

Effect of Chinese Herbal Medicine Jinlida Granule in Treatment of Patients with Impaired Glucose Tolerance

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Abstract

Background: Diabetes mellitus (DM) remains a major health problem worldwide. Several clinical trials have shown the superiority of the Traditional Chinese Medicine in delaying or reversing the development and progression of DM. This study aimed to evaluate the efficacy of Jinlida (JLD) granule, a Chinese herbal recipe, in the treatment of impaired glucose tolerance (IGT) and its effect on the prevention of DM.

Methods: Sixty-five IGT patients were randomized to receive one bag of JLD granules three times daily (JLD group, $n = 34$) or no drug intervention (control group, $n = 31$) for 12 weeks. Oral glucose tolerance test, glycated hemoglobin A_{1c} (HbA_{1c}), body mass index, blood lipids levels, fasting insulin, and insulin resistance calculated using homeostatic model assessment (HOMA-IR) of all the patients were observed and compared before and after the treatment.

Results: Sixty-one participants completed the trial (32 in JLD group and 29 in the control group). There were statistically significant decreases in HbA_{1c} ($P < 0.001$), 2-h plasma glucose ($P < 0.001$), and HOMA-IR ($P = 0.029$) in JLD group compared with the control group after 12 weeks of treatment. After 12 weeks of treatment, two (6.9%) patients returned to normal blood glucose, and five (17.2%) patients turned into DM in control group, while in the JLD group, 14 (43.8%) returned to normal blood glucose and 2 (6.2%) turned into DM. There was a significant difference in the number of subjects who had normal glucose at the end of the study between two groups ($P = 0.001$).

Conclusions: JLD granule effectively improved glucose control, increased the conversion of IGT to normal glucose, and improved the insulin resistance in patients with IGT. This Chinese herbal medicine may have a clinical value for IGT.

Key words: Clinical Observation; Diabetes Mellitus; Impaired Glucose Tolerance; Jinlida Granule

INTRODUCTION

Type 2 diabetes is a growing public health challenge globally. In the year 2013, 382 million people had diabetes mellitus (DM), this number is expected to rise to 592 million by the year 2035.^[1] An even larger segment of the world's population has impaired glucose tolerance (IGT).^[2] IGT, which is a risk factor for type 2 diabetes,^[3,4] is characterized by an increase in the postprandial glucose levels^[5] and considered as an intermediate metabolic state between normal blood glucose and DM. The overall prevalence of DM is estimated to be 11.6% in the Chinese adult population according to the recent national survey.^[6] Some studies have discovered that about 5–10% of IGT will develop into DM within one year.^[7]

IGT could be reversed to normal blood glucose by timely and effective intervention. Therefore, effective interventions for patients with IGT are necessary, which can prevent and delay the development of DM. Several studies have shown that lifestyle or pharmacological therapy could delay the development of DM in patients with IGT,^[8-10] and clinical

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research has shown the superiority of the Traditional Chinese Medicine (TCM) in this field.^[11-13] Jinlida (JLD) granule, a TCM, is an herbal formula developed under the theory that Pi (Spleen)-deficiency appears in the onset of DM. By nourishing Pi and regulating body fluid of DM subjects, JLD granule was used for diabetes management with positive data from the animal and human studies.^[14-18] However, the efficacy of JLD granule in the treatment of IGT patients and its effect on the prevention of DM have never been observed. This study therefore was designed to evaluate the efficacy and safety of JLD granule for the IGT treatment and prevention of DM.

METHODS

Study design

The research procedures were performed in accordance with standards of quality control in Chinese clinical trial and in accordance with the *Declaration of Helsinki*. The study was approved by the Medical Ethical Committee of The First Affiliated Hospital of Xiamen University (No. KYZ-2014-004), and the written informed consent was obtained from all the participants.

The overall design of the study consisted of a screening visit and a 12-week treatment period. After the initial screening, 65 eligible participants from Department of Endocrinology and Diabetes, The First Affiliated Hospital of Xiamen University, between April 2014 and October 2014 were randomly assigned to the JLD group ($n = 34$) and control group ($n = 31$) based on the random block procedure produced by the Random Allocation Software (version 1.0; Isfahan, Iran) [Figure 1]. Participants in JLD group orally took one bag of JLD granules (9 g) three times daily with 120–150 ml warm water after each meal and participants in the control group received no drug treatment. All the participants engaged in standard diet control and exercise therapy. Smoking and alcohol consumption were controlled. During treatment, the use of other TCM that shares similar functional components with JLD granule was prohibited.

Inclusion criteria were as follows: (1) patients with IGT, which was defined as fasting plasma glucose (FPG) concentration <7.0 mmol/L and 2-h plasma glucose (2-h PG) concentration ≥ 7.8 mmol/L and <11.1 mmol/L, according to the World Health Organization criteria,^[19] and diagnosis will have been made after undertaking an oral glucose tolerance test (OGTT); (2) age between 20 years and 80 years; and (3) body mass index (BMI) of 18–30 kg/m².

Exclusion criteria were as follows: (1) Type 1 DM and type 2 DM (T2DM), gestational DM, secondary diabetics, and other special types of DM; (2) ketoacidosis or hyperosmotic coma within 12 weeks; (3) previous history or treatment for type 2 diabetes; (4) serious hepatic and renal function; (5) complicated with severe cardiovascular diseases, severe gastrointestinal disease, or psychiatric diseases; (6) former use of antidiabetic or lipid-lowering drugs; (7) concomitant medication known to interfere with glucose metabolism, such as systemic corticosteroids glucocorticoid within 8 weeks of start date of this study; (8) previous use of growth hormones within 6 months of start date of this study; (9) pregnancy, lactation, or being prepared pregnant women; (10) participated in other clinical trial within the last 2 weeks; or (11) refusing to provide consent for the study.

Study medication

The JLD granules were provided by Shijiazhuang Yiling Pharmaceutical Company (Hebei, China). This herbal drug, prepared in small granules, is dark brown in color and has a bitter taste. The JLD granule contain over a dozen Chinese medicinal herbs, including ginseng (Renshen), puerarin (Gegen), pale white atractylodes rhizome (Cangbaizhu), *Coptis chinensis* (Huanglian), poria cocos (Fuling), radix polygonati officinalis (Yuzhu), and so on. The quality of these herbs and decoction preparation was in accordance with the requirement of Chinese Pharmacopoeia (2005 edition).

Study assessments

Participants meeting preliminary criteria were invited to attend a clinic visit by a physician to confirm eligibility

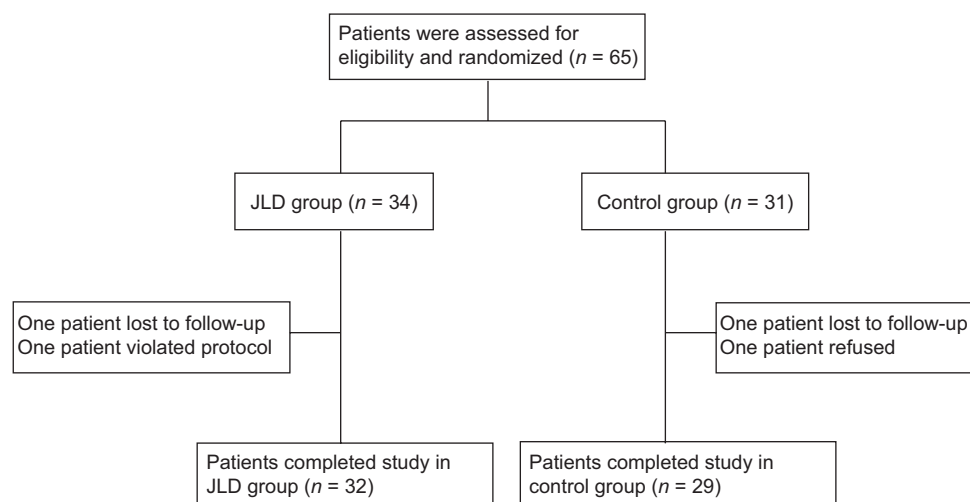


Figure 1: Flow diagram of the participants of this study. JLD: Jinlida.

and have signed an informed consent before any study assessments. All the participants received diabetic education and an exercise program formulated according to age and gender. The following clinical data were collected: demographic data (i.e., gender, age and family history of diabetes), medical history, body weight, height, waist circumference, hip circumference, vital signs, PG, plasma insulin, glycated hemoglobin A_{1c} (HbA_{1c}), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), cholesterol triglycerides (TG), and liver and kidney function.

During this 12-week period, the study assessments were performed at 0, 4, 8, and 12 weeks. Participants received frequent reminders on healthy lifestyle principles. FPG was checked at each visit. At 0 and 12 weeks, OGTT, HbA_{1c}, routine laboratory tests, serum lipids, and physical examination (body weight, BMI, waist circumference and hip circumference, etc.) were checked, plasma insulin levels were measured, and the homeostatic model assessment (HOMA) was performed to quantify insulin resistance (HOMA-IR).

Body weight will be measured in participants wearing light clothes without shoes using a digital scale to the nearest 0.1 kg. Height will be measured using a portable stadiometer to the nearest 0.1 cm. Waist circumference and hip circumference were measured at the first visit and final visit, as well as BMI. The waist circumference measurement was taken at the midpoint between the lower rib margin and the iliac crest in centimeters to the nearest 0.1 cm, and hip circumference was measured at the most prominent area of hip in centimeter to the nearest 0.1 cm.

PG and insulin levels were tested by OGTT. We collected venous blood samples at fasting, 30 min and 2 h after 75 g glucose ingestion. Blood samples collected by venipuncture for metabolic parameters (i.e., FPG, total cholesterol, LDL-cholesterol, HDL-cholesterol, and TGs) were obtained in the early morning after an 8 h fast and were analyzed by Hitachi Automatic Analyzer (Hitachi, Japan). The HbA_{1c} level was measured using a Bio-Rad D10 Automated HbA_{1c} Analyzer (Bio-Rad, Hercules, CA, USA). Patients having symptoms such as polyuria and polydipsia suggesting DM during the study visits would have a random PG measurement taken by a blood glucose monitor (Contour Plus Blood Glucose Monitoring System, Bayer, Germany). A glucose measurement ≥ 11.1 mmol/L was followed up using a venipuncture PG sample for the patient's safety.

HOMA was used to calculate insulin resistance. The calculation was based on FPG and insulin. In general, a high PG level indicates insulin resistance despite hyperinsulinemia. HOMA-IR was calculated as FPG (mmol/L) \times fasting insulin (μ U/ml)/22.5.^[20,21]

Efficacy evaluation

The primary outcome was the changes in HbA_{1c}, FPG, and 2-h PG levels. The secondary outcome included the conversion of IGT to normal blood glucose, the conversion of IGT to T2DM, and changes in insulin resistance (HOMA-IR).

Safety evaluation

The safety evaluations included routine blood tests, liver function, kidney function, and adverse events (AEs) during the therapeutic period. Subjects were interviewed monthly to record adherence and query about AEs. Any AEs were assessed for severity and possible relationship to study drugs and were followed until they either being resolved or no clinical significance determined by the investigators.

Statistical analysis

We calculated the sample size required to detect an effect size of 0.6 (i.e., mean change in the outcome variable over time differs by at least 0.6 standard deviations (SDs) between the two groups) and thirty patients were required in each group to obtain an alpha of 0.05 and a beta of 0.80. We sought to enroll 35 participants per group to allow for 10% withdrawal and noncompliance. These calculations were based on the changes found in an earlier study of JLD granule.^[18]

The statistical analyses were performed using the SPSS Statistics (version 16.0; SPSS Inc., Chicago, IL, USA). Data are expressed as mean \pm SD or median (Q1, Q3) for continuous variables and frequencies (percentages) for categorical variables. For between-group comparisons, Student's *t*-test was performed on variables with normal distributions, Chi-square test for categorical data, and Mann-Whitney's *U*-test for variables with nonnormal distributions. For in-group comparisons, Paired *t*-test or Wilcoxon test was performed. Analysis of covariance (ANCOVA) was used to model outcome at 12 weeks by treatment group corrected for baseline level of the outcome variable. All statistical tests were two-sided and assumed to be statistically significant at a level of $P < 0.05$.

RESULTS

Subject characteristics

A total of 65 patients were enrolled in the study, and 61 (93.8%) patients completed this study. Of these 61 patients, 32 (52.5%) were in the JLD group and 29 (47.5%) in the control group. There were no statistically significant differences between groups in gender, age, BMI, and laboratory data (all $P > 0.05$) [Table 1]. No participants were prescribed other diabetes medications during the study. As the test drug could be taken conveniently, the compliance of patients was generally pretty good.

Comparisons of blood glucose and glycated hemoglobin A_{1c}

After 12 weeks of treatment, 2-h PG was significantly decreased in JLD group ($t = 2.180$, $P = 0.037$) and not significantly changed in control group ($t = -2.030$, $P = 0.052$), compared with baseline. An ANCOVA found that 2-h PG showed a statistically significant difference between JLD group and control group after 12 weeks of treatment ($F = 14.425$, $P < 0.001$). HbA_{1c} was very significantly decreased in JLD group ($t = 4.107$, $P < 0.001$) and not significantly changed in control group ($t = -0.946$, $P = 0.352$), compared with baseline. The ANCOVA showed

a statistically significant difference in HbA_{1c} between two groups after 12 weeks of treatment ($F = 23.340, P < 0.001$). FPG was significantly decreased in both groups compared with baseline ($t = 4.828, P < 0.001$ for JLD group; $t = 3.720, P = 0.001$ for control group), but the difference between

two groups after 12 weeks of treatment was not statistically significant ($F = 1.874, P = 0.176$) [Table 2].

Comparison of insulin resistance index of homeostatic model assessment

After 12 weeks of treatment, HOMA-IR was significantly lower in JLD group ($Z = -2.412, P = 0.015$) and significantly higher in control group ($Z = -3.104, P = 0.001$), compared with baseline. There was a statistically significant difference in HOMA-IR between two groups after 12 weeks of treatment ($Z = -2.181, P = 0.029$) [Table 2].

Comparisons of weight, body mass index, waist/hip ratio, and total cholesterol

After 12 weeks of treatment, significant reduction in weight, BMI, and total cholesterol were observed in both groups compared with baseline (JLD group: $t = 4.238, P < 0.001$ for weight, $t = 4.268, P < 0.001$ for BMI, $t = 3.207, P = 0.003$ for total cholesterol; control group: $t = 3.228, P = 0.003$ for weight, $t = 3.274, P = 0.003$ for BMI, $t = 3.915, P = 0.001$ for total cholesterol); but no significant changes in waist/hip ratio were observed between baseline and after 12 weeks of treatment in both groups (all $P > 0.05$). After 12 weeks of treatment, the differences in weight, BMI, waist/hip ratio, and total cholesterol between two groups were not significantly different (all $P > 0.05$) [Table 2].

Comparison of the conversion of impaired glucose tolerance

After 12 weeks of treatment, 2 (6.9%) patients returned to normal blood glucose, 22 (75.9%) patients remained in IGT, and 5 (17.2%) patients developed DM in control group, while in the JLD group, 14 patients (43.8%) returned to normal blood glucose, 16 (50.0%) patients remained in IGT, and 2 (6.2%) patients developed DM. There was a significant

Table 1: Patient demographic and clinical characteristics of JLD and control groups at baseline

Characteristics	JLD group (n = 32)	Control group (n = 29)	t	P
Age (years)	47.1 ± 7.1	49.9 ± 7.2	-1.527	0.132
Male	17 (53.1)	14 (48.3)	0.143	0.800
Weight (kg)	61.7 ± 9.0	62.7 ± 8.2	-0.453	0.652
BMI (kg/m ²)	22.9 ± 2.5	23.6 ± 2.7	0.945	0.280
Waist (cm)	83.4 ± 9.1	81.5 ± 5.4	0.960	0.341
Waist/hip ratio	0.9 ± 0.1	0.9 ± 0.1	0.957	0.343
FPG (mmol/L)	6.2 ± 0.5	6.3 ± 0.6	-0.956	0.343
2-h PG (mmol/L)	8.5 ± 2.1	9.4 ± 1.6	-1.841	0.071
HbA _{1c} (%)	6.5 ± 0.7	6.5 ± 0.5	0.007	0.994
Fasting insulin (μU/ml)	9.2 (7.0, 15.3)	9.0 (8.1, 10.7)	-0.159	0.874
HOMA-IR	2.4 (2.0, 4.0)	2.5 (2.1, 3.0)	-0.116	0.908
Triglycerides (mg/L)	15.3 ± 7.8	15.4 ± 7.9	-0.026	0.979
Total cholesterol (mg/L)	56.1 ± 10.5	55.5 ± 9.1	0.244	0.808
HDL-C (mg/L)	13.5 ± 3.1	14.2 ± 2.7	-0.905	0.369
LDL-C (mg/L)	33.8 ± 6.2	32.4 ± 8.3	0.740	0.462

Data are shown as mean ± SD, n (%), or median (Q1, Q3). The difference between groups was nonsignificant at the level $P > 0.05$ at baseline tested by Student's *t*-test or Chi-square test. BMI: Body mass index; FPG: Fasting plasma glucose; 2-h PG: 2-h plasma glucose; HbA_{1c}: Glycated hemoglobin A_{1c}; HOMA-IR: Insulin resistance index of homeostasis model assessment; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; JLD: Jinlida; SD: Standard deviation.

Table 2: Clinical variables at baseline and after 12 weeks treatment in JLD and control groups

Variables	JLD group (n = 32)		Control group (n = 29)		After 12 weeks treatment, JLD group versus control group	
	Baseline	After 12 weeks	Baseline	After 12 weeks	Statistical values	P
FPG (mmol/L)	6.2 ± 0.5	5.8 ± 0.6*	6.3 ± 0.55	6.0 ± 0.6*	1.874 [‡]	0.176
2-h PG (mmol/L)	8.5 ± 2.1	7.7 ± 2.0 [†]	9.4 ± 1.6	10.3 ± 2.5	14.425 [‡]	<0.001
HbA _{1c} (%)	6.5 ± 0.7	6.0 ± 0.6*	6.5 ± 0.5	6.5 ± 0.5	23.340 [‡]	<0.001
Fasting insulin (μU/ml)	9.2 (7.0, 15.3)	9.5 (6.5, 11.9) [†]	9.0 (8.1, 10.7)	11.4 (8.3, 12.4)*	-1.813 [§]	0.070
HOMA-IR	2.4 (2.0, 4.0)	2.41 (1.7, 3.9) [†]	2.5 (2.1, 3.0)	3.0 (2.1, 3.3)*	-2.181 [§]	0.029
Weight (kg)	61.7 ± 9.0	60.2 ± 9.6*	62.7 ± 8.2	61.1 ± 7.6*	0.005 [‡]	0.944
BMI (kg/m ²)	22.9 ± 2.5	22.3 ± 2.4*	23.6 ± 2.7	23.0 ± 2.2*	0.271 [‡]	0.605
Waist (cm)	83.4 ± 9.1	82.6 ± 9.4 [†]	81.5 ± 5.4	80.9 ± 4.5	0.002 [‡]	0.965
Waist/hip ratio	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.0	0.135 [‡]	0.715
Triglycerides (mg/L)	15.3 ± 7.8	15.0 ± 7.1	15.4 ± 7.9	13.4 ± 5.4	3.289 [‡]	0.075
Total cholesterol (mg/L)	56.1 ± 10.5	52.4 ± 10.1*	55.5 ± 9.1	49.7 ± 5.6*	2.362 [‡]	0.130
HDL-C (mg/L)	13.5 ± 3.1	13.1 ± 2.7	14.2 ± 2.7	13.3 ± 2.4 [†]	0.268 [‡]	0.606
LDL-C (mg/L)	33.8 ± 6.2	32.6 ± 6.1	32.4 ± 8.3	31.2 ± 5.9	0.267 [‡]	0.607

Data are shown as mean ± SD, or median (Q1, Q3). * $P < 0.01$, [†] $P < 0.05$, compared with baseline in the same group using paired *t*-test or Wilcoxon test. [‡]Analysis of covariance; [§]Mann-Whitney's *U*-test. BMI: Body mass index; FPG: Fasting plasma glucose; 2-h PG: 2-h plasma glucose; HbA_{1c}: Glycated hemoglobin A_{1c}; HOMA-IR: Insulin resistance index of homeostasis model assessment; HDL: High-density lipoprotein cholesterol; LDL: Low-density lipoprotein cholesterol; JLD: Jinlida; SD: Standard deviation.

difference in the number of subjects who had normal glucose at the end of the study between JLD group and control group ($\chi^2 = 10.678, P = 0.001$). The Chi-square test showed no significant difference in comparison of the incidence of DM between the two groups ($\chi^2 = 1.809, P = 0.173$).

Adverse reactions

Results of liver and kidney function in both groups examined before and after treatment were all in the normal range. Following the treatment for 12 weeks, AEs were noted in two patients. All reported AEs were gastrointestinal reactions and mild to moderate in severity. One patient in the JLD group experienced diarrhea and one subject in the control group had nausea. No patients were withdrawn from the study due to these AEs. No hypoglycemia or other serious AEs were reported during the study period.

DISCUSSION

Several large-scale intervention trials have demonstrated that lifestyle changes (including dieting and exercising)^[22-24] and pharmacological interventions^[25-30] (acarbose, voglibose, metformin, thiazolidinediones, etc.) were effective in preventing T2DM. However, lifestyle intervention is impractical to some extent as it could hardly be carried out by patients to achieve satisfactory improvement. There are also many disadvantages of the Western medicine listed above, such as costly price and AEs. In this field, TCM has been used in the prevention of diabetes and showed certain superiority.^[11,12,31-34]

Several clinical trials have revealed that JLD granule can control blood glucose levels and have systemic benefits in patients with diabetes.^[14-18] In an early clinical observational study of 186 patients with T2DM ineffectively managed by metformin monotherapy, 12 weeks of JLD granule treatment as add-on medication decreased HbA_{1c} by $0.92 \pm 1.09\%$ and reduced FPG and 2-h PG levels.^[18] Elevated HbA_{1c} levels that integrated PG overtime was now validated as another indicator of IGT.^[5] Our study showed that patients in JLD group had significantly reduced FPG, 2-h PG, and HbA_{1c} after 12 weeks of treatment, and the levels of 2-h PG and HbA_{1c} were very significantly different between two groups after 12 weeks of treatment. Our data indicated that JLD granule had a good hypoglycemic effect, in accord with the result of the previous clinical study on JLD granule.

Chinese herbal medicine is often used in the prevention of different diseases. To date, no clinical trials have been conducted to evaluate whether JLD granule is effective in treating IGT. IGT can be observed as an intermediate stage in diabetes.^[19] In this study, the JLD granule effectively enhanced the conversion of IGR to normal blood glucose, and the incidence of DM showed a decreased tendency in JLD group compared with control group.

IGT is associated with the insulin resistance syndrome. Insulin resistance syndrome, which is also known as the metabolic syndrome, is characterized by the presence of insulin resistance, dyslipidemia, increased

weight circumference (abdominal obesity), dysglycemia, hypertension, etc.^[35] The clinical characters listed above are risk factors that increase the risk of type 2 diabetes, cardiovascular disease, and all-cause mortality.^[36] Our data showed that insulin resistance, which directly involved in the pathogenesis of T2DM, was significantly decreased in JLD group after 12 weeks of treatment, compared with baseline. Both JLD and control groups showed lowered weight, BMI, and total cholesterol after 12 weeks of treatment, indicating that our subjects may benefit from standard diet control and exercise therapy. Noticing that mean waist circumference of JLD group was reduced after 12 weeks of treatment ($P = 0.037$) while no changes were observed in the control group, which implied that patients with abdominal obesity might benefit from JLD granule.

JLD granule is composed of seventeen Chinese medical herbs. Many components of JLD granule, such as ginsenosides, puerarin, and *C. chinensis*, have been demonstrated to have a hypoglycemic effect.^[37-39] Besides, Wang *et al.*^[40] supposed that the mechanism underlying the antihyperglycemic effect of JLD granule might be associated with its protection of pancreatic β -cells through AMP-activated protein kinase activation. In the current study, no obvious AEs occurred, which suggested that this herbal drug was safe to use. Although the results of our study need to be confirmed by larger and longer clinical trials in the future, JLD granule had promising potential as an effective means in slowing the progression of IGT to T2DM.

Our study had some limitations, such as relatively short study period and small sample size. Given the limitation of this study, the conversion of IGT to T2DM did not reach the significant level based on statistical analysis. In the future, further interventional studies with longer length of treatment and follow-up and larger sample size are needed to verify it.

In summary, the JLD granule effectively improved glucose control, increased the conversion of IGT to normal glucose, and improved the insulin resistance in individuals with IGT. For IGT individuals who are at high risk of developing T2DM, this Chinese herbal medicine may help to prevent diabetes.

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Conflicts of interest

There are no conflicts of interest.

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