkers, the samples were incubated in plates pre-coated with capture antibody overnight at 4°C. The plates were washed and incubated with a biotin-conjugated detection antibody for 2 hours at room temperature. HRP-conjugated streptavidin was added to combine with any biotin from the detection antibody. TMB reagent was added to be catalyzed by HRP. A total of 30 minutes later, the reaction was stopped by the addition of sulfuric acid. Immediately, optical density values were measured with a BioTek ELx800NB microplate reader (BioTek, Winooski, VT, USA). Validation assays were performed using the same samples as in the antibody array. Concentrations of the cytokines in these samples were calculated using the four-parameter method via Sigmaplot 12.0 software. Differences were analyzed using Student's t-tests.

**Table 1.** Blood lipid levels of rats from the different groups (n=10)

| Group | GLU (mmol/L) | TC (mmol/L) | TG (mmol/L) | HDL-C (mmol/L) | LDL-C (mmol/L) | Insulin (mIU/L) | Body weight (g) |
|---|---|---|---|---|---|---|---|
| Control | 5.77±0.63 | 2.50±0.28 | 1.45±0.48 | 0.63±0.09 | 0.32±0.05 | 14.15±1.07 | 753.3±83.1 |
| HFD | 12.00±7.03* | 3.48±0.65* | 2.59±0.98* | 0.79±0.12* | 0.78±0.16* | 16.53±2.70* | 855.9±100.2* |
| JTSHT | 6.37±0.79# | 2.80±0.48# | 1.36±0.43# | 0.52±0.10# | 0.61±0.11# | 14.32±1.15# | 745.5±45.7# |
| *p value | 0.021 | 0.001 | 0.006 | 0.003 | <0.001 | 0.024 | 0.023 |
| #p value | 0.032 | 0.014 | 0.003 | <0.001 | 0.014 | 0.034 | 0.008 |

*HFD vs control group; #JTSHT vs HFD group.

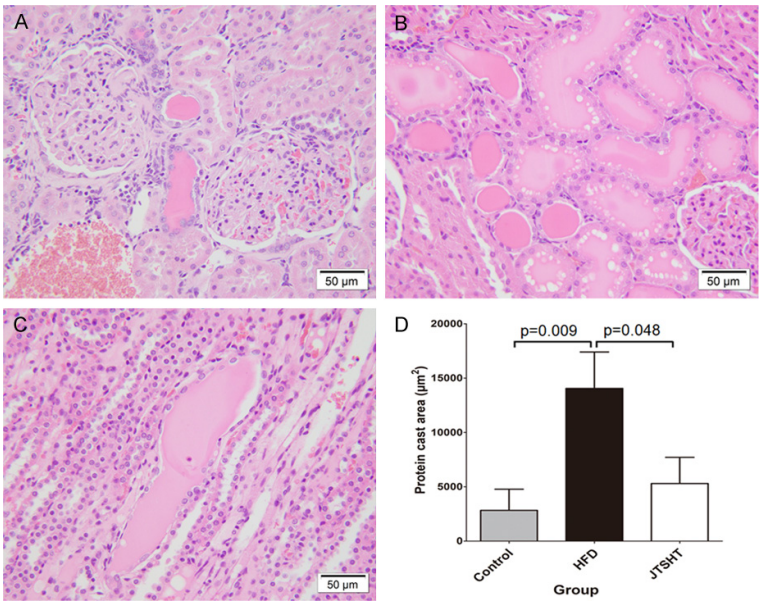


**Figure 1.** Histological changes in kidneys among the three groups. H&E staining showed more normal renal histological features in the control and JTSHT groups, while there were more protein casts and basophilic changes in the renal tubules in HFD group. A. Control group; B. HFD group; C. JTSHT group; D. Protein cast area among three groups.

*Statistical analysis*

Statistical analyses were performed using SPSS 13.0 (IBM Corp., Armonik, NY, USA). Results are presented as mean ± standard deviation (SD). Differences between two groups were determined using Student's t-tests. Results are considered significant when two-sided *P* values <0.05. Fold changes (FC) were also calculated. These values were given to indicate relative expression levels of the cytokines.

## Results

*Blood targets changed after high-fat diet*

As shown in **Table 1**, serum levels of TC, TG, LDL-C, HDL-C, glucose, and insulin, as well as body weights, of the HFD group were markedly higher than those in the control group. These blood biochemical indexes and body weights of the JTSHT group were obviously lower than those in the HFD group. Results suggest that a high-fat diet could cause dyslipidemia and that JTSHT treatment could ameliorate dyslipidemia.

*Histological changes in the kidney*

As shown in **Figure 1**, compared with a standard diet, a high-fat diet caused more obvious renal damage, including proteinaceous casts in the renal tubules, suggesting that dyslipidemia could lead to kidney injuries. However, these histological changes were remarkably alleviated after treatment with JTSHT, with fewer renal tubular casts.

*Altered cytokine levels in high-fat diet-fed rats*

Normalized fluorescent signals reflecting serum levels of cytokines were statistically analyzed by the Student's t-tests with SPSS 13.0 software. TIPM-1, ICAM-1, Gas 1 (Growth arrest-specific 1), TWEAK R, Neuropilin-2 (NRP2), LIX (CXCL6), Activin A, eotaxin, galectin-3, and decorin were significantly upregulated in the serum of high-fat diet rats, compared with control rats (**Table 2** and **Figure 2**).

*Mechanisms of JTSHT protection in high-fat diet-fed rats*

Examining molecular mechanisms by which JTSHT protects against CKDs, advanced antibody array technology was adopted. After statistical analysis of the 67 cytokines measured

**Table 2.** Antibody array results

| Protein name | Protein ID | Gene ID | Signal values | | | HFD vs Control | | JTSHT vs HFD | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Control group | HFD group | JTSHT group | T-TEST *p* value | Fold change | T-TEST *p* value | Fold change |
| TIMP-1 | P30120 | 116510 | 15020 | 45102 | 37066 | <0.001 | 3.003 | 0.155 | 0.822 |
| ICAM-1 | Q00238 | 25464 | 41628 | 96961 | 88636 | <0.001 | 2.329 | 0.459 | 0.914 |
| Gas 1 | M0RBH9 | 683470 | 16368 | 24748 | 21222 | 0.001 | 1.512 | 0.132 | 0.858 |
| TWEAK R | Q80XX9 | 302965 | 19886 | 34727 | 29395 | 0.002 | 1.746 | 0.259 | 0.846 |
| Neuropilin-2 | O35276 | 81527 | 7898 | 20133 | 16931 | 0.003 | 2.549 | 0.372 | 0.841 |
| LIX | P29456 | 25325 | 37239 | 45433 | 46469 | 0.004 | 1.220 | 0.747 | 1.023 |
| Activin A | P18331 | 29200 | 3269 | 19355 | 10028 | 0.013 | 5.921 | 0.120 | 0.518 |
| Eotaxin | P97545 | 29397 | 67360 | 93897 | 75135 | 0.015 | 1.394 | 0.066 | 0.800 |
| Decorin | Q01129 | 29139 | 3527 | 9940 | 8279 | 0.049 | 2.818 | 0.684 | 0.833 |
| Galectin-3 | P08699 | 83781 | 8703 | 17381 | 8887 | 0.035 | 1.997 | 0.039 | 0.511 |

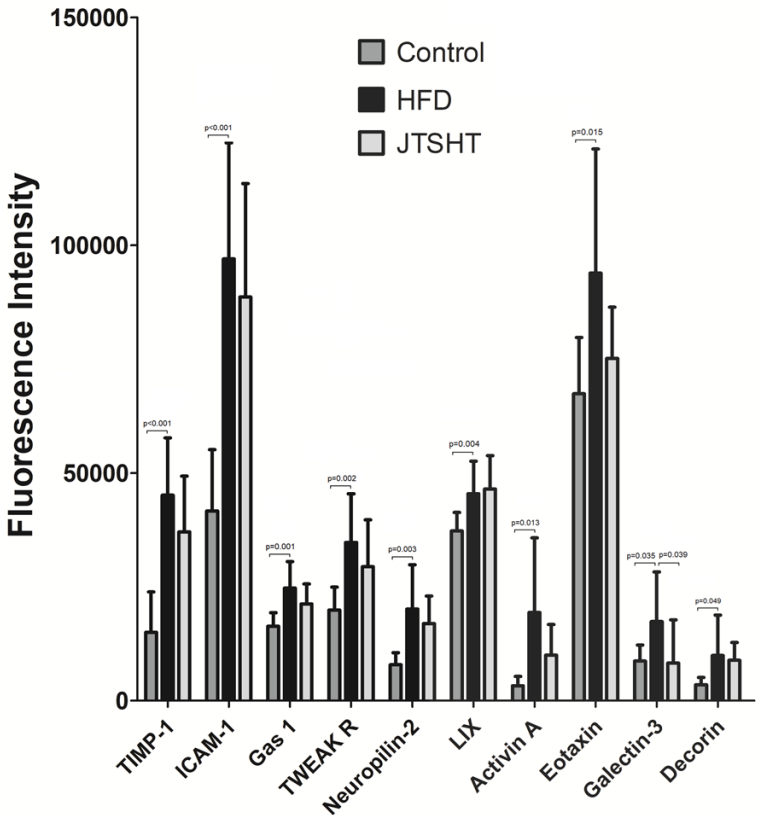


**Figure 2.** Histogram display of serum cytokines differentially-expressed among the three groups. Fluorescence intensity values were statistically analyzed by Student's t-tests and are shown with the histogram.

in JTSHT and HFD groups, galectin-3, upregulated in high-fat diet rats, was found to be under-expressed after treatment with JTSHT. As shown in **Figure 3**, which is the most representative of each group, fluorescent signal spots of galectin-3 in the three groups are marked in the red boxes. Stronger fluorescence intensities reflect higher expression levels of galectin-3. Transformed fluorescence intensity values are exhibited in boxplots (**Figure 4**), showing the alteration of galectin-3 expression among the three groups.

*Validation results*

Due to limited sample volume, some of the differential cytokines identified in the antibody array results were chosen for validation, including galectin-3, TIMP-1, ICAM-1, and Neuropilin-2. Levels of the four cytokines were significantly differential (**Figure 5**), identical to the results of the microarray. This further proves that these cytokines participate in the pathology of kidney damage.

## Discussion

JTSHT is prepared from eight Traditional Chinese Medicine ingredients, including *Astragalus membranaceus, Radix Rehmanniae*, *Ophiopogon japonicas*, *Scrophularia ningpoensis*, liquorice, peach kernel, *Ramulus Cinnamomi (Gui Zhi)*, rhubarb, and sulfate mineral mirabilite. *Astragalus membranaceus*, one of the most widely used herbs in Traditional Chinese

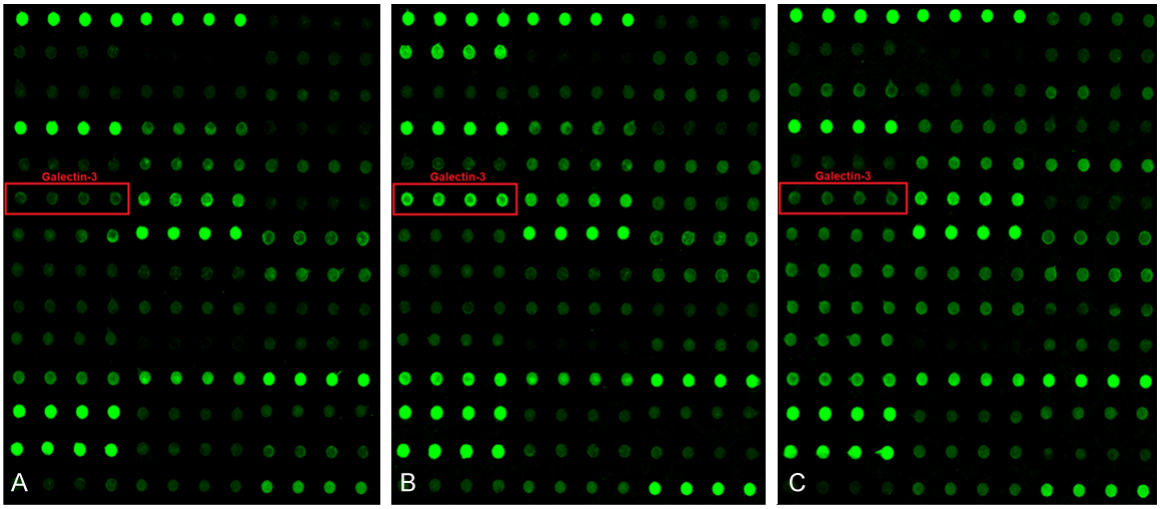


**Figure 3.** Array profile of galectin-3 among the three rat groups. The galectin-3 location in the array is labeled with a red box. Fluorescence intensity is positively proportional to expression levels of galectin-3. In the array, each protein was measured in duplicate. A. Control group; B. HFD group; C. JTSHT group.

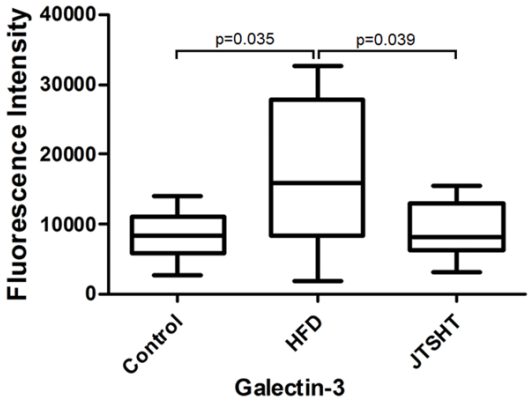


**Figure 4.** Boxplot display of galectin-3 among the three groups. Fluorescence intensity values of galectin-3 among the three groups were statistically analyzed by Student's t-tests. The data is shown as a boxplot. Center line indicates the median for each data set.

Medicine for treatment of kidney diseases, has been found to decrease proteinuria, while increasing hemoglobin and serum albumin [7]. Extracts of *Radix Rehmanniae* and *Ophiopogon japonicus* have been reported to ameliorate diabetic nephropathy [8, 9]. *Scrophularia ningpoensis* is a species of the genus *Scrophularia*. Plants belonging to this genus are traditionally used for treatment of kidney diseases [10]. Liquorice is the dry peeled or unpeeled root of *Glycyrrhiza glabra*, commonly known for its sweet flavor. It has been reported that liquorice is effective in ameliorating gentamicin (GM)-induced acute tubular necrosis [11]. Peach kernels have been used for cardiovascular diseases [12, 13]. However, there are no reports concerning the protective effects against CKDs. Modern medical research has shown that the combination of *Ramulus cinnamomi* with *Rhizoma polygoni cuspidati* protects renal function and ameliorates pathological changes in the kidneys [14]. Rhubarb, an important herbal medicine, plays a beneficial role in slowing the progression of CKDs [15]. Mirabilite has not been shown to have protective effects against CKDs. In summary, most of these components have anti-CKD properties.

In the present study, rats had abnormal serum lipid levels and vast protein casts in renal tissues after a high-fat diet, suggesting that a high-fat diet could induce dyslipidemia and renal injuries. Cast formation is quite diffuse and widespread. It plays the important role of intrarenal obstruction in the pathogenesis of renal failure [16]. JTSHT was used to treat rats fed with a high-fat diet. Interestingly, JTSHT treatment significantly decreased intratubular protein cast formation, demonstrating that JTSHT has protective effects against renal injuries induced by a high-fat diet.

However, the mechanisms by which JTSHT ameliorates high-fat diet-induced kidney injuries have not been elucidated. Therefore, the current study utilized an advanced technology antibody array to expose the molecular mechanisms. In this study, serum levels of 67 cytokines were measured in the three rat groups.

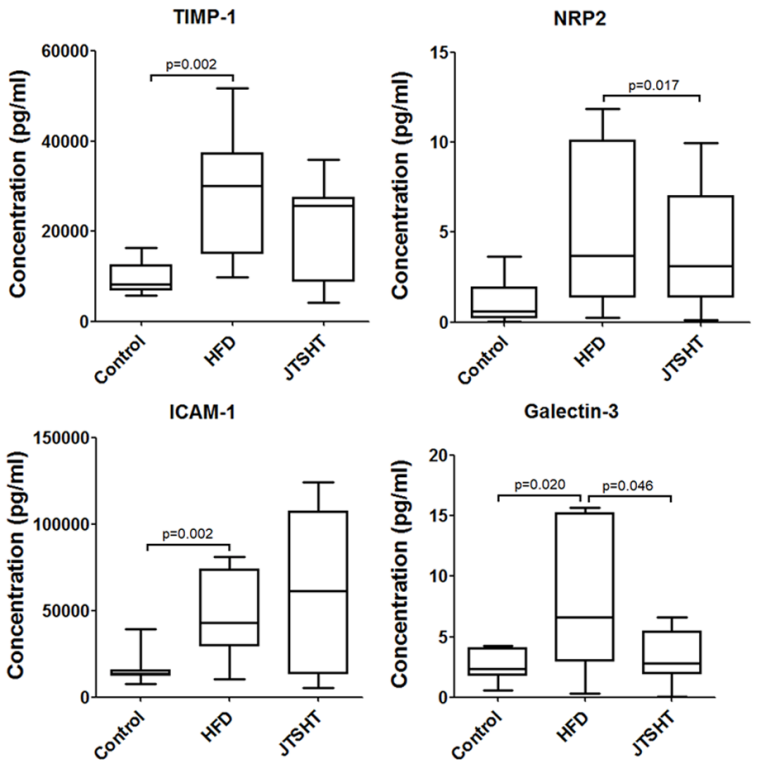


**Figure 5.** Validation of five differentially-expressed cytokines among the three groups. ELISA data is shown in a scatter diagram with median.

After being fed with a high-fat diet, TIMP-1, ICAM-1, Gas 1, TWEAK R, Neuropilin-2, LIX, Activin A, eotaxin, galectin-3, and decorin were upregulated. Previous studies have shown TIMP-1, ICAM-1, TWEAK R, LIX, Activin A, eotaxin, and galectin-3 overexpression in renal injuries [17-23], suggesting that this high-fat diet-induced renal injury rat model was successfully established. Furthermore, the current study found that two novel targets, Gas 1 and Neuropilin-2, were elevated in rats fed with a high-fat diet, hinting that these two proteins might be able to be developed into candidate serum biomarkers or therapeutic targets for patients with renal injuries.

After treatment with JTSHT, among these upregulated cytokines, only levels of galectin-3 were found to be significantly decreased, equal to that of the control group. Galectin-3, a multifunctional lectin protein, is expressed by macrophages, epithelial cells, and endothelial cells. Shown through clinical and experimental evidences, galectin-3 participates in heart failure, fibrosis, obesity, impaired glucose metabolism, ventricular remodeling, infections, various autoimmune and inflammatory processes, and cancer [24-29]. Furthermore, galectin-3 plays an important role in kidney fibrosis and renal failure. It is inversely correlated with estimated glomerular filtration rates in humans, a key factor for renal injury progression [30, 31]. Increases of galectin-3 in the blood also increases risks of chronic kidney disease, rapid renal function decline, progressive renal impairment, diabetic nephropathy, systemic lupus erythematosus (SLE), and nephritis [23, 32-34]. It has been shown that galectin-3 is a predictor of renal dysfunctionality and that inhibiting galectin-3 could ameliorate renal diseases [35-37]. Galectin-3 is a major player in extracellular matrix remodeling in the kidneys. It has been found to promote renal fibrosis via a variety of pathways [38].

Although galectin-3 is upregulated in kidney diseases, the relative importance of its different domains and functions are poorly understood. Galectin-3 usually functions by its carbohydrate recognition domain, such as the regulation of cell growth, differentiation, and inflammation. Kolatsi-Joannou et al. [39] found that expression of galectin-3 was changed in mice with acute kidney injuries when treated with modified citrus pectin (MCP). They supposed that the protective effects of MCP against acute kidney injuries might be via carbohydrate binding-related functions of galectin-3. In the present study, JTSHT was prepared with ingredients containing abundant polysaccharides, such as astragalus polysaccharide, *radix rehmanniae* polysaccharide, ophiopogon polysaccharide, glycyrrhiza polysaccharide, and rhubarb polysaccharide. Galectin-3 is a 30-kDa β-galactoside-binding lectin. These polysaccharides in JTSHT may be rich in β-galactose and may play the role of a galectin-3 inhibitor. Previous studies have demonstrated that galectin-3 inhibition improves renal remodeling in hyperaldosteronism, is beneficial against acute kidney injuries, and protects against hyperten-

sive nephropathy [36, 37, 39]. Moreover, a recent phase II study treating patients with CKD stage 3b showed that a galectin-3 inhibitor (GCS-100) played a role in significant improvement of estimated glomerular filtration rates. Hong-yan Li et al. [40] found that MCP attenuates renal injury progression in cisplatin-induced nephrotoxicity through the mediation of protein kinase C α, which maintains normal renal function [41]. In the current study, JTSHT was found to act as a galectin-3 inhibitor for the amelioration of high-fat diet induced kidney injuries. The mechanisms, however, require further investigation.

In summary, the present study showed that JTSHT might be a novel galectin-3 inhibitor, improving long-term renal injuries by reducing galectin-3 expression, possibly due to its polysaccharide compositions rich in β-galactose. This inhibits carbohydrate binding-related functions of galectin-3.

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## Disclosure of conflict of interest

None.

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