Efficacy and Safety of Mulberry Twig Alkaloids Tablet for the Treatment of Type 2 Diabetes: A Multicenter, Randomized, Double-Blind, Double-Dummy, and Parallel Controlled Clinical Trial

Ling Qu,[1] Xiaochun Liang,[1] Guoqing Tian,[1] Gaili Zhang,[1] Qunli Wu,[1] Xiumei Huang,[1] Yazhong Cui,[1] Yuling Liu,[2] Zhufang Shen,[2] Changqing Xiao,[3] Yingfen Qin,[4] Heng Miao,[5] Yongyan Zhang,[6] Ziling Li,[7] Shandong Ye,[8] Xuezhi Zhang,[9] Jing Yang,[10] Guiwen Cao,[11] Yi Li,[12] Gangyi Yang,[13] Ji Hu,[14] Xiaoyue Wang,[15] Zhengfang Li,[16] Yukun Li,[17] Xiuzhen Zhang,[18] Guangde Zhang,[19] Li Chen,[20] Wenjin Hua,[21] Ming Yu,[22] Chunyan Lu,[23] Xiaomei Zhang,[24] and Hong Jiang[25]

Diabetes Care 2021;44:1324–1333 | https://doi.org/10.2337/dc20-2109

OBJECTIVE

This study aimed to evaluate the efficacy and safety of mulberry twig alkaloids (Sangzhi alkaloids [SZ-A]) in the treatment of type 2 diabetes (T2D).

RESEARCH DESIGN AND METHODS

This was a multicenter, randomized, double-blind, double-dummy, and parallel controlled noninferiority clinical trial that was conducted for 24 weeks. A total of 600 patients were randomly allocated to the SZ-A group ($n = 360$) or acarbose group ($n = 240$). The primary efficacy end point was the change of glycosylated hemoglobin (HbA_{1c}) compared with baseline. In addition, adverse events (AEs), severe AEs (SAEs), treatment-related AEs (TAEs), and gastrointestinal disorders (GDs) were monitored.

RESULTS

After treatment for 24 weeks, the change in HbA_{1c} was –0.93% (95% CI –1.03 to –0.83) (–10.2 mmol/mol [–11.3 to –9.1]) and –0.87% (–0.99 to –0.76) (–9.5 mmol/mol [–10.8 to –8.3]) in the SZ-A and acarbose groups, respectively, and the least squares mean difference was –0.05% (95% CI –0.18 to 0.07) (–0.5 mmol/mol [–2.0 to 0.8]) between the two groups, with no significant difference on the basis of covariance analysis ($P > 0.05$). The incidence of TAEs and GDs was significantly lower in the SZ-A group than the acarbose group ($P < 0.01$), but no differences for AEs or SAEs between the two groups were observed ($P > 0.05$).

CONCLUSIONS

SZ-A exhibited equivalent hypoglycemic effects to acarbose in patients with T2D. Nevertheless, the incidence of TAEs and GDs was lower following SZ-A treatment than acarbose treatment, suggesting good safety.

According to the International Diabetes Federation's *IDF Diabetes Atlas* (9th edition), an estimated 463 million people are currently living with diabetes globally,

[1]*Department of Traditional Chinese Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*
[2]*Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*
[3]*Department of Endocrinology and Metabolism, The First Affiliated Hospital, Guangxi Medical University, Guangxi, China*
[4]*Department of Endocrinology, The First Affiliated Hospital, Guangxi Medical University, Guangxi, China*
[5]*Department of Endocrinology, The Second Affiliated Hospital, Nan Jing Medical University, Jiangsu, China*
[6]*Department of Endocrinology, Shengjing Hospital of China Medical University, Liaoning, China*
[7]*Department of Endocrinology, Inner Mongolia Baogang Hospital, Baotou, Inner Mongolia Autonomous Region, China*
[8]*Department of Endocrinology, The First Affiliated Hospital of University of Science and Technology of China (USTC), Division of Life Sciences and Medicine, USTC, Hefei, Anhui, China*
[9]*Traditional Chinese Medicine and Integrative Medicine Department, Peking University First Hospital, Beijing, China*
[10]*Department of Endocrinology, The First Affiliated Hospital, Shanxi Medical University, Shanxi, China*
[11]*Department of Endocrinology, The Fourth Affiliated Hospital, Jilin University, Jilin, China*
[12]*Department of Traditional Chinese Medicine, Beijing Hospital, Beijing, China*
[13]*Department of Endocrinology, The Second Affiliated Hospital, Chongqing Medical University, Chongqing, China*
[14]*Department of Endocrinology, The Second Affiliated Hospital, Suzhou University, Jiangsu, China*

and ~90% of these individuals have type 2 diabetes (T2D). The number of people with diabetes is projected to reach 578 million by 2030 (1). The standardized incidence of diabetes in the Chinese adult population is 10.9–11.2%; however, only 32.2–49.0% of these individuals receive treatment, and approximately one-half of all treated patients do not achieve satisfactory glycemic control (2,3). Although new hypoglycemic agents have recently been introduced to the market (4–9), these drugs still do not meet the clinical demand for glycemic control.

The use of herbal medicines for the prevention and treatment of T2D is well documented in China and other countries. Herbal medicines often have a wide range of pharmacological effects. There has been an increasing interest in the use of herbal medicines for the treatment of diabetes (10,11). Previous studies have demonstrated the hypoglycemic effect of some herbs derived from parts of the mulberry tree (12,13). The main components of mulberry twigs include alkaloids, flavonoids, polysaccharides, coumarin, amino acids, and organic acids (12,14). Studies have shown that mulberry twig alkaloids (Sangzhi alkaloids [SZ-A]) are the active component of alkaloids extracted and isolated from the Chinese herbal medicine "mulberry twig" and are mainly composed of 1-deoxyrijolymycin (1-DNJ), fagomine (FA), 1,4-dideoxy-1,4-imino-D-arabitol (DAB), and other polyhydroxyalkaloids. The total content of alkaloids is not less than 50% in SZ-A. Among the active components of alkaloids, the content of 1-DNJ, FA, and DAB account for >90%, and 1-DNJ is the predominant alkaloid (Supplementary Material 1). SZ-A has been shown to reduce fasting and nonfasting glucose levels and prolong peak glucose concentrations after sucrose or starch load in alloxan-induced diabetic mice and rats (15). In addition, animal experiments have revealed that SZ-A improves insulin resistance, increases basal insulin levels, and enhances glucose-stimulated insulin secretion (16,17). Pharmacological studies have suggested that the beneficial effects of SZ-A in the treatment of diabetes may be mediated through several therapeutic targets. Of these, intestinal α-glucosidase is the most well-characterized target of SZ-A.

People in East Asia usually rely on starchy foods as their main source of calories; therefore, α-glucosidase inhibitors are often used as the first-line drug for the treatment of patients with diabetes in this region (18–20). However, these drugs are associated with a high incidence of gastrointestinal disorders (GDs), such as abdominal distension, abdominal pain, and diarrhea, because of low selectivity to α-glucosidase (5,21,22). In vitro experiments have shown that SZ-A imparts a significant inhibitory effect on sucrase and maltase, which is equal to or slightly stronger than that of acarbose. However, the inhibitory effect of SZ-A on amylase is much weaker than acarbose. This suggests that SZ-A has stronger disaccharidase selectivity and may help in reducing GDs, such as flatulence (23–26).

A placebo-controlled, randomized, double-blind, and multicenter trial showed that change in glycosylated hemoglobin (HbA_{1c}) was significantly decreased compared with baseline after treatment for 16 weeks, and the effect was much better than that of placebo (data not published). In this study, we evaluated the efficacy and safety of SZ-A in the treatment of patients with T2D, using acarbose as positive control, to provide evidence for its clinical application. To our knowledge, this is the largest randomized controlled trial of SZ-A in patients with T2D in the world. In addition, it is the largest randomized controlled trial of natural botanical drugs for diabetes that have been marketed globally.

RESEARCH DESIGN AND METHODS

Study Design and Participants

This multicenter, randomized, double-blind, double-dummy, and parallel controlled clinical trial was conducted across 23 institutions in China. The lead-in period was 4 weeks, and the treatment period was 24 weeks. It used a positive-controlled (acarbose), multicenter, phase III noninferiority clinical research design, and each center competed for the entry.

Patients who qualified on the basis of 1999 World Health Organization diagnostic criteria for T2D and who had not received antidiabetic medical therapy before enrollment or who had received antidiabetic medical therapy for no more than 3 months at any time in the past were eligible for participation. The inclusion criteria were *1*) age range of 18–70 years, *2*) provision of written informed consent, *3*) HbA_{1c} level of 7.0–10.0% (53–86 mmol/mol), *4*) fasting blood glucose (FBG) <13 mmol/L (<234 mg/dL), and *5*) BMI of 19–30 kg/m^2.

The main exclusion criteria were *1*) >2.5 mmol/L (>45 mg/dL) variation in FBG level between the first follow-up and second follow-up; *2*) allergy or intolerance to α-glucosidase inhibitors; 3) history of severe diabetic complications (the proliferative stage of diabetic retinopathy, diabetic nephropathy stage V, diabetic ketoacidosis, diabetic hyperosmolar coma, and diabetic lactic acidosis); *4*) combined therapy with drugs that affect glucose metabolism, such as antidiabetic herbal medicine or gluco-

[15]Department of Endocrinology, The First People's Hospital of Yueyang, Hunan, China
[16]Department of Endocrinology, The Second Affiliated Hospital, Kunming Medical University, Yunnan, China
[17]Department of Endocrinology, The Third Affiliated Hospital, Hebei Medical University, Hebei, China
[18]Department of Endocrinology, Tongji Hospital, Tongji University, Shanghai, China
[19]Department of Endocrinology, Xiyuan Hospital, Chinese Academy of Chinese Medical Sciences, Beijing, China
[20]Department of Endocrinology, Qilu Hospital, Shandong University, Shandong, China
[21]Department of Endocrinology, The Third People's Hospital of Wuxi, Jiangsu, China
[22]Department of Endocrinology, Central Hospital of Putuo District, Shanghai, China
[23]Department of Endocrinology, West China Hospital, Sichuan University, Sichuan, China
[24]Department of Endocrinology, The First Affiliated Hospital of Bengbu Medical College, Anhui, China
[25]Department of Endocrinology, The Second Affiliated Hospital of Liaoning University of Traditional Chinese Medicine, Liaoning, China
Corresponding authors: Xiaochun Liang, xcliang@vip.sina.com, and Guoqing Tian, gq_tian@126.com

Received 24 August 2020 and accepted 17 February 2021
Clinical trial reg. no. ChiCTR2000034289, www.chictr.org.cn
This article contains supplementary material online at https://doi.org/10.2337/figshare.14128430.
X.L. and G.T. contributed equally to this work.

corticoids; *5*) hyperlipidemia with a history of irregular intake of lipid-lowering drugs; *6*) chronic gastrointestinal dysfunction, obvious digestive and absorptive disorders, or endocrine diseases such as hyperthyroidism, hypercortisolism, and acromegaly; *7*) medical conditions that may be aggravated by flatulence (e.g., severe hernia, ileus, postoperative intestinal surgery, intestinal ulcers); *8*) serious heart disease, myocardial infarction, unstable angina pectoris, or chronic cardiac insufficiency (New York Heart Association class III and IV); poorly controlled blood pressure (BP) (systolic BP $\geq$160 mmHg or diastolic BP $\geq$100 mmHg); *9*) impaired liver function (serum ALT or AST $>2\times$ the upper limit of normal [ULN] reference range or total bilirubin $>2\times$ ULN) or kidney function (serum creatinine $>1\times$ ULN or creatinine clearance $<$60 mL/min); *10*) serious medical conditions likely causing terminal illness during the treatment and follow-up periods; *11*) mental or neurological disorders and inability to express wishes correctly; *12*) participation in clinical trials of other drugs or medical devices in the immediately preceding 3 months; *13*) substantial alcohol consumption (episodic drinking of $>$5 units of alcohol for men and $>$4 units for women at once [1 unit = 10 g of pure ethanol]) or drug abuse or addiction; *14*) pregnancy; and *15*) unlikelihood of completing the expected course of treatment and follow-up (on the basis of the expert team's opinion).

The study (version number HY-SZIIIa-Pro-131020-01) protocol was approved by the ethics review committee of the Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, and other participating institutions. Written informed consent was obtained from all participants before their enrollment. The trial was performed in accordance with the principles of the Declaration of Helsinki.

Randomization and Treatment

The data analysis system for electronic data capture and clinical trial central randomization was used for randomization and dispensing of drugs. Electronic emergency letters were set up, and each center competed for enrollment.

A double-blind, double-dummy design was adopted to ensure that the two groups of drugs were consistent in terms of usage, dosage, and appearance. Because there are significant differences in appearance, smell, flavor, and quantity between the trial drug SZ-A and the control drug acarbose, in consideration of the scientificity of clinical study, the placebo of SZ-A and acarbose tablets were prepared to ensure the similarity of treatment between SZ-A and acarbose treatment groups in terms of usage, dosage, and appearance. To maintain similarity in taste and smell between SZ-A tablets and placebo, 1/20th of the dosage of SZ-A tablet was added in the preparation process of the placebo, which is a clinically ineffective dose. Acarbose placebos were prepared according to the shape, color, and weight of acarbose. The preparation of placebos absolutely satisfies the requirement of double blinding in a clinical trial.

All participants received one SZ-A placebo tablet and acarbose placebo tablet three times a day for a 4-week lead-in period. Subsequently, participants in the SZ-A group were provided an SZ-A tablet (50 mg) and acarbose placebo tablet, and those in the acarbose group were provided an acarbose tablet (50 mg) and SZ-A placebo tablet for 4 weeks. In the subsequent treatment period, the doses of SZ-A tablets and SZ-A placebo tablets were doubled. All the tablets were administered orally with the first bite of food (Supplementary Materials 2 and 3 and Supplementary Fig. 1).

SZ-A tablets (50 mg/tablet; active ingredient SZ-A, mainly 1-DNJ) were produced by Beijing Wehand-Bio Pharmaceutical Co., Ltd. SZ-A placebo tablets (2.5 mg/tablet; active ingredient SZ-A, mainly 1-DNJ; blank excipient added) and acarbose placebo tablets were both manufactured by the same company. Acarbose tablets (50 mg/tablet) were produced by Bayer Healthcare Pharmaceutical Inc. (Berlin, Germany). To render the tablets indistinguishable in terms of appearance, weight, and taste, the SZ-A placebo tablets contained a 5% dose of SZ-A, while the acarbose placebo tablet contained the corresponding blank excipient to mimic the acarbose tablet.

End Points

The primary efficacy end point was the change in HbA_{1c} compared with baseline after treatment for 24 weeks (Supplementary Material 4). The secondary efficacy end point included the proportion of patients with HbA_{1c} $<$7% ($<$53 mmol/mol) after 24 weeks of treatment as well as changes in FBG, 1-h postprandial blood glucose (1h-PBG), 2-h PBG (2h-PBG), area under the curve of the PBG ($AUC_{0-2\ h}$) (Supplementary Material 5), body weight, and BMI compared with baseline. Safety indicators included the incidence of adverse events (AEs), severe AEs (SAEs), treatment-related AEs (TAEs), and GDs (Supplementary Material 6).

Data Analysis and Statistics

A reduction in HbA_{1c} level after treatment was the primary efficacy end point; noninferiority design was adopted with the unilateral test $\alpha = 0.025$, $\beta = 0.2$ (power = 80%). On the basis of the phase II clinical study of SZ-A (the relevant results have not been published yet), the expected variation in HbA_{1c} was –0.82% (–9.0 mmol/mol) in the experimental group and –0.84% (–9.2 mmol/mol) in the acarbose group; the expected common SD was 0.88%, and the noninferior standard δ was 0.3% (3 mmol/mol). According to the 2007 "drug registration management approach" of traditional Chinese medicine, the minimum sample size required for a phase III clinical trial group is 300. Accounting for a dropout rate of 20%, with the ratio of 3:2 between the treatment group and acarbose group, the total number of patients was finally determined to be 600, including 360 in the SZ-A group and 240 in the acarbose group.

SAS 9.3 software was used for all statistical analyses. The noninferiority test was represented by a bilateral 95% CI of the difference between the groups. Bilateral tests were used for all statistical tests, and two-sided $P <$ 0.05 was considered indicative of statistical significance. Descriptive statistics were generated for demographic data and baseline analysis. Continuous variables are presented as the mean, SD, and 95% CI. Categorical variables are presented as frequency and percentage. Inferential statistical results are listed as descriptive results.

The primary efficacy end point was analyzed by covariance, with groups as fixed effects. The differences between the two groups and the bilateral 95% CIs were

calculated. The upper limit of the bilateral 95% CI and the preset noninferior standard of 0.3% (3 mmol/mol) were compared to determine whether the experimental group was noninferior to the acarbose group. The primary end point was analyzed using full analysis set (FAS) and per-protocol set (PPS) as well as the intention-to-treat population.

Diachronic analysis was performed for the proportion of patients with HbA_{1c} <7% (<53 mmol/mol), and the between-group difference was assessed using the χ^2 test. Changes in HbA_{1c}, FBG, 1h-PBG, 2h-PBG, $AUC_{0-2\ h}$, body weight, and BMI from baseline were analyzed over time, and the between-group differences were assessed using the *t* test. Paired *t* test was used to compare the pre- and posttreatment levels of various parameters. Secondary efficacy end points were analyzed by FAS.

AEs are coded according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use *International Medical Dictionary for Regulatory Activities*. The incidence rates of AEs, SAEs, TAEs, and GDs were calculated, and the between-group differences were assessed using the χ^2 test. Safety indicators were analyzed by security data set.

RESULTS

Baseline Characteristics

A total of 600 patients were recruited, and 517 completed the study. The dropout rates of the SZ-A and acarbose groups were 13.89% and 13.75%, respectively. Approximately 50 patients in the SZ-A group and 33 in the acarbose group dropped out between 25 March 2014 and 15 July 2015 (Supplementary Fig. 2). HbA_{1c} and other parameters, such as age, sex, course of diabetes, FBG, 1h-PBG, 2h-PBG, weight, and BMI, did not differ between the two groups. The baseline characteristics of the study population are summarized in Table 1.

Changes in HbA_{1c}

In the FAS analysis, the mean change in HbA_{1c} level at 24 weeks (24–0 weeks) in the SZ-A and acarbose groups was –0.93% (95% CI –1.03 to –0.83) (–10.2 mmol/mol [–11.3 to –9.1]) and –0.87% (–0.99 to –0.76) (–9.5 mmol/mol [–10.8 to –8.3]), respectively; covariance analysis revealed no significant between-

Table 1—Baseline characteristics of the study population (FAS)

	SZ-A group (n = 321)	Acarbose group (n = 222)
Sex, *n* (%)		
Male	156 (48.6)	118 (53.2)
Female	165 (51.4)	104 (46.8)
Marital status, *n* (%)		
Married	319 (99.4)	221 (99.5)
Unmarried	2 (0.6)	1 (0.5)
Occupation, *n* (%)		
Manual worker	53 (16.5)	34 (15.3)
Nonmanual worker	268 (83.5)	188 (84.7)
Ethnicity, *n* (%)		
Han	299 (93.1)	206 (92.8)
Other	22 (6.9)	16 (7.2)
Drinking, *n* (%)		
Never	247 (76.9)	171 (77.0)
Drinking	52 (16.2)	37 (16.7)
Abstinence	22 (6.9)	14 (6.3)
Smoking, *n* (%)		
Never	235 (73.2)	151 (68.0)
Smoking	68 (21.2)	55 (24.8)
Abstinence	18 (5.6)	16 (7.2)
Age		
Mean ± SD	54.9 ± 9.41	54.2 ± 9.01
95% CI	53.9–55.9	53.0–55.4
Course of diabetes (months), median (Q1–Q3)	24.00 (6.00–60.00)	24.00 (8.00–60.00)
Duration of diet control (months), median (Q1–Q3)	15.00 (6.00–38.00)	18.00 (6.00–45.00)
Duration of exercise (months), median (Q1–Q3)	15.00 (6.00–38.00)	18.00 (6.00–45.00)
Resting heart rate (beats/min)		
Mean ± SD	74.9 ± 8.46	76.0 ± 9.28
95% CI	74.0–75.9	74.8–77.2
Systolic BP (mmHg)		
Mean ± SD	127.0 ± 11.03	127.4 ± 11.68
95% CI	125.8–128.2	125.9–129.0
Diastolic BP (mmHg)		
Mean ± SD	76.9 ± 8.22	77.8 ± 8.23
95% CI	76.0–77.8	76.7–78.9
Weight (kg)		
Mean ± SD	69.16 ± 10.86	69.65 ± 10.33
95% CI	67.97–70.36	68.28–71.01
Height (cm)		
Mean ± SD	164.9 ± 7.89	165.3 ± 7.78
95% CI	164.0–165.8	164.2–166.3
BMI (kg/m^2)		
Mean ± SD	25.34 ± 2.84	25.41 ± 2.68
95% CI	25.03–25.65	25.06–25.76
HbA_{1c}		
%		
Mean ± SD	7.90 ± 0.79	7.95 ± 0.87
95% CI	7.81–7.99	7.84–8.07
mmol/mol		
Mean ± SD	63 ± 8.6	63 ± 9.5
95% CI	62–64	62–65
FPG[a]		
mmol/L		
Mean ± SD	8.52 ± 2.17	8.58 ± 1.96
95% CI	8.28–8.76	8.32–8.84

Continued on p. 1328

group difference ($P = 0.368$). The mean difference between the SZ-A and acarbose groups (least squares mean difference) was –0.05% (95% CI –0.18 to 0.07) (–0.5 mmol/mol [–2.0 to 0.8]). According to the noninferior standard of 0.3% (3 mmol/mol), the SZ-A group was not inferior to the acarbose group. PPS and intention-to-treat analyses generated similar results (Fig. 1*A* and Supplementary Material 7).

There was no significant between-group difference with respect to HbA_{1c} levels at baseline. At the 8-, 16-, and 24-week follow-up evaluations, HbA_{1c} levels were all significantly lower than baseline ($P < 0.001$) in both the SZ-A and the acarbose groups; however, there was no significant between-group difference ($P > 0.05$) (Fig. 1*B*).

Table 1—Continued

	SZ-A group ($n = 321$)	Acarbose group ($n = 222$)
mg/dL		
Mean ± SD	153 ± 39	154 ± 35
95% CI	149–158	150–159
1h-PBG[b]		
mmol/L		
Mean ± SD	14.37 ± 3.20	14.00 ± 2.70
95% CI	14.02–14.73	13.64–14.39
mg/dL		
Mean ± SD	259 ± 58	252 ± 49
95% CI	252–265	246–259
2h-PBG[c]		
mmol/L		
Mean ± SD	14.60 ± 3.95	14.52 ± 3.39
95% CI	14.17–15—Q3	14.07–14.97
mg/dL		
Mean ± SD	263 ± 71	261 ± 61
95% CI	255–271	253–269

Q1–Q3, quartile 1–quartile 3. [a]SZ-A group, $n = 320$; acarbose group, $n = 219$. [b]SZ-A group, $n = 319$; acarbose group, $n = 221$. [c]SZ-A group, $n = 318$; acarbose group, $n = 221$.

Proportion of Patients With HbA_{1c} <7% (<53 mmol/mol)

Taking HbA_{1c} <7% (<53 mmol/mol) as the target of treatment, the number of patients who achieved the target showed a gradual increase with treatment. At 24 weeks, 153 patients in the SZ-A group had achieved the target with a rate of reaching the standard of 47.7%, and 100 patients achieved the target in the acarbose group with a rate of reaching the standard of 45.0%. There was no significant between-group difference ($P = 0.548$) (Fig. 1*C*).

Changes in Blood Glucose Levels

Changes in FBG, 1h-PBG, 2h-PBG, and $AUC_{0–2\ h}$ from baseline showed no significant between-group differences (Table 2). After 8, 16, and 24 weeks of treatment, FBG, 1h-PBG, 2h-PBG, and $AUC_{0–2\ h}$ in both groups showed a significant decrease from the respective baseline levels ($P < 0.001$ for all). However, there were no significant between-group differences at the indicated time points with the exception of 2h-PBG at 8 weeks and 1h-PBG at 16 weeks (Fig. 1*D*–*G*).

Changes in Body Weight and BMI

After 24 weeks of treatment, changes in body weight in the SZ-A group (–0.68 ± 2.23 kg [95% CI –0.94 to –0.42]) did not significantly differ from those in the acarbose group (–0.76 ± 2.46 kg [–1.11 to –0.42]; $P = 0.698$). BMI in the SZ-A group changed by –0.25 ± 0.81 kg/m^2 (–0.34 to –0.16), while that in the acarbose group changed by –0.28 ± 0.90 kg/m^2 (–0.41 to –0.16) compared with the respective baseline levels; the between-group difference was not statistically significant ($P = 0.664$).

Adverse Reactions

In the SZ-A group, 189 AEs (incidence rate 53.7%) and 19 SAEs (incidence rate 5.4%) were recorded during the treatment. Among these, 54 (15.3%) were TAEs, but none were serious TAEs. In the acarbose group, 135 AEs (incidence rate 57.2%) and 9 SAEs (incidence rate 3.8%) were recorded. Among these, 67 (28.4%) were TAEs (Supplementary Materials 8–10). There were no significant between-group differences with respect to the incidence of AEs or SAEs ($P = 0.402$ and $P = 0.377$, respectively). The incidence of TAEs in the SZ-A group was significantly lower than that in the acarbose group ($P < 0.001$) (Fig. 2*A*).

GDs were the main TAEs in both groups. There were 43 cases of GDs in the SZ-A group (incidence rate 12.2%), which accounted for 79.6% of TAEs in this group. There were 58 cases of GDs in the acarbose group (incidence rate 24.6%), which accounted for 86.6% of TAEs. The incidence of GDs in the acarbose group was significantly higher than that in the SZ-A group ($P < 0.001$) (Fig. 2*A*). Diachronic analysis showed that newly reported GDs occurred mainly at 4–8 weeks, and the incidence showed a gradual decrease with treatment. However, the incidence of newly reported GDs in the SZ-A group was lower than in the acarbose group at all time points; the between-group differences in this respect were statistically significant at 4 and 8 weeks ($P = 0.033$ and $P = 0.013$, respectively) (Fig. 2*B*).

There were seven patients with cardiovascular and cerebrovascular SAEs, including four in the SZ-A group (incidence rate 1.1%) and three in the acarbose group (incidence rate 1.3%), with no significant between-group difference ($P = 1.000$). According to the determination of researchers and independent experts in the condition of unexposed blindness, none of the SAEs mentioned above had anything to do with therapeutic drugs. No hypoglycemia events occurred in either group during the trial.

CONCLUSIONS

Previous studies have demonstrated diverse pharmacological effects of SZ-A, such as regulation of blood glucose concentration, insulin secretion, and status of insulin resistance (15–17). The inhibitory effect of SZ-A on α-glycosidase may account for its hypoglycemic effect (23,25). Acarbose, a type of α-glycosidase inhibitor, can reduce HbA_{1c} by 0.5–1.0% (5.5–10.9 mmol/mol) with a curative effect. It is widely used for the treatment of T2D, especially in regions with a predominantly cereal diet (18,27–32). Therefore, acarbose was selected as positive control.

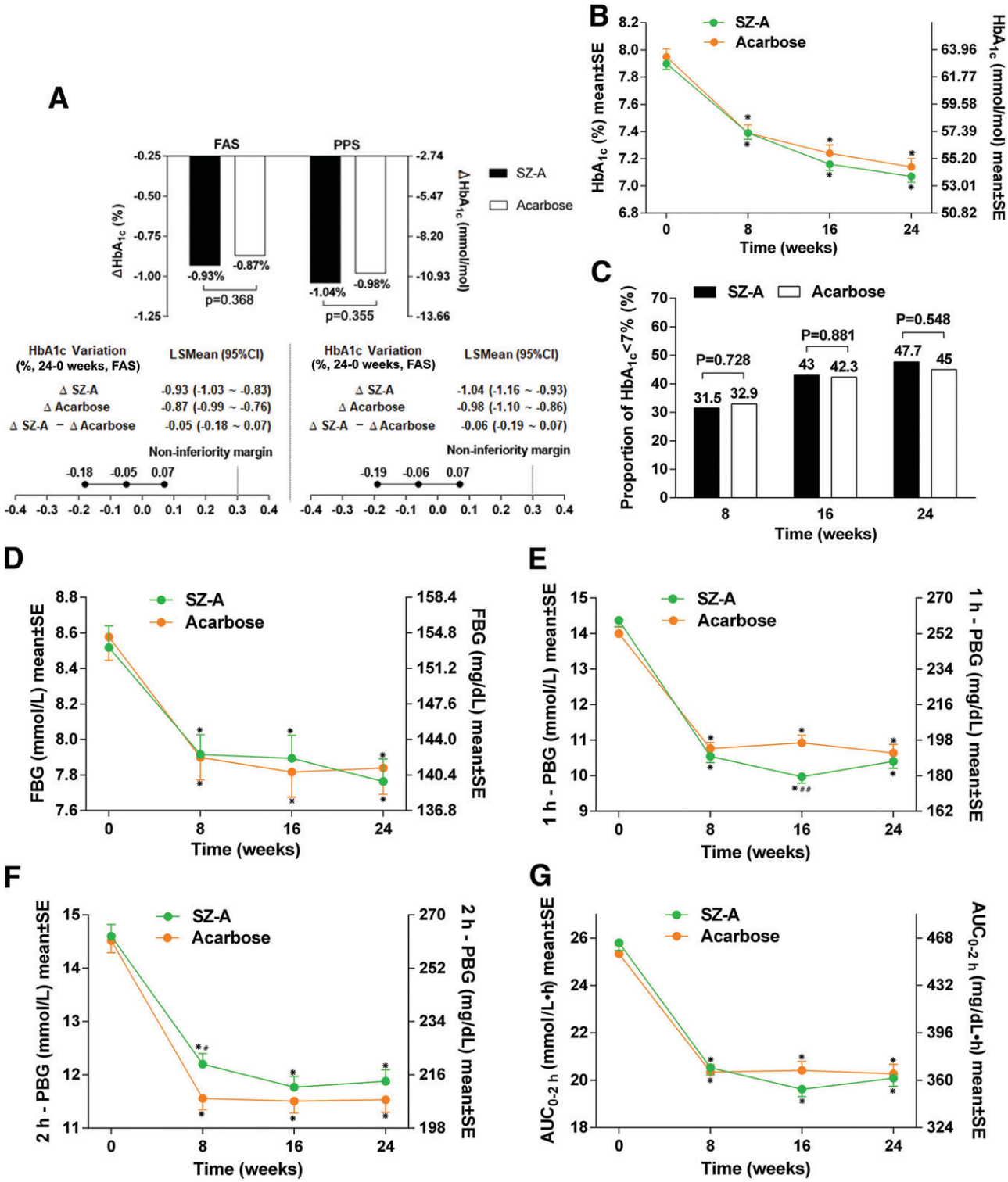

Figure 1—Blood glucose control. *A*: Analysis of changes in HbA_{1c} level (24–0 weeks, FAS and PPS). *B*: Diachronic analysis of HbA_{1c} levels (FAS). *C*: Analysis of proportion of patients with HbA_{1c} <7% (<53 mmol/mol) (FAS). *D*: Diachronic analysis of FBG levels (FAS). *E*: Diachronic analysis of 1h-PBG levels (FAS). *F*: Diachronic analysis of 2h-PBG levels (FAS). *G*: Diachronic analysis of $AUC_{0-2\ h}$ (FAS). LSMean, least squares mean. *$P < 0.001$ vs. baseline level; #$P < 0.05$ vs. acarbose group; ##$P < 0.001$ vs. acarbose group.

We adopted a double-blind and double-dummy study design to obtain more robust results and to minimize potential bias. With respect to randomization, each participating center competed for inclusion through the central stochastic system.

This study observed that SZ-A imparts a good hypoglycemic effect. After treatment for 24 weeks, the primary efficacy end point HbA_{1c} decreased by 0.93% (10.2 mmol/mol), which was comparable to that achieved with acarbose (50 mg t.i.d.). The UK Prospective Diabetes Study demonstrated that the risks of diabetes-

Table 2—Analysis of change in blood glucose levels (FAS)

Efficacy parameter	SZ-A group	Acarbose group	Statistical quantity	*P* value	Method
FBG					
8–0 weeks					
n (*n* missing)	301 (20)	203 (19)	0.705	0.481	*t*' test[a]
mmol/L					
Mean ± SD	−0.56 ± 1.89	−0.67 ± 1.54			
95% CI	−0.78 to −0.35	−0.89 to −0.46			
mg/dL					
Mean ± SD	−10 ± 34	−12 ± 28			
95% CI	−14 to −6	−16 to −8			
16–0 weeks					
n (*n* missing)	281 (40)	196 (26)	1.028	0.304	*t* test
mmol/L					
Mean ± SD	−0.54 ± 2.10	−0.74 ± 2.06			
95% CI	−0.79 to −0.30	−1.03 to −0.45			
mg/dL					
Mean ± SD	−10 ± 38	−13 ± 37			
95% CI	−14 to −5	−19 to −8			
24–0 weeks					
n (*n* missing)	292 (29)	199 (23)	0.140	0.889	*t*' test
mmol/L					
Mean ± SD	−0.69 ± 2.28	−0.72 ± 2.00			
95% CI	−0.96 to −0.43	−1.00 to −0.44			
mg/dL					
Mean ± SD	−12 ± 41	−13 ± 36			
95% CI	−17 to −8	−18 to −8			
1h-PBG					
8–0 weeks					
n (*n* missing)	292 (29)	206 (16)	1.949	0.052	*t*' test
mmol/L					
Mean ± SD	−3.81 ± 3.46	−3.27 ± 2.78			
95% CI	−4.21 to −3.41	−3.65 to −2.88			
mg/dL					
Mean ± SD	−69 ± 62	−59 ± 50			
95% CI	−76 to −61	−66 to −52			
16–0 weeks					
n (*n* missing)	276 (45)	194 (28)	3.831	<0.001	*t* test
mmol/L					
Mean ± SD	−4.32 ± 3.44	−3.12 ± 3.20			
95% CI	−4.73 to −3.91	−3.57 to −2.66			
mg/dL					
Mean ± SD	−78 ± 62	−56 ± 58			
95% CI	−85 to −70	−64 to −48			
24–0 weeks					
n (*n* missing)	281 (40)	195 (27)	1.386	0.167	*t*' test
mmol/L					
Mean ± SD	−3.87 ± 3.85	−3.41 ± 3.32			
95% CI	−4.32 to −3.42	−3.88 to −2.94			
mg/dL					
Mean ± SD	−70 ± 69	−61 ± 60			
95% CI	−78 to −62	−70 to −53			
2h-PBG					
8–0 weeks					
n (*n* missing)	294 (27)	206 (16)	1.664	0.097	*t*' test
mmol/L					
Mean ± SD	−2.35 ± 3.96	−2.90 ± 3.39			
95% CI	−2.81 to −1.90	−3.37 to −2.44			
mg/dL					
Mean ± SD	−46 ± 71	−52 ± 61			
95% CI	−51 to −34	−61 to −44			
16–0 weeks					
n (*n* missing)	275 (46)	194 (28)			
mmol/L			0.682	0.496	*t* test
Mean ± SD	−2.76 ± 3.49	−2.99 ± 3.65			
95% CI	−3.17 to −2.35	−3.50 to −2.47			

Continued on p. 1331

Table 2—Continued

Efficacy parameter	SZ-A group	Acarbose group	Statistical quantity	*P* value	Method
mg/dL					
Mean ± SD	−50 ± 63	−54 ± 66			
95% CI	−57 to −42	−63 to −44			
24–0 weeks					
n (*n* missing)	284 (37)	195 (27)	0.838	0.402	*t* test
mmol/L					
Mean ± SD	−2.63 ± 4.11	−2.94 ± 3.65			
95% CI	−3.11 to −2.15	−3.45 to −2.42			
mg/dL					
Mean ± SD	−47 ± 74	−53 ± 66			
95% CI	−56 to −39	−62 to −44			
$AUC_{0-2\ h}$					
8–0 weeks					
n (*n* missing)	298 (23)	208 (14)	0.552	0.581	*t*' test
mmol/L · h					
Mean ± SD	−5.22 ± 5.92	−4.95 ± 5.12			
95% CI	−5.90 to −4.54	−5.65 to −4.25			
mg/dL · h					
Mean ± SD	−94 ± 107	−89 ± 92			
95% CI	−106 to −82	−102 to −77			
16–0 weeks					
n (*n* missing)	278 (43)	197 (25)	2.019	0.044	*t* test
mmol/L · h					
Mean ± SD	−6.02 ± 5.77	−4.92 ± 5.89			
95% CI	−6.70 to −5.34	−5.75 to −4.09			
mg/dL · h					
Mean ± SD	−108 ± 104	−89 ± 106			
95% CI	−121 to −96	−104 to −74			
24–0 weeks					
n (*n* missing)	287 (34)	197 (25)	0.789	0.430	*t*' test
mmol/L · h					
Mean ± SD	−5.59 ± 6.46	−5.15 ± 5.60			
95% CI	−6.34 to −4.83	−5.94 to −4.37			
mg/dL · h					
Mean ± SD	−101 ± 116	−93 ± 101			
95% CI	−114 to −87	−107 to −79			

[a]*t*' test was used when variance was not homogenous.

related end events, diabetes-related death, diabetes-related myocardial infarction, and diabetes-related microvascular complications will decrease by 21%, 21%, 14%, and 37%, respectively, along with the reduction of HbA_{1c} by 1% (10.9 mmol/mol) (33). According to contemporary clinical guidelines, HbA_{1c} <7% (<53 mmol/mol) can effectively reduce the occurrence of chronic complications of diabetes and reduce the incidence of hypoglycemia (18,20,27,30). The proportion of patients who achieved HbA_{1c} <7.0% (<53 mmol/mol) in the SZ-A group (47.7%) was similar to that in the acarbose group (45.0%).

The above results indicate that the hypoglycemic effect of SZ-A is comparable to that of acarbose. The results of the current study are consistent with those of the single-center study we previously reported (34). Weight gain is an important issue in the treatment of diabetes; effective weight management is of utmost significance for the achievement of therapeutic effect (8,20,27,30). Our findings suggest that SZ-A has no negative effect on weight compared with acarbose.

Safety is an important consideration during the evaluation of new drugs. In this study, there was no significant between-group difference with respect to the incidence of AEs or SAEs. Furthermore, the incidence of TAEs in the SZ-A group was significantly lower than in the acarbose group. GDs are the main side effects of acarbose. In our study, the incidence of GDs in the acarbose group (24.6%) was similar to that in previous reports (5,21,22,28,29,31,32,35). The incidence of GDs in the SZ-A group was 12.2%, which was much lower than the acarbose group, showing a significant difference. In vitro experiments have demonstrated a strong inhibitory effect of SZ-A on maltase and sucrase, which is similar to that of acarbose. However, SZ-A showed no inhibitory effect on amylase at 100 g/mL, while acarbose had an obvious inhibitory effect on α-amylase (IC_{50} 1.74–2.4 g/mL). It can be concluded that SZ-A has stronger selectivity in inhibiting maltase and sucrase. The main active ingredients of SZ-A, namely, 1-DNJ, FA, and DAB, are more likely to form hydrogen bonds with the active structural domains of maltase and sucrase, which explains their greater affinity for disaccharidases (36,37). These findings may partly explain the underlying mechanism of the reduced incidence of GDs in the SZ-A group in our study.

In previous studies, after oral intake of 40, 200, and 1,000 mg/kg of SZ-A, the main components of 1-DNJ, FA, and

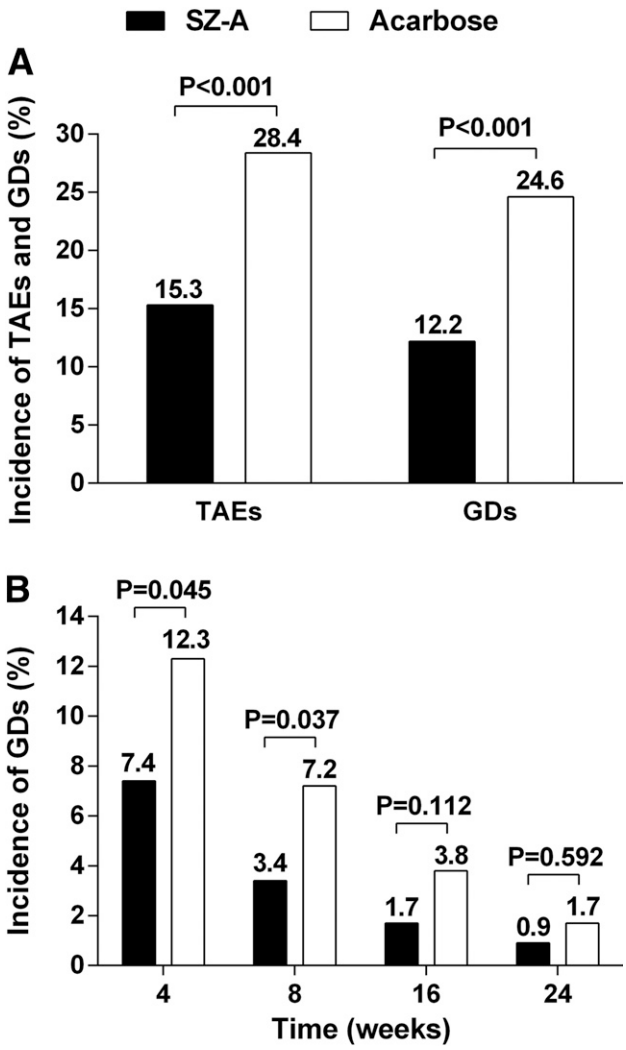

Figure 2—Safety analysis. *A*: Incidence of TAEs and GDs (security data set). *B*: Diachronic analysis of incidence of GDs (security data set).

DAB showed absorption saturation with an increase in dose; the absolute bioavailability was 33.3–72.4%, 29.9–77.5%, and 40.1–78.2%, respectively. After oral administration, these drugs are mainly distributed in the gastrointestinal tract, partially absorbed into the blood, and excreted by the kidneys in their original form rather than metabolized by the liver; therefore, these have no obvious effect on hepatic enzymes. The 24-h urine and feces recovery of 1-DNJ, FA, and DAB was nearly 100%, indicating no significant accumulation of SZ-A in the body (23). In our study, we did not find an incidence of TAEs, such as abnormal liver and kidney function, in the SZ-A group, which may be related to the plasma pharmacokinetic characteristics of SZ-A. However, the effects of SZ-A on liver and renal function still need to be paid attention in clinical application.

Some limitations of our study should be considered while interpreting the results. First, the observation period was only 24 weeks; a longer observation period is more conducive in further evaluating the efficacy and safety of SZ-A. Second, SAEs related to cardiovascular and cerebrovascular diseases were observed in both the SZ-A and the acarbose groups. However, these SAEs were determined by researchers and independent experts who were blinded to the group identity and were found to be unrelated to drug therapy; moreover, there was no significant between-group difference with respect to the incidence of SAEs. The Acarbose Cardiovascular Evaluation trial has confirmed that acarbose is similar to placebo without any adverse effects on cardiovascular end points (38). Therefore, we hypothesize that SZ-A may not produce adverse cardiovascular and cerebrovascular effects; however, further studies are required to evaluate its impact on cardiovascular and cerebrovascular end events. Third, because this study excluded patients with irregular drug intake regardless of lipid-lowering or glucose-lowering ones, it is not known whether the effect of SZ-A in these patients was consistent with that in this study population. In addition, animal studies have demonstrated other pharmacological effects of SZ-A, such as hypolipidemic effect, improvement in basal insulin level, alleviation of insulin resistance, and insulin secretion stimulated by glucose (16,17). Future studies should explore the extensive targets of SZ-A in multiple tissues and organs. Furthermore, phase IV clinical studies should observe the impact of SZ-A on metabolic syndrome, weight control, and cardiovascular risk and complications and evaluate its comprehensive benefits during long-term treatment of patients with T2D.

In summary, in this study, SZ-A and acarbose showed similar effects in reducing HbA_{1c}. The effect of SZ-A on body weight was equal to that of acarbose without hypoglycemia. In addition, SZ-A caused fewer TAEs and GDs than acarbose, suggesting good tolerance in patients with T2D.

Acknowledgments. The authors thank Prof. Qingshan Zheng, Pharmaceutical Clinical Research Center of Shanghai University of Traditional Chinese Medicine, for statistical support. In addition, the authors thank the participants, experimenters, and researchers for their participation. The authors thank LetPub (https://www.letpub.com) for linguistic assistance during the preparation of this manuscript.

Funding. This study was supported by the National Science and Technology Major Project (2013ZX09101005).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. L.Q. contributed to drafting and revising the manuscript. L.Q., X.L., G.T., Ga.Z., Q.W., X.H., Y.C., Y. Liu, Z.S., C.X., Y.Q., H.M., Y.Z., Zi. Li, S.Y., Xu.Z., J.Y., G.C., Yi Li, G.Y., J.H., X.W., Zh. Li, Yu. Li, Xiu.Z., Gu.Z., L.C., W.H., M.Y., C.L., Xia.Z., and H.J. contributed to the clinical data collection. X.L. and G.T. designed the study and contributed to the final approval of the manuscript. Y. Liu and Z.S. contributed to the study conception. G.T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity

of the data and the accuracy of the data analysis.

References

1. International Diabetes Federation. *IDF Diabetes Atlas*. 9th edition. Gent, Belgium, International Diabetes Federation, 2019
2. Wang L, Gao P, Zhang M, et al. Prevalence and ethnic pattern of diabetes and prediabetes in China in 2013. JAMA 2017;317:2515–2523
3. Li Y, Teng D, Shi X, et al. Prevalence of diabetes recorded in mainland China using 2018 diagnostic criteria from the American Diabetes Association: national cross sectional study. BMJ 2020;369:m997
4. Perkovic V, Jardine MJ, Neal B, et al.; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295–2306
5. Du J, Liang L, Fang H, et al. Efficacy and safety of saxagliptin compared with acarbose in Chinese patients with type 2 diabetes mellitus uncontrolled on metformin monotherapy: results of a phase IV open-label randomized controlled study (the SMART study). Diabetes Obes Metab 2017;19: 1513–1520
6. Wakisaka M. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:1799–1800
7. Rosenstein R, Hough A. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2016;374:1093–1094
8. Qaseem A, Barry MJ, Humphrey LL; Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline update from the American College of Physicians. Ann Intern Med 2017;166:279–290
9. Patorno E, Schneeweiss S, Gopalakrishnan C, Martin D, Franklin JM. Using real-world data to predict findings of an ongoing phase IV cardiovascular outcome trial: cardiovascular safety of linagliptin versus glimepiride. Diabetes Care 2019;42:2204–2210
10. Pang GM, Li FX, Yan Y, et al. Herbal medicine in the treatment of patients with type 2 diabetes mellitus. Chin Med J (Engl) 2019;132:78–85
11. Chukwuma CI, Matsabisa MG, Ibrahim MA, Erukainure OL, Chabalala MH, Islam MS. Medicinal plants with concomitant anti-diabetic and anti-hypertensive effects as potential sources of dual acting therapies against diabetes and hypertension: a review. J Ethnopharmacol 2019;235:329–360
12. Chan EW, Lye PY, Wong SK. Phytochemistry, pharmacology, and clinical trials of Morus alba. Chin J Nat Med 2016;14:17–30
13. Mudra M, Ercan-Fang N, Zhong L, Furne J, Levitt M. Influence of mulberry leaf extract on the blood glucose and breath hydrogen response to ingestion of 75 g sucrose by type 2 diabetic and control subjects. Diabetes Care 2007;30: 1272–1274
14. Zhang L, Tao G, Chen J, Zheng ZP. Characterization of a new flavone and tyrosinase inhibition constituents from the twigs of Morus alba L. Molecules 2016;21:1130
15. Ye F, Shen Z, Xie M. Alpha-glucosidase inhibition from a Chinese medical herb (Ramulus mori) in normal and diabetic rats and mice. Phytomedicine 2002;9:161–166
16. Ye F, Shen ZF, Qiao FX, Zhao DY, Xie MZ. Experimental treatment of complications in alloxan diabetic rats with alpha-glucosidase inhibitor from the Chinese medicinal herb Ramulus mori. Yao Xue Xue Bao 2002;37:108–112
17. Shuai-Nan L, Quan L, Su-Juan S, et al. Anti-diabetic effects of the fraction of alkaloids from Ramulus Mori, an innovative Sangzhi alkaloids as an α-glucosidase inhibitor. Yao Xue Xue Bao 2019;7:1225–1233
18. Ko SH, Hur KY, Rhee SY, et al.; Committee of Clinical Practice Guideline of Korean Diabetes Association. Antihyperglycemic agent therapy for adult patients with type 2 diabetes mellitus 2017: a position statement of the Korean Diabetes Association. Diabetes Metab J 2017;41:337–348
19. Haneda M, Noda M, Origasa H, et al. Japanese clinical practice guideline for diabetes 2016. Diabetol Int 2018;9:1–45
20. Chinese Diabetes Society. Chinese guideline for the prevention and treatment of type 2 diabetes mellitus (2017 edition). Chin J Diabetes Mellitus 2018;10:4–67
21. Yang W, Liu J, Shan Z, et al. Acarbose compared with metformin as initial therapy in patients with newly diagnosed type 2 diabetes: an open-label, non-inferiority randomised trial. Lancet Diabetes Endocrinol 2014;2:46–55
22. Wettergreen SA, Sheth S, Malveaux J. Effects of the addition of acarbose to insulin and non-insulin regimens in veterans with type 2 diabetes mellitus. Pharm Pract (Granada) 2016;14:832
23. Yang S, Mi J, Liu Z, et al. Pharmacokinetics, tissue distribution, and elimination of three active alkaloids in rats after oral administration of the effective fraction of alkaloids from Ramulus mori, an innovative hypoglycemic agent. Molecules 2017;22:22
24. Gao K, Zheng C, Wang T, et al. 1-Deoxynojirimycin: occurrence, extraction, chemistry, oral pharmacokinetics, biological activities and in silico target fishing. Molecules 2016;21:1600
25. Kimura T, Nakagawa K, Kubota H, et al. Food-grade mulberry powder enriched with 1-deoxynojirimycin suppresses the elevation of postprandial blood glucose in humans. J Agric Food Chem 2007;55:5869–5874
26. Yang S, Wang B, Xia X, et al. Simultaneous quantification of three active alkaloids from a traditional Chinese medicine Ramulus mori (Sangzhi) in rat plasma using liquid chromatography-tandem mass spectrometry. J Pharm Biomed Anal 2015;109: 177–183
27. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2019. Diabetes Care 2019; 42(Suppl. 1):S90–S102
28. Scheen AJ. Clinical efficacy of acarbose in diabetes mellitus: a critical review of controlled trials. Diabetes Metab 1998;24:311–320
29. Sun W, Zeng C, Liao L, Chen J, Wang Y. Comparison of acarbose and metformin therapy in newly diagnosed type 2 diabetic patients with overweight and/or obesity. Curr Med Res Opin 2016;32:1389–1396
30. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2019 executive summary. Endocr Pract 2019;25:69–100
31. Hoffmann J, Spengler M. Efficacy of 24-week monotherapy with acarbose, glibenclamide, or placebo in NIDDM patients. The Essen Study. Diabetes Care 1994;17:561–566
32. Coniff RF, Shapiro JA, Robbins D, et al. Reduction of glycosylated hemoglobin and postprandial hyperglycemia by acarbose in patients with NIDDM. A placebo-controlled dose-comparison study. Diabetes Care 1995;18:817–824
33. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–412
34. Li M, Huang X, Ye H, et al. Randomized, double-blinded, double-dummy, active-controlled, and multiple-dose clinical study comparing the efficacy and safety of mulberry twig (Ramulus mori, Sangzhi) alkaloid tablet and acarbose in individuals with type 2 diabetes mellitus. Evid Based Complement Alternat Med 2016;2016: 7121356
35. Zhang JP, Wang N, Xing XY, Yang ZJ, Wang X, Yang WY. Efficacy of acarbose and metformin in newly diagnosed type 2 diabetes patients stratified by HbA1c levels. J Diabetes 2016;8:559–567
36. Liu Z, Yang Y, Dong W, et al. Investigation on the enzymatic profile of mulberry alkaloids by enzymatic study and molecular docking. Molecules 2019;24:1776
37. Liu SN, Liu Q, Sun SJ, et al. Anti-diabetic effects of the fraction of alkaloids from Ramulus mori, an innovative Sangzhi alkaloids as an α-glucosidase inhibitor. Yao Xue Xue Bao 2019; 54:1225–1233
38. Holman RR, Coleman RL, Chan JCN, et al.; ACE Study Group. Effects of acarbose on cardiovascular and diabetes outcomes in patients with coronary heart disease and impaired glucose tolerance (ACE): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2017;5:877–886