CURATIVE EFFECT OF SANGZHI TOTAL ALKALOID TABLETS IN THE TREATMENT OF PRE-TYPE 2 DIABETES AND ITS EFFECT ON SERUM GLUCOSE TRANSPORTER 4 AND NESFATIN-1

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ABSTRACT

Objective: *To investigate the clinical efficacy of Sangzhi total alkaloid tablets in the treatment of pre-type 2 diabetes mellitus (T2DM) and the effect on serum glucose transporter 4 (GLUT4) and nesfatin-1.*

Methods: *A total of 100 patients with pre-T2DM who were admitted to our hospital from June 2021 to June 2022 were selected and divided into the control group and the observation group according to the random number table method, with 50 cases in each group. Patients in the control group were given basic treatment, and patients in the observation group were treated with Sangzhi total alkaloid tablets on the basis of the control group. The clinical efficacy, TCM symptom and serological indexes were compared between the two groups, and the incidence of complications was compared between the two groups.*

Results: *The total effective rate of treatment in the observation group was significantly higher than that in the control group (P<0.05). After treatment, the thoracic abdominal distention, fullness after eating, obesity, chest tightness, nausea, fatigue, limb heavy, stool viscosity scores in the observation group were strikingly lower than those before treatment and the control group (P<0.05). After treatment, the levels of FPG, HbA1c, 2h PG, and HOMA-IR in the two groups were markedly lower than those before treatment (P<0.05), and those of the observation group was obviously lower than the control group (P<0.05). After treatment, the levels of TG, TC and LDL-C in the two groups were significantly lower than those before treatment (P<0.05), and those of the observation group was significantly lower than the control group (P<0.05). After treatment, the GLUT4 level in the two groups were significantly higher than that before treatment, and that of the observation group was remarkably higher than the control group (P<0.05). The level of nesfatin-1 in the two groups were dramatically lower than that before treatment, and that of the observation group was significantly lower than the control group (P<0.05). The incidence of complications in the observation group was significantly lower than that in the control group (P<0.05).*

Conclusions: *Sangzhi total alkaloid tablet has good clinical efficacy in the treatment of pre-T2DM patients, which can effectively reduce insulin resistance, increase insulin sensitivity, reduce serum nesfatin-1 level, elevate serum GLUT4 level, and alleviate clinical symptoms of patients.*

Keywords: *Pre-Type 2 diabetes mellitus, sangzhi total alkaloid tablets, curative effect, glucose transporter 4, nesfatin-1.*

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Introduction

With the improvement of people's living standards and the change of living habits, the incidence of diabetes patients in our country is on the rising trend, with type 2 diabetes (T2DM) accounting for more than 90% of patients with diabetes, about 1 in 10 people with T2DM[(1)]. Pre-T2DM, also known as impaired glucose regulation, is a transition stage from normal glucose metabolism to diabetes. The blood glucose value of patients increases, but has not reached the abnormal state of the diagnostic criteria for diabetes. As the reserve army of diabetes patients, pre-T2DM is also an important risk factor for cardiovascular and cerebrovascular diseases. Early diagnosis and treatment of pre-T2DM patients at this time is of great significance to prevent and delay the occurrence and development of lesions and reduce the incidence of T2DM[(2)]. At present, non-drug therapy is mainly used in clinical intervention

for patients with pre-T2DM, such as diet control and strengthening exercise, but the efficacy of non-drug therapy is limited and the overall therapeutic effect is limited. Therefore, the comprehensive therapy of traditional Chinese medicine combined with non-drug therapy is gradually adopted in clinical treatment for patients with pre-T2DM[3].

The Sangzhi total alkaloid is the extract of mulberry branch, which is the main active ingredient of polyhydroxylated alkaloids obtained from mulberry branch in the process of mulberry planting and silkworm rearing by extraction, separation and purification[4-5]. The previous study showed that the Sangzhi total alkaloid had strong α-glucosidase inhibitory activity. The clinical application of Sangzhi total alkaloid is similar to acarbose, which can be used as α-glucosidase inhibitor to inhibit the competition between small intestinal wall cells and oligosaccharides, slow down the hydrolysis of oligosaccharides and disaccharides to monosaccharides, thereby delaying the degradation of carbohydrates and reducing and delaying the rise of postprandial blood glucose[6].

This study aims to investigate the clinical efficacy of Sangzhi total alkaloid tablets in the treatment of pre-T2DM and its effect on serum GLUT4 and Nesfatin-1, in order to provide reference for clinical treatment.

Data and methods

Research object

A total of 100 patients with pre-T2DM who were admitted to our hospital from June 2021 to June 2022 were selected and divided into the control group and the observation group according to the random number table method, with 50 cases in each group. There was no significant difference in the general data between the two groups (P>0.05), which was comparable, as shown in Table 1. This study was reviewed and approved by the ethics committee of our hospital, and all patients signed informed consent.

Inclusion criteria:

• Patients were diagnosed as pre-T2DM by clinical symptoms, signs and serological indicators[7];

• Patients with good treatment compliance;

• Patients with complete clinical medical records.

Exclusion criteria:

• Patients combined with ketoacidosis and other serious diabetic complications;

• Patients with other endocrine diseases;

• Patients with severe cardiac, hepatic and renal insufficiency;

• Patients with a previous history of drug allergy.

Groups	n	Gender (n)		Age ($\bar{x}$±s, years old)	Body mass index ($\bar{x}$±s, kg/m²)
		Male	Female		
Control group	50	31	19	53.11±9.69	27.32±5.23
Observation group	50	32	18	52.64±10.53	27.06±5.56
t/χ^2		0.043		0.232	0.241
P		0.836		0.817	0.810

Table 1: Comparison of the patient's clinical data.

Methods

Patients in the control group were given basic treatment after admission: patients were instructed to control diet, exercise properly, quit smoking and limit alcohol, and closely monitor blood glucose, etc. On the basis of the treatment of the control group, patients in the observation group were treated with Sangzhi total alkaloid tablets 1 tablet/time in the first 4 weeks, and then adjusted to take Sangzhi total alkaloid tablets 2 tablets/time in the last 12 weeks. Patients chew it up and take it with the first bite or a few bites of food, 3 times a day for 16 weeks.

Observational indicators

Clinical efficacy

At the end of treatment, the clinical efficacy of the two groups of patients was evaluated. Significantly effective: If TCM syndrome score reduced by more than or equal to 70%, the clinical symptoms and signs were significantly improved.

Effective

If the TCM syndrome score decreased by more than or equal to 30%, the clinical symptoms and signs were improved.

Ineffective

If the TCM syndrome score decreased by less than 30%, it indicated that the clinical symptoms and signs did not improve, and even tended to worsen. Total effective rate = (significantly effective + effective) number of cases/total number of cases ×100%[8].

TCM symptom score

TCM symptoms of pre-T2DM patients were

evaluated according to TCM symptom score scale[9]. The main symptom scoring criteria included chest distension and postprandial fullness, and the score ranged from 0 points to 6 points. The higher the score, the more serious the symptoms of the patient. The score criteria for the secondary symptoms included obesity, chest tightness, nausea, fatigue, limb heavy, and stool viscosity, and the score ranged from 0 points to 3 points; the higher the score, the more severe the symptoms.

Serological indicators

In the morning before and after treatment, 5 ml of fasting peripheral venous blood was taken from the two groups, centrifuged at 3000 R/min, and the supernatant was collected and stored in a refrigerator at 4°C for further detection. Fasting blood glucose (FPG) and 2h postprandial blood glucose (2h PG) were detected by radioimmunoassay, fasting insulin (FINS) was detected by enzyme-linked immunosorbent assay, and insulin resistance index was calculated by [HOMA-IR= (FPG × FINS)/22.5]. All kits were provided by Shanghai Enzyme-linked Biotechnology Co., Ltd., and operated in strict accordance with the kit instructions. The levels of triglyceride (TG) and total cholesterol (TC) were detected by enzyme-linked immunosorbent assay. The levels of low density lipoprotein cholesterol (LDL-C) were detected by surfactant clearance method. Serum GLUT4 and nesfatin-1 levels were detected by enzyme-linked immunosorbent assay.

Occurrence of complications

The complications of the two groups were observed and recorded, including flatulence, hyperactivity of bowel sounds, nausea and vomiting, hypoglycemia, etc.

Statistical methods

SPSS 20.0 software was used for statistical analysis. The counting data were compared by χ^2 test. The measurement data were expressed as mean ± standard deviation ($\bar{x}\pm s$), and comparison was performed by t test. P<0.05 was considered the difference was statistically significant.

Results

Comparison of treatment effect between two groups

The total effective rate of the observation group was significantly higher than that of the control group (P<0.05). The results are shown in Table 2.

Groups	Cases	Significantly effective	Effective	Ineffective	Total effective rate
Observation group	50	16 (32.00)	25 (50.00)	9 (18.00)	41 (82.00)
Control group	50	9 (18.00)	21 (42.00)	20 (40.00)	30 (60.00)
χ^2					5.877
P					0.015

Table 2: Comparison of treatment effect between two groups [cases (%)].

Comparison of TCM symptom scores between the two groups

Before treatment, there was no significant difference in TCM symptom scores between the two groups (P>0.05).

After treatment, the thoracic abdominal distention, fullness after eating, obesity, chest tightness, nausea, fatigue, limb heavy, stool viscosity scores in the observation group were strikingly lower than those before treatment and the control group (P<0.05). The results were shown in Table 3.

Groups	Cases	Time	Thoracic abdominal distention	Fullness after eating	Obesity	Chest tightness, nausea	Fatigue, limb heavy	Stool viscosity
Observation group	50	Before treatment	4.13±1.24	4.24±0.38	1.92±0.62	1.75±0.45	2.03±0.55	1.94±0.48
		After treatment	0.94±0.20*	1.85±0.56*	0.64±0.15*	0.55±0.12*	0.95±0.26*	1.05±0.20*
t			17.959	24.972	14.189	18.220	12.553	12.102
P			0.000	0.000	0.000	0.000	0.000	0.000
Control group	50	Before treatment	4.20±1.16	4.18±0.45	1.88±0.57	1.80±0.53	1.97±0.64	1.90±0.51
		After treatment	1.44±0.52	2.43±0.67	0.98±0.24	0.94±0.22	1.32±0.37	1.41±0.25
t			15.352	15.332	10.290	10.597	6.217	6.100
P			0.000	0.000	0.000	0.000	0.000	0.000

Table 3: Comparison of TCM symptom scores between the two groups.
*Notes: compared with the control group: *P<0.05.*

Comparison of blood glucose indexes between the two groups before and after treatments

Before treatment, there was no significant difference in blood glucose indexes between the two groups (P>0.05).

After treatment, the levels of FPG, HbA1c, 2h PG, and HOMA-IR in the two groups were markedly lower than those before treatment (P<0.05), and those of the observation group was obviously lower than the control group (P<0.05). The results were shown in Table 4.

Groups	Cases	FPG (mmol/L)		HbA1c (%)		2h PG (mmol/L)		HOMA-IR	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	50	8.45±1.24	7.29±0.98*	8.53±1.18	7.51±1.09	13.01±1.72	10.22±1.47*	3.86±0.72	2.87±0.55*
Observation group	50	8.32±1.07	6.57±1.01*	8.41±1.12	6.64±0.87	12.83±1.66	8.63±1.25*	3.77±0.67	2.43±0.48*
t		0.561	3.618	0.522	4.411	0.533	5.827	0.647	4.262
P		0.576	0.000	0.603	0.000	0.596	0.000	0.519	0.000

Table 4: Comparison of blood glucose indexes between the two groups before and after treatments ($\bar{x}\pm s$).
*Notes: compared with patients in this group before treatment: *P<0.05.*

Comparison of blood lipid indexes between the two groups before and after treatment

Before treatment, there was no significant difference in blood lipid indexes between the two groups (P>0.05). After treatment, the levels of TG, TC and LDL-C in the two groups were significantly lower than those before treatment (P<0.05), and those of the observation group was significantly lower than the control group (P<0.05). The results are shown in Table 5.

Groups	Cases	TG		TC		LDL-C	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	50	2.57±0.61	1.97±0.42*	5.23±0.96	4.41±0.91	3.69±1.02	3.01±0.76*
Observation group	50	2.53±0.57	1.62±0.38*	5.21±1.13	3.94±0.77	3.63±0.95	2.65±0.41*
t		0.339	4.370	0.095	2.788	0.304	2.948
P		0.736	0.000	0.924	0.006	0.762	0.004

Table 5: Comparison of blood lipid indexes between the two groups before and after treatment ($\bar{x}\pm s$, mmol/L).
*Notes: compared with patients in this group before treatment: *P<0.05.*

Comparison of serum GLUT4 and nesfatin-1 levels between the two groups

Before treatment, there was no significant difference in serum GLUT4 and nesfatin-1 levels between the two groups (P>0.05). After treatment, the GLUT4 level in the two groups were significantly higher than that before treatment, and that of the observation group was remarkably higher than the control group (P<0.05). The level of nesfatin-1 in the two groups were dramatically lower than that before treatment, and that of the observation group was significantly lower than the control group (P<0.05). The results were shown in Table 6.

Comparison of the occurrence of complications between the two groups

The incidence of complications in the observation group was significantly lower than that in the control group (P<0.05). The results were shown in Table 7.

Groups	Cases	nesfatin-1 (mg/ml)		GLUT4	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	50	5.62±1.14	4.24±1.18*	2.64±0.52	6.43±2.28*
Control group	50	5.70±1.52	4.92±1.73*	2.72±0.88	4.34±1.11*
t		-0.298	-2.296	-553	5.828
P		0.767	0.024	0.581	0.000

Table 6: Comparison of serum GLUT4 and nesfatin-1 levels between the two groups.
*Notes: compared with the control group: *P<0.05.*

Groups	Cases	nesfatin-1 (mg/ml) GLUT4				
		Flatulence	Hyperactivity of bowel sounds	Nausea and vomiting	Hypoglycemia	Total
Observation group	50	1 (2.00)	1 (2.00)	1 (4.00)	0 (0.00)	3 (6.00)
Control group	50	5 (10.00)	3 (6.00)	1 (2.00)	1 (2.00)	10 (20.00)
χ^2						4.332
P						0.037

Table 7: Comparison of the occurrence of complications between the two groups [cases (%)].

Discussion

Diabetes mellitus is a group of metabolic diseases characterized by chronic elevated blood glucose levels, among which T2DM accounts for 90% of the disease population and is the main incidence population[10]. T2DM has more complications, and high disability and mortality, which seriously threatens the life and health safety of patients[11]. Pre-diabetes is a state between diabetes and normal blood sugar, which is considered a necessary stage of diabetes. Previous studies have shown that nearly half of people with impaired glucose tolerance develop diabetes within 5 to 10 years. If reasonable intervention is carried

out at this stage, the occurrence of diabetes can be reduced. α-glycosidase inhibitor is one of the clinical oral hypoglycemic drugs, often used in the treatment of T2DM patients, including acarbose, miglitol and other drugs. α-glucosidase inhibitors slow down the hydrolysis of oligosaccharides and disaccharides to monosaccharides by inhibiting the competition between small intestinal wall cells and oligosaccharides, thereby delaying the degradation of carbohydrates and reducing and delaying the rise of postprandial blood glucose[12]. Studies have found that α-glucosidase inhibitors can reduce postprandial blood glucose in patients with T2DM.

However, the long-term use of western medicines such as acarbose has a high incidence of adverse reactions, including flatulence, hyperactivity of bowel sounds, diarrhea, abdominal distension, etc., which limits its clinical application to a certain extent[13]. In recent years, with the continuous progress and development of Chinese medicine, the use of traditional Chinese medicine to treat diabetes and other endocrine diseases has become a clinical treatment trend. Chinese herbal medicine is a treasure trove of natural products with original advantages in China. Combining with modern separation and analysis technology, the study of chemical composition and pharmacological activity can explore the innovative medicine from natural products. The Sangzhi total alkaloid is active ingredient obtained from mulberry branch in the process of mulberry planting and silkworm rearing by extraction, separation and purification. The Sangzhi total alkaloid has the advantages of clear composition, clear target and clear mechanism. In addition to highly selective inhibition of intestinal glycosidase, it also has a wide range of pharmacological effects, such as improving glucose-stimulated insulin secretion, protecting islet β-cells, regulating glucose and lipid metabolism and intestinal flora, and stimulating glucagon-like peptide-1 secretion[14].

The results of this study showed that the total effective rate of the observation group was significantly higher than that of the control group. After treatment, the thoracic abdominal distention, fullness after eating, obesity, chest tightness, nausea, fatigue, limb heavy, stool viscosity scores in the observation group were strikingly lower than those before treatment and the control group. After treatment, the levels of FPG, HbA1c, 2h PG, and HOMA-IR in the two groups were markedly lower than those before treatment ($P<0.05$), and those of the observation group were obviously lower than the control group. It is suggested that Sanzhi total alkaloid tablet has a good clinical effect in the treatment of patients with pre-T2DM, which can effectively improve the disorder of glucose and lipid metabolism and alleviate the clinical symptoms of patients. Modern pharmacological studies have found that the Sanzhi total alkaloid mainly include 1-deoxynojirimycin, methycoline and other components, among which the main hypoglycemic effect is 1-deoxynojirimycin. 1-deoxynojirimycin can act on small intestinal microvillus wall cells and reversibly bind to sucrase, isomaltase, maltase and lactase. Among them, it has the strongest inhibitory effect on sucrase, thereby inhibiting the activity of enzyme, delaying the degradation of carbohydrates, slowing down the absorption of intestinal glucose, reducing and delaying the rise of postprandial blood glucose, achieving the purpose of lowering blood glucose, effectively improving the disorder of glucose and lipid metabolism, and alleviating the clinical symptoms of patients[15].

Currently, it is generally believed that insulin resistance and/or insulin secretion dysfunction of islet β-cells are the pathogenesis of T2DM[16]. Insulin resistance is a condition in which the body's liver, adipose tissue and skeletal muscle respond less to insulin due to various reasons, resulting in the production of a normal dose of insulin than the normal biological effect. Insulin resistance in T2DM is manifested by impaired liver glycogenolysis and impaired absorption of blood glucose by fat and muscle tissues, resulting in increased blood sugar content and further deterioration of islet β-cell function caused by hyperglycemia[17]. The results of this study found that after treatment, the levels of TG, TC and LDL-C in the two groups were significantly lower than those before treatment, and those of the observation group was significantly lower than the control group. It is suggested that Sanzhi alkaloid tablet is beneficial to reduce insulin resistance, increase insulin sensitivity and improve insulin secretion function in the treatment of patients with pre-T2DM. Studies have found that long-term treatment of Sanzhi total alkaloid in pre-diabetic HFC57 mice can increase the responsiveness of mouse islet β cells to glucose to a certain extent, increase insulin sensitivity, improve glucose-stimulated insulin secretion function, and thus reduce fasting serum insulin level[18].

Studies have shown that GLUT4 and nesfatin-1 are associated with the development of islet β-cell

abnormalities in diabetic patients. Nesfatin-1, a sensitive secreted peptide of insulin, is composed of 82 amino acids and is widely expressed in the central nervous system, pancreatic islet cells, adipose tissue, stomach, pituitary and other organs and tissue cells. It plays a role in promoting insulin secretion by acting on L-type Ca^{2+} channels and kinase A in pancreatic islet β cells[19)].

In addition, nesfatin-1 increased glucose uptake and improved insulin sensitivity in skeletal muscle cells. Besides, nesfatin-1 can inhibit food intake. As an inhibitory factor of gastric emptying, nesfatin-1 can inhibit gastric emptying, thereby reducing energy intake and indirectly lowering blood glucose in the body. Studies have found that a high glucose level in the body can stimulate the secretion of nesfatin-1 by rat pancreatic β-cells[20)]. Other studies have found that nesfatin-1 mRNA expression is decreased in pancreatic cells of patients with T2DM, thus it is speculated that nesfatin-1 may be related to insulin resistance[21)]. The results of this study found that the level of nesfatin-1 in the two groups was dramatically lower than that before treatment, and that of the observation group was significantly lower than the control group. These results suggested that Sangzhi total alkaloid tablets can effectively reduce the serum nesfatin-1 level in patients with pre-T2DM. This may be because the Sangzhi total alkaloid effectively inhibits α-glucosidase activity in the small intestine, reduce and delay the rise of postprandial blood glucose, achieve the purpose of lowering blood glucose, and then reduce the compensatory effect of nesfatin-1, thus effectively reducing the serum nesfatin-1 level[22)].

GLUT4 is a transmembrane glucose transporter localized in some vascular smooth muscle, glomeruli and medullary thick ascending limb, which is an insulin-regulated glucose transporter. GLUT4 plays an important role in maintaining glucose homeostasis by assisting glucose to freely pass through the cell membrane, and its expression changes can affect the regulation of blood glucose[23)]. Studies have found that impaired GLUT4 function or dysregulated expression can lead to insulin resistance in the body, resulting in decreased insulin sensitivity, so the decreased GLUT4 level is related to the pathogenesis of T2DM[24)]. The results of this study found that after treatment, the GLUT4 level in the two groups were significantly higher than that before treatment, and that of the observation group was remarkably higher than the control group. These results suggest that Sangzhi total alkaloid tablets can effectively increase serum GLUT4 level in patients with pre-T2DM. Sangzhi total alkaloid can up-regulate GLUT4 expression, but the specific mechanism of how to regulate GLUT4 expression has not been determined, which may be related to the improvement of insulin resistance, which needs further study[25)].

In conclusion, Sangzhi total alkaloid tablet has good clinical efficacy in the treatment of pre-T2DM patients, which can effectively reduce insulin resistance, increase insulin sensitivity, reduce serum nesfatin-1 level, elevate serum GLUT4 level, and alleviate clinical symptoms of patients.

References

1) Huang R, Wang H, Shen Z, et al. Increased Glycemic Variability Evaluated by Continuous Glucose Monitoring is Associated with Osteoporosis in Type 2 Diabetic Patients. Front Endocrinol (Lausanne). 2022 Jun 6; 13: 861131. doi: 10.3389/fendo.2022.861131.
2) Kabir MT, Ferdous Mitu J, Akter R, et al. Therapeutic potential of dopamine agonists in the treatment of type 2 diabetes mellitus. Environ Sci Pollut Res Int. 2022 Jul; 29(31): 46385-46404. DOI: 10.1007/s11356-022-20445-1.
3) Xia QS, Wu F, Wu WB, et al. Berberine reduces hepatic ceramide levels to improve insulin resistance in HFD-fed mice by inhibiting HIF-2α. Biomed Pharmacother. 2022 Jun; 150: 112955. DOI: 10.1016/j.biopha.2022.112955.
4) Zhu MD, Li Q, Yuan JQ, et al. Alleviation of Diabetic Tendon Injury via Activation of Tendon Fibroblasts Autophagy under Berberine Treatment. J Vis Exp. 2022 Mar 11; (181). DOI: 10.3791/63224.
5) Chen YM, Lian CF, Sun QW, et al. Ramulus Mori (Sangzhi) Alkaloids Alleviate High-Fat Diet-Induced Obesity and Nonalcoholic Fatty Liver Disease in Mice. Antioxidants (Basel). 2022 May 5; 11(5):905. doi: 10.3390/antiox11050905.
6) Ji T, Wang J, Xu Z, et al. Combination of mulberry leaf active components possessed synergetic effect on SD rats with diabetic nephropathy by mediating metabolism, Wnt/β-catenin and TGF-β/Smads signaling pathway. J Ethnopharmacol. 2022 Jun 28; 292: 115026. doi: 10.1016/j.jep.2022.115026.
7) Chu CC, Chen YC, Lin MH, et al. Association between Clinical Use of Colchicine and Risk of Type 2 Diabetes Mellitus among Gouty Patients: A Nationwide Cohort Study. Int J Environ Res Public Health. 2022 Mar 14; 19(6): 3395. DOI: 10.3390/ijerph19063395.

8) Li M, Trapika IGSC, Tang SYS, et al. Mechanisms and Active Compounds Polysaccharides and Bibenzyls of Medicinal Dendrobiums for Diabetes Management. Front Nutr. 2022 Jan 28; 8: 811870. doi: 10.3389/fnut.2021.811870.
9) Zhang L, Han L, Ma J, et al. Exploring the synergistic and complementary effects of berberine and paeoniflorin in the treatment of type 2 diabetes mellitus by network pharmacology. Eur J Pharmacol. 2022 Mar 15; 919: 174769. doi: 10.1016/j.ejphar.2022.174769.
10) Liu Y, Zhao X, Yang Z, et al. Correlation between serum C-peptide-releasing effects and the risk of elevated uric acid in type 2 diabetes mellitus. Endocr J. 2022 Jul 28; 69(7): 773-784. doi: 10.1507/endocrj.EJ21-0492.
11) Ren X, Xing Y, He L, et al. Effect of 1-Deoxynojirimycin on insulin resistance in prediabetic mice based on next-generation sequencing and intestinal microbiota study. J Ethnopharmacol. 2022 May 10; 289: 115029. doi: 10.1016/j.jep.2022.115029.
12) Ramadan S, Hegab AM, Al-Awthan YS, et al. Comparison of the Efficiency of Lepidium sativum, Ficus carica, and Punica granatum Methanolic Extracts in Relieving Hyperglycemia and Hyperlipidemia of Streptozotocin-Induced Diabetic Rats. J Diabetes Res. 2021 Dec 21; 2021: 6018835. DOI: 10.1155/2021/6018835.
13) Li JS, Ji T, Su SL, et al. Mulberry leaves ameliorate diabetes via regulating metabolic profiling and AGEs/RAGE and p38 MAPK/NF-κB pathway. J Ethnopharmacol. 2022 Jan 30; 283: 114713. doi: 10.1016/j.jep.2021.114713.
14) Cao H, Ji W, Liu Q, et al. Morus alba L. (Sangzhi) alkaloids (SZ-A) exert anti-inflammatory effects via regulation of MAPK signaling in macrophages. J Ethnopharmacol. 2021 Nov 15; 280: 114483. doi: 10.1016/j.jep.2021.114483.
15) Liu Q, Liu S, Cao H, et al. Ramulus Mori (Sangzhi) Alkaloids (SZ-A) Ameliorate Glucose Metabolism Accompanied by the Modulation of Gut Microbiota and Ileal Inflammatory Damage in Type 2 Diabetic KKAy Mice. Front Pharmacol. 2021 Apr 15; 12: 642400. DOI: 10.3389/fphar.2021.642400.
16) Hu W, Li M, Sun W, et al. Hirsutine ameliorates hepatic and cardiac insulin resistance in high-fat diet-induced diabetic mice and in vitro models. Pharmacol Res. 2022 Mar; 177: 105917. DOI: 10.1016/j.phrs.2021.105917.
17) Li L, Shi Z, Ma L, et al. Analysis of the correlation between plasma coagulation factor VII, PAI-1, and uric acid with insulin resistance and macrovascular complications in elderly patients with type 2 diabetes. Ann Palliat Med. 2021 Jan; 10(1): 664-671. DOI: 10.21037/APM-20-2609.
18) Qu L, Liang XC, Tian GQ, et al. Efficacy and Safety of Mulberry Twig Alkaloids Tablet for Treatment of Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled Multicenter Clinical Study. Chin J Integr Med. 2022 Apr; 28(4): 304-311. DOI: 10.1007/s11655-021-2885-9.
19) Durst M, Könczöl K, Ocskay K, et al. Hypothalamic Nesfatin-1 Resistance May Underlie the Development of Type 2 Diabetes Mellitus in Maternally Undernourished Non-obese Rats. Front Neurosci. 2022 Mar 21; 16: 828571. doi: 10.3389/fnins.2022.828571.
20) Xu D, Yu Y, Xu Y, et al. Plasma Nesfatin-1: Potential Predictor and Diagnostic Biomarker for Cognitive Dysfunction in T2DM Patient. Diabetes Metab Syndr Obes. 2021 Aug 10; 14: 3555-3566. DOI: 10.2147/DMSO.S323009.
21) He S, He Y, Jin F, et al. Correlation analysis of IGF-1, ZAG, nesfatin-1, HbA1c levels, and type 2 diabetes mellitus complicated with hypothyroidism. Medicine (Baltimore). 2021 Apr 16; 100(15): e25432. DOI: 10.1097/MD.0000000000025432.
22) Qu L, Liang X, Tian G, et al. 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. Diabetes Care. 2021 Jun; 44(6): 1324-1333. DOI: 10.2337/dc20-2109.
23) Wang DS, Wang JM, Zhang FR, et al. Ameliorative Effects of Malonyl Ginsenoside from Panax ginseng on Glucose-Lipid Metabolism and Insulin Resistance via IRS1/PI3K/Akt and AMPK Signaling Pathways in Type 2 Diabetic Mice. Am J Chin Med. 2022; 50(3): 863-882. doi: 10.1142/S0192415X22500367.
24) Aiken A, Li B, Liu P, et al. Melatonin treatment improves human umbilical cord mesenchymal stem cell therapy in a mouse model of type II diabetes mellitus via the PI3K/AKT signaling pathway. Stem Cell Res Ther. 2022 Apr 12; 13(1): 164. DOI: 10.1186/s13287-022-02832-0.
25) Eruygur N, Dural E. Determination of 1-Deoxynojirimycin by a developed and validated HPLC-FLD method and assessment of In-vitro antioxidant, α-Amylase and α-Glucosidase inhibitory activity in mulberry varieties from Turkey. Phytomedicine. 2019 Feb; 53: 234-242. DOI: 10.1016/j.phymed.2018.09.016.

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