ARTICLE

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Analysis of the anti-T2DM components in dichloromethane fraction of *Schisandra sphenanthera* and its mechanism

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Author contributions

Deng C, Feng SB, and Jiang HH conceptualized and designed the experiments. Feng SB and Jiang HH performed the experiments. Zhang DD and Feng SB carried out the writing work. Kang HL performed statistical analyses and original draft preparation. Jiang Y, Zhang HW and Song XM provided editorial advice. Feng SB, Li YZ and Huang WL searched and collected literature. All authors agreed on final approval for publication.

Competing interests

The authors declare no conflicts of interest.

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Peer review information

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Abbreviations

SDP, the dichloromethane part of *Schisandra sphenanthera*; T2DM, type 2 diabetes mellitus; OGTT, oral glucose tolerance test; GC-MS, gas chromatograph-mass spectrometer; HPLC, high performance liquid chromatography; BW, body weight; GHb, glycated hemoglobin; INS, insulin; AMPK, AMP-activated protein kinase; HOMA-IR, homeostatic model assessment for insulin resistance; NC, control group; Mod, model group; Met, positive group; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SOD, superoxide dismutase; MDA, malondialdehyde; GSH-PX, glutathione peroxidase; OTU, operational taxonomic unit; NEFA, nonesterified free fatty acids; SCFAs, short-chain fatty acids; ACE, acetic acid; PRO, propionic acid; BUT, butyric acid; PYY, peptide YY; GPR, G Protein-coupled receptor.

Citation

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Abstract

Background: The type 2 diabetes mellitus (T2DM) pharmacodynamic study of various parts of *Schisandra sphenanthera* was conducted in the previous stage, and it was found that dichloromethane extracted part (SDP) had a significant hypoglycemic effect. Therefore, the components of SDP were analyzed, and the specific mechanism of its anti-T2DM was explored. **Methods:** We used a high-fat, high-sugar diet in combination with streptozotocin to induce a T2DM rat model, and the model rats were divided into two groups according to body weight and blood glucose. Triglyceride, oral glucose tolerance test, fasting blood glucose, low density lipoprotein cholesterol, superoxide dismutase, insulin, glycated hemoglobin, total cholesterol, nonesterified free fatty acids, alanine aminotransferase, high-density lipoprotein cholesterol, aspartate aminotransferase, malondialdehyde, and glutathione peroxidase were measured, organ indices were calculated, and pathological sections of pancreas and liver were observed. The 16S rRNA V3–V4 region of intestinal flora was sequenced to explore the effect of SDP on biochemical indicators and intestinal flora. Based on the above indicators, the anti-T2DM mechanism of SDP in *Schisandra sphenanthera* was analyzed. **Results:** After six weeks of administration, the biochemical indices of diabetic rats were diminished compared to the control group. And SDP could significantly increase the gut microbial α-diversity index, resulting in significant changes in the flora of T2DM rats, with increased richness and diversity, reduced harmful flora, and significantly back-regulated the levels of acetic acid, propionic acid, and butyric acid. **Conclusion:** SDP can improve the symptoms associated with elevated blood glucose, dyslipidemia, elevated fasting insulin levels, and damaged glucose tolerance in rats. SDP against T2DM may be through the control of intestinal flora to normalize and exert anti-diabetic effect; its main active components may be lignans and terpenoids.

Keywords: *Schisandra sphenanthera*; T2DM; intestinal flora; HPLC

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Highlights

The dichloromethane site of *Schisandra sphenanthera* has the ability to regulate the levels of blood glucose, lipids, insulin, oxidative stress status and intestinal flora in type 2 diabetic rats.

Medical history of objective

Schisandra sphenanthera, a plant of the *Schisandra* family, from the "*Shennong's Classic of the Materia Medica*" of the Han Dynasty of China. In ancient times, *Schisandra sphenanthera* was known for its astringent and astringent properties, and calming the mind and tranquillising the spirit. Modern research has shown that *Schisandra sphenanthera* has hepatoprotective, neuroprotective, anti-inflammatory and anti-HIV effects.

Background

Type 2 diabetes mellitus (T2DM) is a persistent endocrine metabolic disorder characterized by metabolic dysregulation, including elevated lipid levels (hyperlipidemia), high blood sugar (hyperglycemia), and diminished sensitivity to insulin (INS) (INS resistance) [1, 2]. This condition can result in severe complications such as coronary artery disease, lower extremity artery disease, retinopathy, and diabetic nephropathy, significantly affecting the quality of life for individuals worldwide [3]. It has emerged as a significant public health concern on a global scale.

S. sphenanthera, also known as "Nan-Wuwezi" or "Huazhong-Wuweizi" in Chinese, has been used as classical Chinese medicine for thousand years [4]. As a renowned traditional Chinese medicine, it is commonly utilized in the management of gastrointestinal tract, respiratory failure, hyperhidrosis, and insomnia. While it is also a good anticonvulsant, tonic, and sedative [5]. So far, over 310 distinct chemical compounds have been isolated from this plant, with lignans, triterpenoids, monoterpenoids, and sesquiterpenoids being the main bioactive components [6]. Research indicates that *S. spenanthera*'s extracts or single-unit forms exhibit diverse biological characteristics both within living organisms and outside living organism, including antioxidative, anti-inflammatory, anti-cancer, antiviral, kidney-protective, and immune-adjusting properties [7–10]. Studies have shown that *S. spenanthera* polysaccharide possessed antidiabetic effects on T2DM, reducing fasting glucose by increasing fasting INS and increasing glucose tolerance [11]. It has been demonstrated that gomisin N could accelerate glucose transporter 4 (GLUT4) translocation to enhance glucose uptake by Adenosine 5-monophosphate (AMP)-activated protein kinase (AMPK), thereby improving glucose tolerance and hyperglycemia induced by high-glucose and high-fat diets in mice [12]. Furthermore, gomisin A has been shown to exhibit antioxidant effects by inhibiting oxidative stress through upregulation of heme oxygenase 1 (HO-1) expression and mitochondrial biogenesis factors. This mechanism helps maintain normal mitochondrial function, thereby potentially ameliorating diabetes [13, 14].

In previous studies, pharmacodynamic investigations of T2DM were carried out on different components of *S. spenanthera*. Among these, the dichloromethane extracted part (SDP) demonstrated notable hypoglycemic effects. Subsequent research focused on conducting compositional analyses and elucidating the anti-T2DM mechanism of action specifically within the SDP fraction.

Materials and methods

Preparation of SDP from *S. spenanthera*

Weighed 5.5 kg of *S. spenanthera*, pounded and added ten times the amount of 80% concentration of ethanol, extracted three times for 2 h each time and then filtered to obtain the dried extract, added an appropriate amount of aqueous solution to make a mixed solution, extracted with petroleum ether followed by dichloromethane, and obtained 72.02 g of SDP with a yield of 1.3%. All the herbal materials used in our study were identified as *S. spenanthera* by professor Yong-Gang Yan (Shaanxi University of Chinese Medicine).

Gas chromatograph-mass spectrometer (GC-MS) analysis of SDP

An Agilent Technologies (Santa Clara, CA, USA) HP-5 MS quartz capillary chromatography column GC was utilized to perform GC-MS examination of SDP. The equipment used for the experiment included an Agilent Technologies HP-5 MS mass spectrum detector and a quartz capillary chromatography column (30 m × 0.25 mm, 0.25 μm film thickness, Agilent Technologies, Santa Clara, CA, USA). The separation conditions were as stated below: the initial temperature of 60 °C was maintained for 2 min, then increased to 150 °C at 15 °C/min and held for another 2 min. Subsequently, the temperature was raised to 250 °C at 8 °C/min and held for 2 min. Lastly, the temperature was elevated from 250 °C to 300 °C at a rate of 10 °C/min and maintained for 8 min. The injector was set to 260 °C, and the carrier gas (helium) flowed at 1.0 mL/min. The spectra were acquired over a mass range of m/z 20–550 using electron ionization with an electron energy of 70 eV. The ion source temperature was set to 250 °C, and the quadrupole temperature was 150 °C. The shunt ratio was 10:1, with a solvent delay time of 3 min, a total run time of 39.5 min, and an injection volume of 1 μL.

Determination of 8 lignans in SDP

On the basis of GC-MS, we then investigated the content of the major lignans in *S. sphenanthera*. The lignans, flavonoids, organic acids, amino acids, and other chemical substances are abundant in *S. sphenanthera*, among which lignans are currently considered as one of the main active ingredients for the traditional medicinal effects [15]. In this study, the content of eight lignans, including the active compounds Schisandrol A, Schisandrin A, and Schisandrin B, in SDP was examined by high performance liquid chromatography (HPLC), in order to clarify the content of the main components of lignans. The Thermo BETASIL C18 column (4.6 mm × 250 mm, 5 μm, Waltham, MA, USA) was used for chromatography. The mobile phase consisted of acetonitrile (A) and water (B) with gradient elution conditions. The temperature was maintained at 30 °C, with a flow rate of 1.0 mL/min and an injection volume of 10 μL. The ratios of mobile phase gradient elution are shown in Table 1.

Table 1 Mobile phase elution ratio for SDP

Time (min)	A (acetonitrile)	B (water)
0	55	45
5	56	44
30	56	44
55	96	4
60	96	4
61	55	45
65	55	45

Diabetic rat model establishment

With the aim of clarifying the anti-T2DM effect of SDP, we conducted animal experiments to verify the anti-T2DM effect of SDP. Male Sprague-Dawley (6–8 weeks) rats weighing 180–200 g were purchased from the Chengdu Da Shuo Experimental Animal Co., Ltd. (Chengdu, China). The animal production license is No. SCXK 2020-030 and the animals were maintained in the Shaanxi University of Traditional Chinese Medicine Pharmacology Laboratory. The animals used in the experiments, agreed by the Medical Ethics Committee of Shaanxi University of Chinese Medicine (SUCMDL 20210308005), were conducted in accordance with internationally recognized principles for the use and care of laboratory animals. Clean grade Sprague-Dawley rats weighing 180–200 g were selected and fed adaptively for one week. The control group (NC) consisted of ten rats selected randomly and fed with normal feed. And leftover rats were administered high-fat and high-sugar feed (ratio: common feed 59%, lard 18%, egg yolk 3%, sugar 20%) for 4 weeks as a model group. Following a period of 4 weeks, all rats underwent a 12-h fast without access to water. Streptozotocin 42 mg/kg (freshly prepared 1% Streptozotocin sterile solution with 0.1 mol/L citric acid-sodium citrate buffer) was injected intraperitoneally at once, while the NC was only injected with the same volume of citrate-sodium citrate buffer [16]. Taking the blood glucose concentration > 16.7 mmol/L as the index of successful modeling (blood glucose meter: Sanuo Bio-Sensing Co., Ltd., Changsha, China) [17]. According to body mass and blood glucose, the successfully modeled animals were randomly divided into model group (Mod), SDP-Low, SDP-Hig (21 mg/kg and 42 mg/kg), and positive group (recorded as Met group).

Effect of SDP on short-chain fatty acids (SCFAs) and intestinal flora in T2DM rats

To elucidate the impact of SDP on the intestine, cecal contents were subsequently collected for analysis. After the rats were executed, the cecum contents were immediately removed in sterilized eppendorf tubes, quickly frozen in liquid nitrogen, and promptly transferred to −80 °C. The Shanghai Majorbio (Shanghai, China) conducted examinations on the gut microbiota, extracted microbiome DNA from stool samples, and utilized PCR to amplify the V3–V4 region of the 16S RNA. The data were mainly analyzed and processed by using the online data processing beauty developed by Shanghai Meiji Biomedical Technology Co., Ltd. (Shanghai, China) and Bioconfidence Cloud (http://www.majorbio.com/). The faecal SCFAs were measured using Agilent 7890A equipped gas chromatography mass spectrometry system (Agilent, Santa Clara, CA, USA), fitted with a WM-FFAP column (30 × 0.32 mm × 0.5 μm, Agilent, Santa Clara, CA, USA) [18, 19].

Statistic analysis

The variance in the data was assessed through a one-way analysis of variance test. The consequences were presented as mean ± standard deviation, with statistical significance defined as $P < 0.05$.

Results

Analysis of components in SDP sites

The results indicated that the major components of the SDP were lignans, terpenoids containing oxygen derivatives, fatty acids, and other compounds, such as Schisantherin A (6.97%), Schisandrin A (5.80%), Anwulignan (4.03%), 14-Methyl-5α-Cholestan-15-one (2.49%), and β-sitosterol (2.41%) (Figure 1A, Table 2).

Determination of the content of 8 lignans in SDP

The sample was weighed about 100 mg, measured under the chromatographic conditions under (Table 1, Figure 1B, 1C). The levels of the eight lignans in the samples were calculated (Table 3).

Table 2 Results of chemical composition analysis of SDP

No.	Time	Compound	Molecular weight	Chemical abstracts service	Relative content	Compound type
1	5.05	3-methyl-2,5-furandione	112	616-02-4	0.06	Carboxylic acids
2	5.857	3-methoxy-toluene	122	104-93-8	0.04	Aromatic hydrocarbon
3	6.651	Undecane	156	1120-21-4	0.13	Alkane
4	6.815	P-Cresol	108	106-44-5	0.08	Phenol
5	7.037	Maltol	126	118-71-8	0.09	Hydroxy pyranone
6	7.948	Benzoic acid	122	65-85-0	1.09	Carboxylic acid
7	10.53	Vanillin	152	121-33-5	0.24	Aldehyde
8	10.64	4-hydroxy-benzaldehyde	122	123-08-0	0.51	Hydroxybenzaldehyde
9	11.09	Trans-isoeugenol	164	5932-68-3	0.33	Phenolic
10	11.37	Gamma-muurolene	204	30021-74-0	0.15	Sesquiterpene
11	11.48	(–)-Beta-chamigrene	204	18431-82-8	0.23	Sesquiterpene
12	11.71	Alpha-cadinene	204	31983-22-9	0.30	Sesquiterpene
13	11.89	Cuparene	202	16982-00-6	0.68	Sesquiterpene
14	11.96	Gamma-cadinene	204	39029-41-9	0.58	Sesquiterpene
15	12.05	Beta-cadinene	204	523-47-7	0.20	Sesquiterpene
16	12.25	Beta-himachalene	204	1461-03-6	0.14	Sesquiterpene
17	12.44	Alpha-calacorene	200	21391-99-1	0.20	Sesquiterpene
18	12.6	1,3,3-Trimethyl-2-hydroxymethyl-3,3-dimethyl-4-(3-methylbut-2-enyl)-cyclohexene	222	997284-53-3	0.08	Terpene
19	13.39	6-Methyl-2-(4-methylcyclohex-3-en-1-yl)hepta-1,5-dien-4-ol	220	38142-56-2	0.07	Terpene
20	13.57	2H-1-benzopyran-6-ol, 3,4-dihydro-2,2-dimethyl-4-(1-methylethyl)-	220	997274-68-3	0.15	Benzopyranol

Traditional Medicine Research 2025;10(1):3. https://doi.org/10.53388/TMR20240224002

Table 2 Results of chemical composition analysis of SDP (*continued*)

No.	Time	Compound	Molecular weight	Chemical abstracts service	Relative content	Compound type
21	14.01	T-Cadinol	222	5937-11-1	0.33	Sesquiterpene alcohol
22	14.39	4-(3-hydroxypropyl)-2-methoxyphenol	182	2305-13-7	0.24	Phenol
23	14.62	(+)-Longifolene	204	475-20-7	0.11	Sesquiterpene
24	14.9	Alpha-santalol	220	115-71-9	1.17	Sesquiterpene alcohol
25	15.91	((1R,4S,5R)-1-Methyl-4-(prop-1-en-2-yl)spiro[4.5] dec-7-en-8-yl)methanol	220	149496-35-5	0.37	Terpene alcohol
26	16.26	Acremine E	220	997273-96-0	3.47	Sesquiterpene
27	16.41	Cyperotundone	218	3466-15-7	0.36	Sesquiterpene
28	16.51	Alpha-costal	218	4586-01-0	0.35	Sesquiterpene
29	17.06	Khusimyl methyl ether	234	300349-20-6	0.87	Sesquiterpene ether
30	17.73	(–)-Isolongifolol, methyl ether	236	997333-54-4	0.28	Sesquiterpene ether
31	18.13	Clovanediol	238	2649-64-1	0.36	Sesquiterpene
32	18.56	Thunbergol	290	25269-17-4	0.07	Sesquiterpene alcohol
33	18.92	Valerenol	220	101628-22-2	0.05	Sesquiterpene alcohol
34	19.46	Hexadecanoic acid, ethyl ester	284	628-97-7	0.33	Fatty acid ethyl ester
35	20.15	9.beta.-Bromo-4,8.beta.,11,11-tetramethylbicyclo [6.3.0]undec-4-ene	284	997503-65-1	0.44	Bicyclic compound
36	20.67	Decahydro-8a-ethyl-1,1,4a,6-tetramethylnaphthalene	222	997284-79-7	0.09	Terpene
37	20.71	Methyl linoleate	294	112-63-0	0.27	Fatty acid ester
38	20.78	Caparratriene	206	997228-60-6	0.08	Terpene
39	21.39	Ethyl linoleate	308	544-35-4	0.11	Fatty acid ester
40	21.67	Oleamide	281	301-02-0	0.11	Fatty acid amide
41	22.92	2-hydroxycyclopentadecan-1-one	240	4727-18-8	0.09	Ketone
42	23.21	9-Octadecenamide	281	3322-62-1	0.31	Fatty acid amide
43	24.13	4-Bromo-3,5-di-t-butylbenzamide	311	997596-68-8	0.02	Benzamide
44	25.38	N,N-phthaloyl-2-thia-10,11-diaza-9,17-dimethyl-(3.2)-metacyclophan	400	997832-45-5	0.70	Cyclophane
45	26.21	2-(p-Ethoxyphenyl)-3-(2'-thieny)xanthone	398	997828-77-5	0.22	Xanthone
46	26.38	(5.alpha.,22E)-Stigmast-22-ene	398	54412-02-1	1.85	Sterol
47	26.52	Schizandrin A	416	61281-38-7	5.80	Lignan
48	26.6	Anwulignan	328	107534-93-0	4.03	Lignan
49	26.91	15alpha-hydroxysteviol methyl ester	348	997713-30-5	0.47	Diterpenoid ester
50	27.39	14-Methyl-5alpha-cholestan-15-one	400	54515-29-6	2.49	Steroid
51	28.28	9-Amino-1-(4-hydroxyphenylmethyl)-3,6-diazahomoadamantane	273	147084-70-6	0.48	Amine
52	28.38	3-[(3-nitro-4-pyridinyl)amino]benzoic acid	259	997413-23-5	1.18	Amino acid derivative
53	28.69	3-Acetyl-2-(4-hydroxy-phenylamino)-6-methyl-pyran-4-one	259	997413-99-2	0.98	Pyranone derivative
54	29.18	Schisantherin A	536	58546-56-8	28.69	Terpenoid
55	29.33	Cannabidiol dimethyl ether	342	1242-67-7	3.29	Cannabinoid derivative
56	30.13	Pregomisin	390	66280-26-0	0.91	Terpenoid
57	30.23	(Dimethylhydroxymethyl)phenyl]-17,20-didehydro -21,22,23,24,25,26,27-heptanorvitamin D3	434	997886-95-6	0.96	Vitamin D derivative
58	31.18	Benzenamine	343	997699-03-9	0.70	Amine
59	31.62	9,14-Dioxo-3a,3d,6a,7,8,9,14,15,16,16adecahydro-1H,6H-dicyclopenta[2,1-a:1,2-k]naphtho[2,3-f]4,7-phenanthroline	394	997821-25-1	0.62	Heterocyclic compound
60	36.89	Beta-sitosterol	414	83-46-5	2.41	Phytosterol

Table 3 Content determination results

Number	Compound	Content (ug/mg)
1	Schisandrol A	0.143 ± 0.003
2	Schisantherin C	2.952 ± 0.029
3	Schisantherin A	33.024 ± 0.023
4	Schisantherin B	1.135 ± 0.000
5	Anwulignan	0.537 ± 0.007
6	Schisandrin A	1.028 ± 0.007
7	Schisandrin B	0.088 ± 0.001
8	Schisandrin C	0.329 ± 0.004

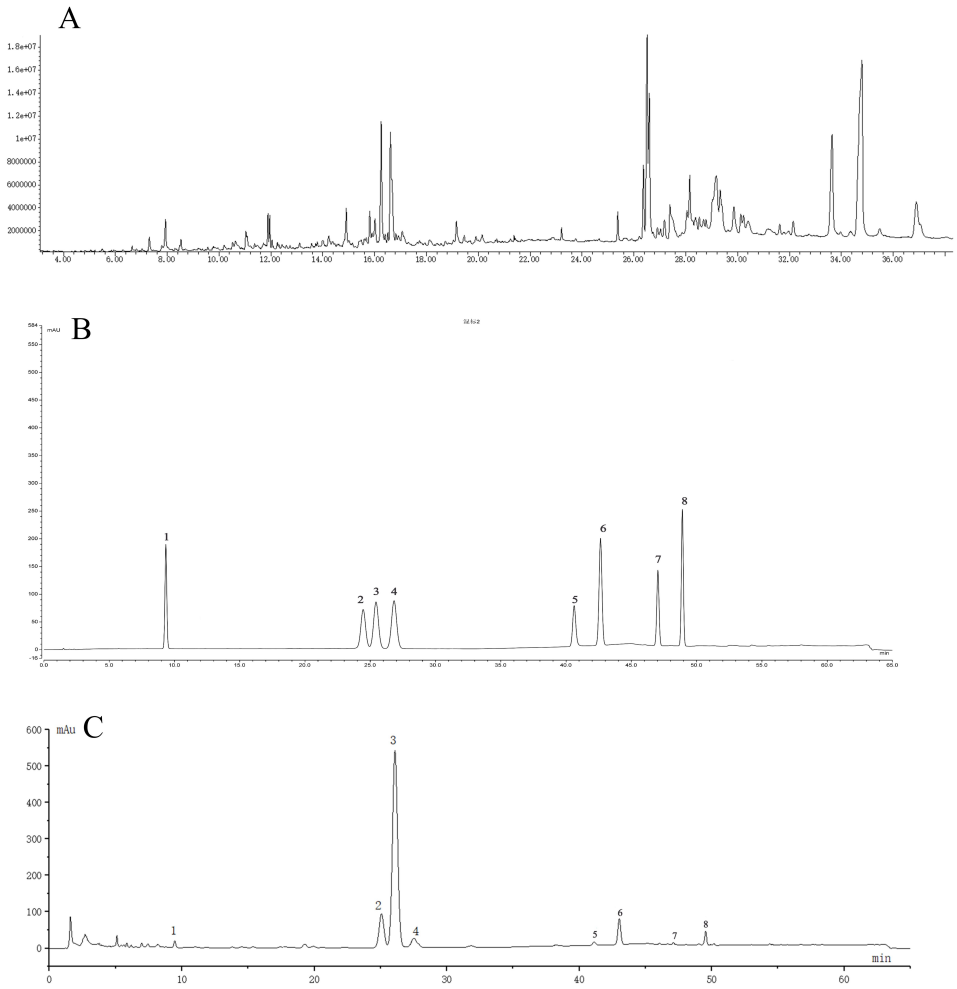

Figure 1 Analysis of SDP by GC-MS and HPLC. (A) Total ion flow diagram of GC-MS analysis at SDP site. (B) The HPLC chromatograms of standards and SDP. (C) Mixed standards. 1: Schisandrol A; 2: Schisantherin C; 3: Schisantherin A; 4: Schisantherin B; 5: Anwulignan; 6: Schisandrin A; 7: Schisandrin B; 8: Schisandrin C.

Pharmacodynamic evaluation of SDP in T2DM rats

From the beginning of successful modeling, the rats in the Mod always had lesser body weight than all other groups. The NC group exhibited a slight raise in body weight (Figure 2A).

After 6 weeks of gavage, lipid levels showed an obvious improvement in the SDP and Met contrasted with the Mod, while the fasting blood glucose (FBG) levels were notably lesser in the Met and SDP groups compared to the Mod ($P < 0.05$) (Figure 2B). To elucidate the influence of SDP on glycaemic control, an oral glucose tolerance test (OGTT) was performed. As shown in Figure 2C, blood glucose levels rose to a peak at 90 min after glucose loading. Afterwards, we observed a notable decrease in blood glucose in the Met, SDP-Low, SDP-Hig treatment group and a slight decrease in the Mod. The results of organ weight and organ index in each group are shown in Figure 3. These results demonstrated that the liver index in the Mod surpassed that of the NC ($P < 0.01$), while the kidney index in the Mod was higher than that of the NC ($P > 0.05$). Moreover, the kidney organ index in the Mod exceeded that of the NC ($P < 0.01$). Collectively, it showed that the mode was successfully built, and there was a decreasing trend of hepatosomatic ratio index in the SDP compared to the Mod. In the pancreatic index, the SDP-Hig exhibited a higher pancreatic index contrasted with the Mod ($P < 0.05$). Regarding the renal body index, a notable difference was observed between the Met and SDP-low in comparison to Mod, showing a meaningful reduction as compared to the Mod ($P < 0.05$).

Traditional Medicine Research 2025;10(1):3. https://doi.org/10.53388/TMR20240224002

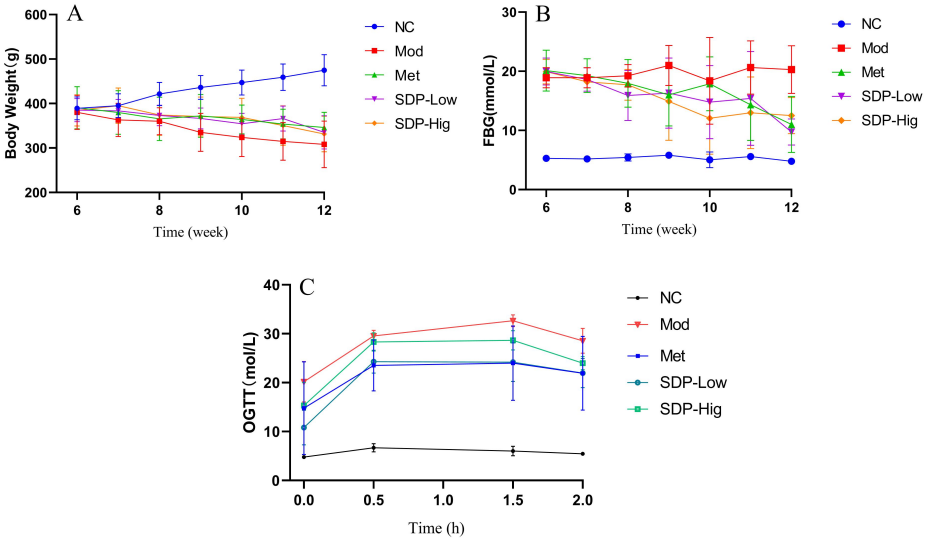

Figure 2 Changes in body weight at the SDP (A), FBG (B) and OGTT (C). NC, control group; Mod, model group; Met, positive group; SDP, the dichloromethane part of *Schisandra sphenanthera*; FBG, fasting blood glucose; OGTT, oral glucose tolerance test.

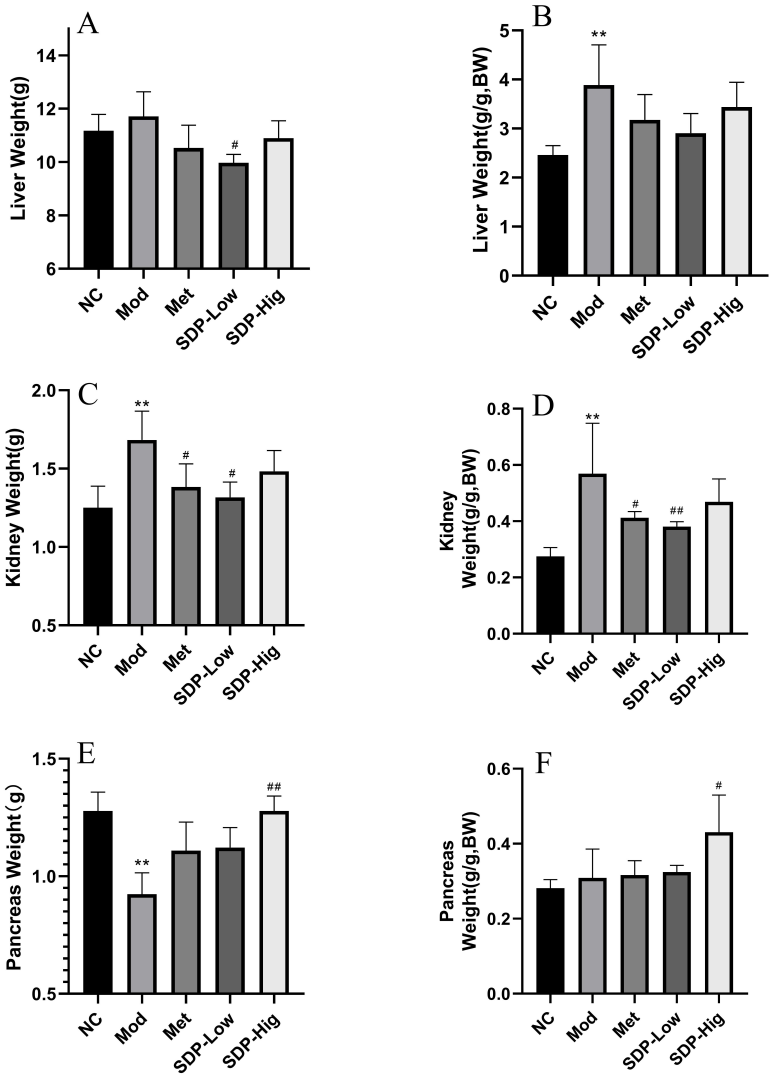

Figure 3 Effects on liver weight (A), liver-to-body ratio (B), pancreas weight (C), pancreas-to-body ratio (D), and kidney-to-body ratio, in each group of rat weight (E), and renal body ratio (F). Compared with NC, $^{**}P < 0.01$. Compared with model, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ (n ≥ 6). NC, control group; Mod, model group; Met, positive group; SDP, the dichloromethane part of *Schisandra sphenanthera*.

Traditional Medicine Research 2025;10(1):3. https://doi.org/10.53388/TMR20240224002

After 6 weeks of treatment, glycated hemoglobin (GHb), triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), INS, and homeostatic model assessment for insulin resistance (HOMA-IR) levels were down-regulated and high-density lipoprotein cholesterol (HDL-C) levels were up-regulated (Figure 4, 5). In SDP and Met, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were down-regulated in serum and liver (Figure 6). The impact of SDP on glutathione peroxidase (GSH-PX), superoxide dismutase (SOD), malondialdehyde (MDA), and nonesterified free fatty acids (NEFA) levels in rats is illustrated in Figure 7. Compared to NC, SOD levels in both serum and liver were noticeably lower in the Mod ($P < 0.01$). Moreover, MDA and NEFA levels in the serum of the Mod were noticeably higher than those in the NC ($P < 0.05$), while MDA increased in the liver of the Mod and GSH-PX levels decreased significantly in the liver of the Mod contrasted with the NC ($P < 0.01$). Compared to Mod, a significant raise in SOD content was detected in the Met, as well as SDP-Low and SDP-Hig groups ($P < 0.05$). Conversely, the levels of MDA and NEFA in the serum were noticeably reduced in all drug groups contrasted with the Mod ($P < 0.05$), with similar reductions noted in the liver across all drug groups. Moreover, the content of GSH-PX in the liver exhibited a meaningful growth in all dosing groups contrasted with the Mod, with statistical importance ($P < 0.05$).

The effects of SDP on rat liver histopathology are demonstrated in Figure 8. The findings indicated that the degree of hepatocyte swelling was relatively mild in the SDP-Low and SDP-Hig groups, with a relatively neat arrangement of hepatocytes and a small amount of hepatocyte degeneration. Figure 8 shows the impacts of SDP on the histopathology of the rat pancreas. Contrasted with Mod rats, the quantity of islets and intracellular cells within the islets in the SDP increased and the morphological structure was improved. The most notable enhancement was Detected in SDP-Hig.

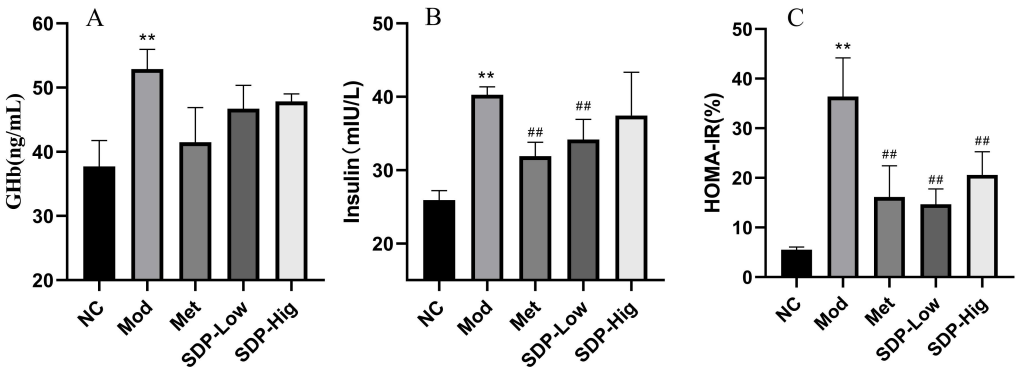

Figure 4 Effects on GHb (A), INS (B) and HOMA-IR (C) of rats in each group. Compared with NC, $^{**}P < 0.01$. Compared with Mod, $^{\#\#}P < 0.01$ ($n \geq 6$). NC, control group; Mod, model group; Met, positive group; SDP, the dichloromethane part of *Schisandra sphenanthera*; GHb, glycated hemoglobin; HOMA-IR, homeostatic model assessment for insulin resistance.

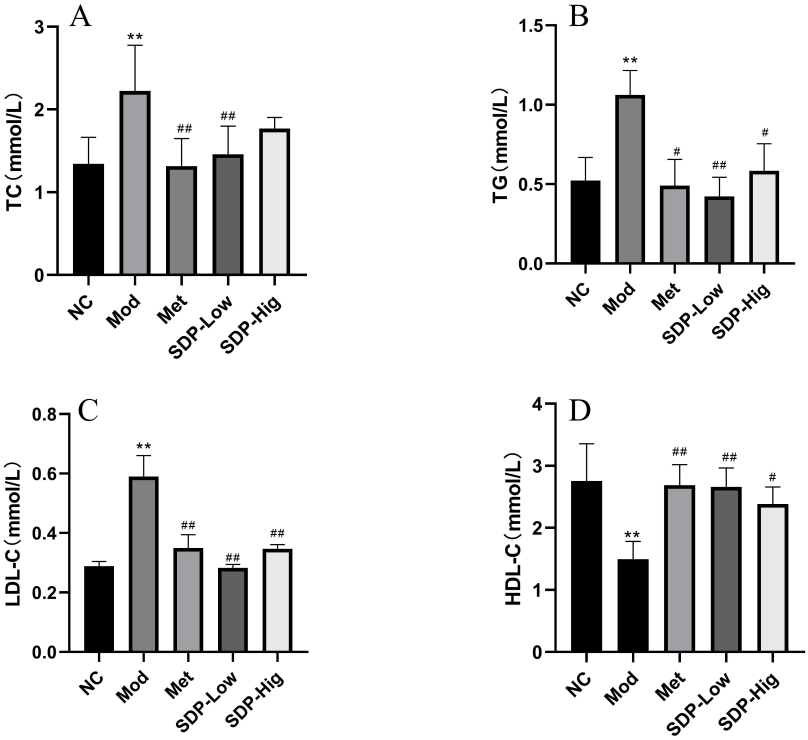

Figure 5 Effects on TC (A), TG (B), LDL-C (C), and HDL-C (D) in each group of rats. Compared with NC, $^{**}P < 0.01$. Compared with Mod, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ ($n \geq 6$). NC, control group; Mod, model group; Met, positive group; SDP, the dichloromethane part of *Schisandra sphenanthera*; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

Traditional Medicine Research 2025;10(1):3. https://doi.org/10.53388/TMR20240224002

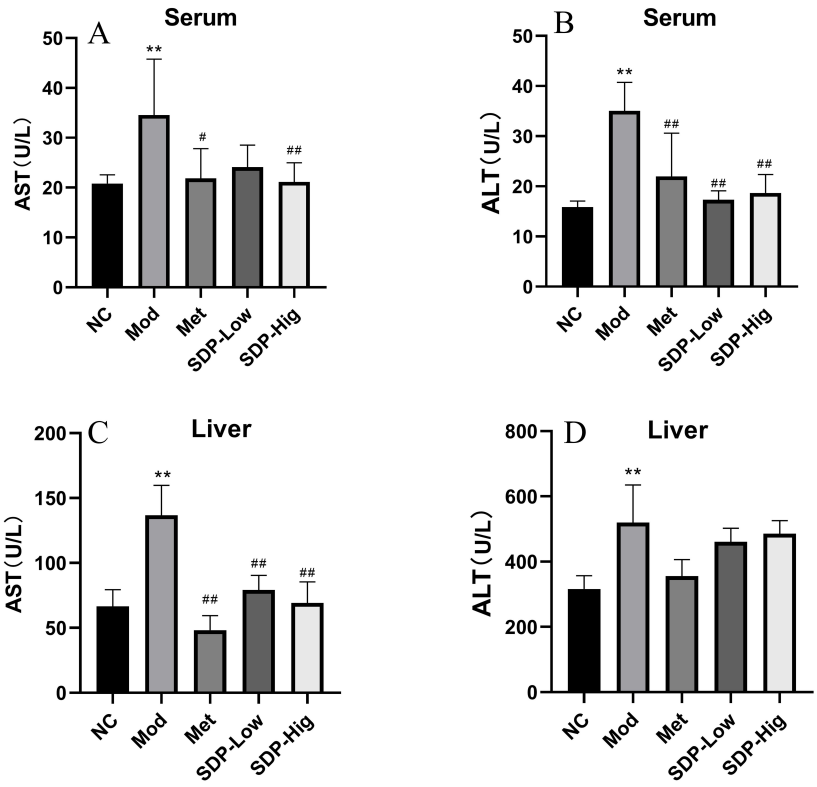

Figure 6 Effects on AST (A) and ALT (B) in serum and AST (C) and ALT (D) in liver of rats in each group in the liver. Compared with NC, $^{**}P < 0.01$. Compared with Mod, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ (n ≥ 6). NC, control group; Mod, model group; Met, positive group; SDP, the dichloromethane part of *Schisandra sphenanthera*; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

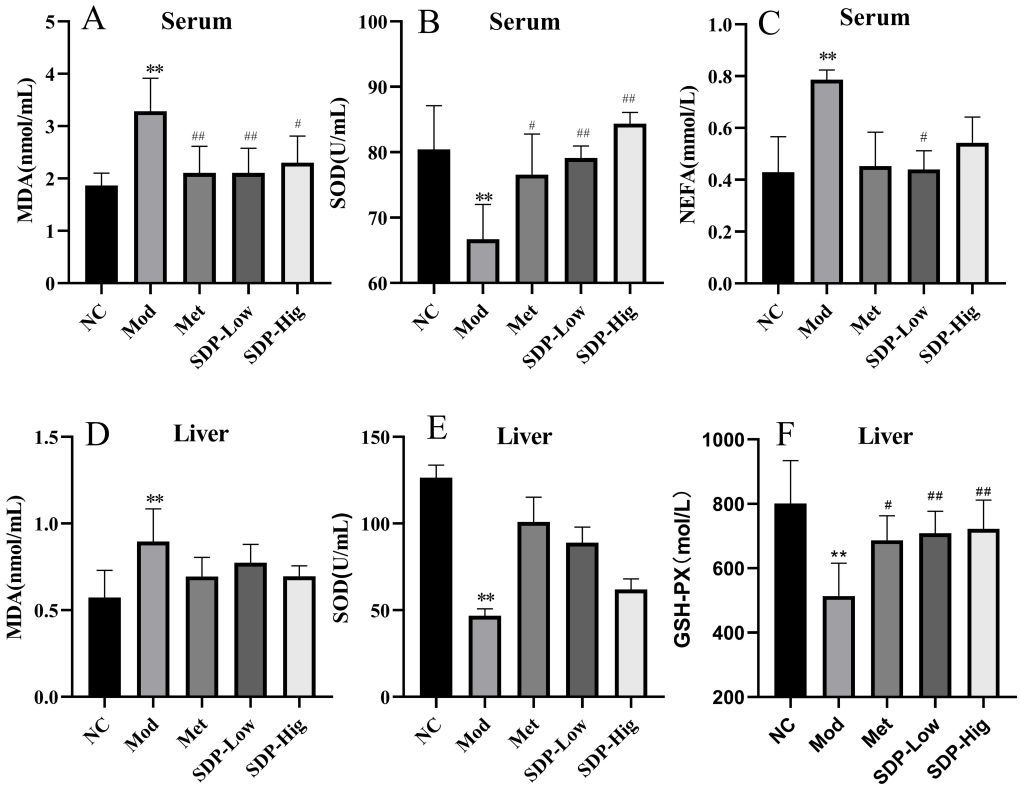

Figure 7 Effects on SOD (A), MDA (B) and NEFA(C) in serum, SOD (D), MDA (E) and GSH-PX (F) in liver of rats in each group. Compared with NC, $^{**}P < 0.01$. Compared with Mod, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ (n ≥ 6). NC, control group; Mod, model group; Met, positive group; SDP, the dichloromethane part of *Schisandra sphenanthera*; SOD, superoxide dismutase; MDA, malondialdehyde; GSH-PX, glutathione peroxidase; NEFA, nonesterified free fatty acids.

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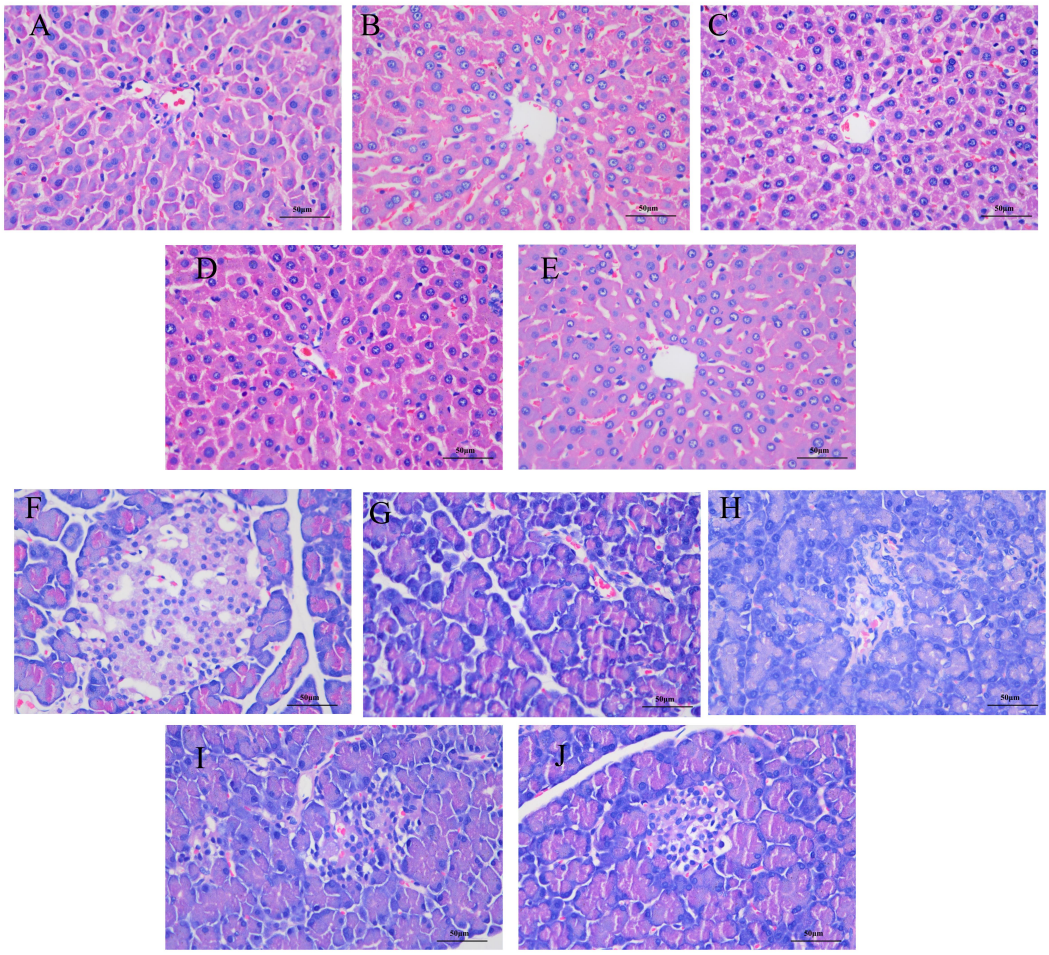

Figure 8 Effect of SDP on liver and pancreas histopathology in various (Hematoxylin-eosin staining, Scale bar = 50 μm). Liver (A) NC group; (B) Mod group; (C) Met group; (D) SDO-Low group; (E) SDP-Hig group. Pancreas (F) NC group; (G) Mod group; (H) Met group; (I) SDO-Low group; (J) SDP-Hig group.

Impact of SDP on intestinal flora in T2DM rats

The Rank-Abundance curve can be used to illustrate the species richness and community evenness of diversity. In comparison of microbial diversity, the species diversity of Mod was markedly lower than that of NC and each administration group (Figure 9A). The findings of Pan/Core species analysis were shown in Figure 9B, 9C, Mod group number growth and the number of core species was markedly lesser than the NC and each treatment group.

Alpha diversity is the species diversity in the sample. The outcomes were demonstrated in Figure 10A, 10B, which were the sobs and shannon indices of each group, respectively. The findings denoted that the microbial variety and abundance of the flora of diabetic rats changed noticeably in comparison with the rats in the NC group, and the sobs index and shannon index of Mod group rats had a noticeable decrease ($P < 0.05$). Compared to the Mod group, enrichment and diversity of flora were improved after drug treatment, and differed markedly between the Mod and Blank groups, Met group, SDP-Low group, and SDP-Hig group ($P < 0.05$). The findings were demonstrated in Figure 10D. The experimental curve tends to be gentle, indicating that the statistics are correct and reasonable, and can express the absolute majority of microbial diversity statistics in each sample. It shows that SDP administration can increase the diversity of intestinal microorganisms in diabetic rats.

The species composition and relative abundance of each group of rat samples were examined across various phyla and genus, and Figure 11A indicates that at the phylum level, the more abundant groups of rat intestinal flora in all six groups were Firmicutes, Bacteroidota, with a total content of more than 95%. The diabetic rats demonstrated a notable reduction in Firmicutes as contrasted with the NC of relative abundance, whereas there was a correspondingly higher proportion of Bacteroidota and Proteobacteria. Figure 11B indicates that the dominant abundance groups at the genus level are *Lactobacillus*, Lachnospiraceae, *Colidextribacter*, and *Romboutsia*. The findings above suggest a significant alteration in the composition of the flora of diabetic rats at both the phylum and genus levels. Additionally, treatment with SDP appeared to have a regulatory effect on the flora structure of diabetic rats, which played a certain regulatory role in the direction of normal flora structure.

Based on the UnweightedUniFrac distance method, the clustering analysis was performed at the operational taxonomic unit (OTU) level for each sample, and the findings were demonstrated in Figure 12A, the NC group of rats became one category, indicating that the flora was noticeably different from that of NC in diabetic rats; among the remaining classifications, where the Mod group became 1 category alone, indicating that the composition of the flora of diabetic rats was changed in the treatment of SDP. PCoA analysis was conducted utilizing the Bray Curtis distance algorithm at the OTU level, and the results showed that intestinal microorganisms were significantly clustered into three categories in the NC, Mod, and drug administration treatment groups, indicating that diabetic disease causes significant changes in the rat flora. In contrast, the administration of SDP can significantly regulate the flora of diabetic rats after treatment, and the findings were demonstrated in Figure 12B, non-metric multidimensional scaling analysis was also performed, and the findings were demonstrated in Figure 12C. The difference with the findings of PCoA analysis was not significant.

Traditional Medicine Research 2025;10(1):3. https://doi.org/10.53388/TMR20240224002

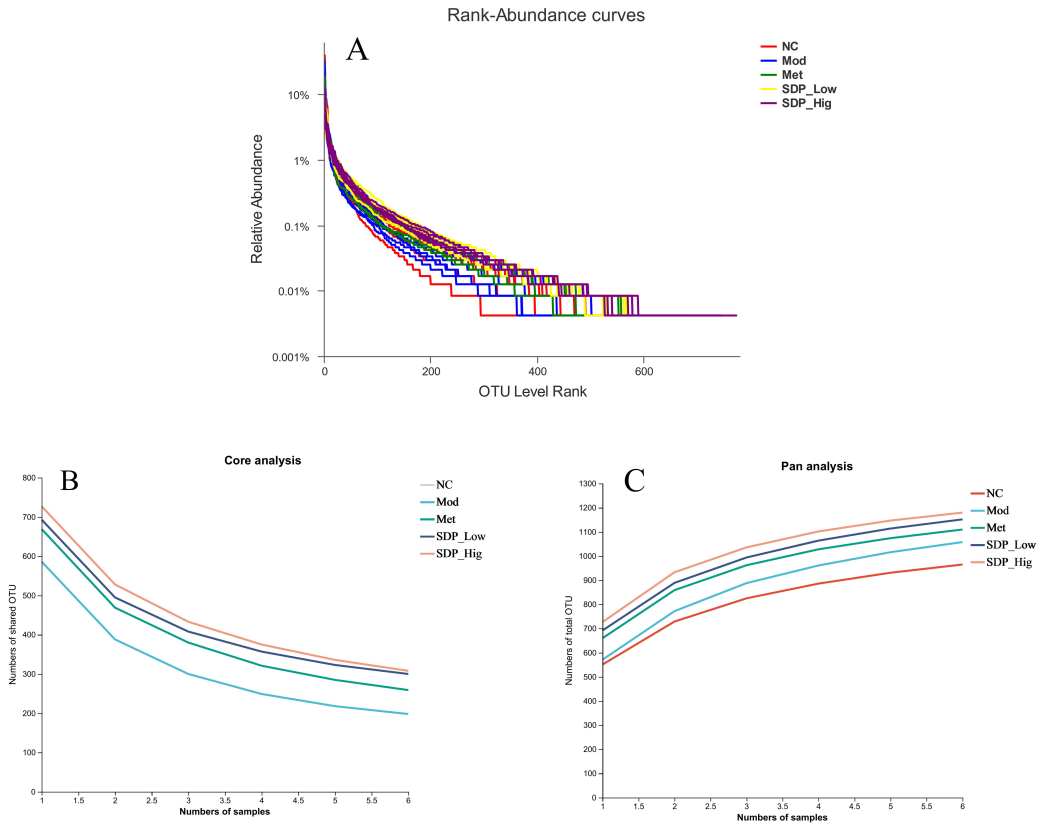

Figure 9 Rank-Abundance curve (A), Pan curve (B), Core curve (C). NC, control group; Mod, model group; Met, positive group; SDP, the dichloromethane part of *Schisandra sphenanthera*; OTU, operational taxonomic unit.

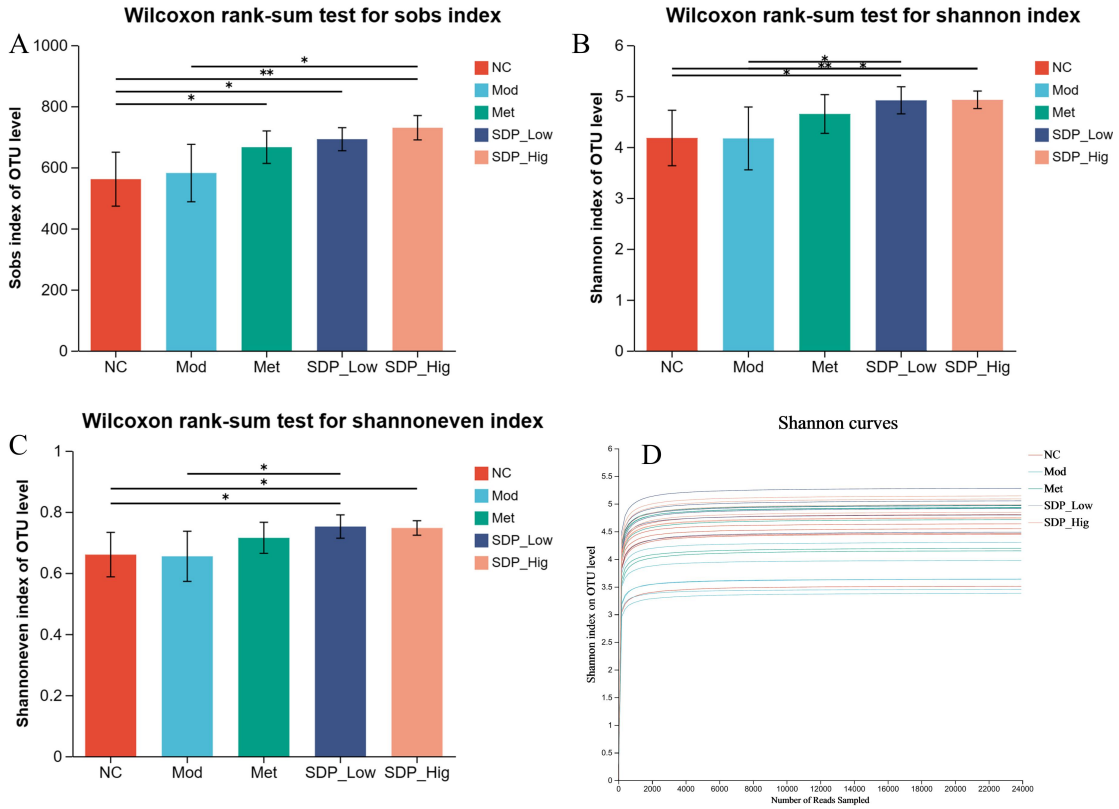

Figure 10 Sobs (A), Shannon curve (B), Shannoneven (C), dilution curve (D). $^{*}P < 0.05$; $^{**}P < 0.01$ ($n \geq 6$). NC, control group; Mod, model group; Met, positive group; SDP, the dichloromethane part of *Schisandra sphenanthera*; OTU, operational taxonomic unit.

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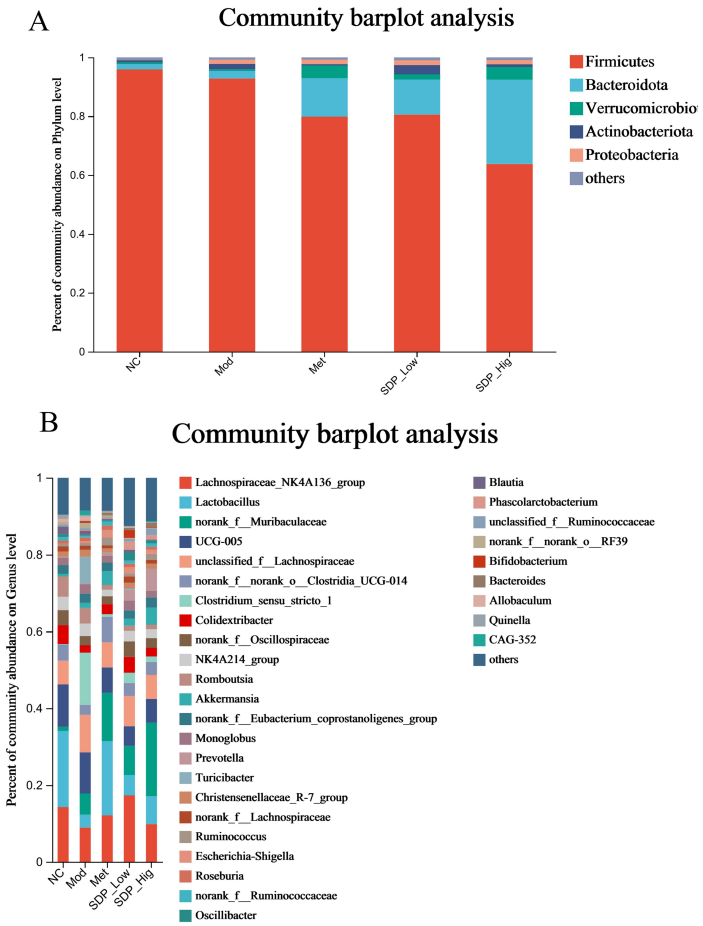

Figure 11 Relative abundance of rat intestinal microbiota at the phylum level (A) and genus level (B) in each group. NC, control group; Mod, model group; Met, positive group; SDP, the dichloromethane part of *Schisandra sphenanthera*.

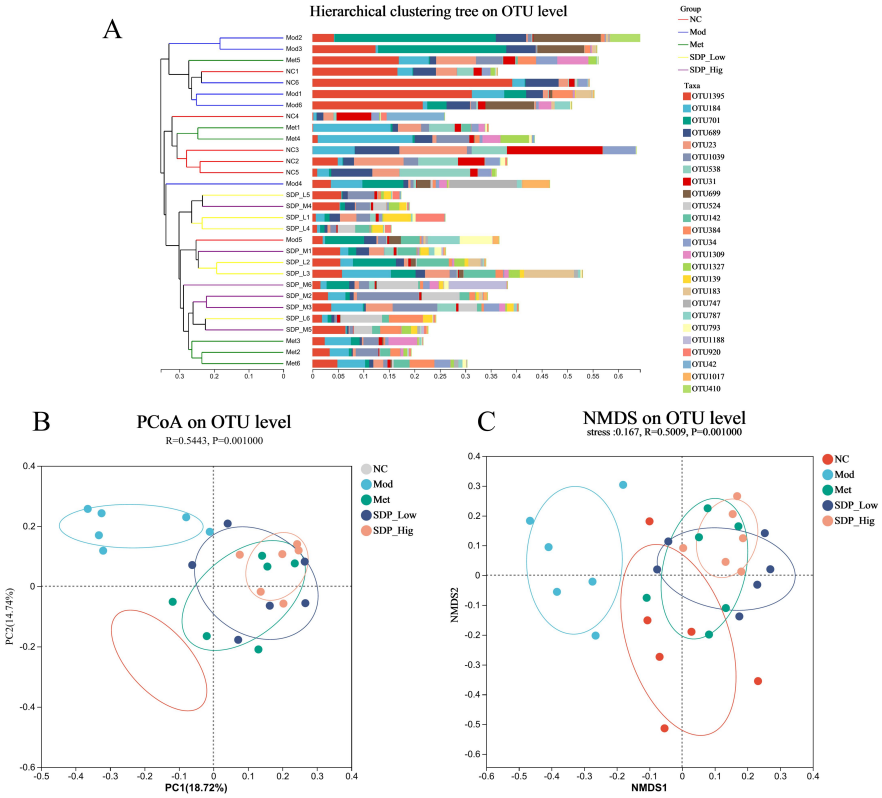

Figure 12 Cluster analysis (A), PCoA analysis (B), non-metric multidimensional scaling analysis (C). NC, control group; Mod, model group; Met, positive group; SDP, the dichloromethane part of *Schisandra sphenanthera*; OTU, operational taxonomic unit.

Traditional Medicine Research 2025;10(1):3. https://doi.org/10.53388/TMR20240224002

The groups that showed differences in abundance in the intestinal flora were analyzed, and Figure 13A shows that at the phylum level, the dominant phylum demonstrated noticeable changes in the abundance of Firmicutes, Bacteroidota, and Proteobacteria, diabetes induced significant decrease of Firmicutes and significant increase of Bacteroidetes in intestinal flora of rats. After administration intervention, the abundance of Firmicutes and Bacteroidetes will be reversed. At the genus level, the findings were demonstrated in Figure 13B, most of the top-ranked genera have undergone noticeable changes. In addition, the SDP-Hig group significantly regulated the intestinal flora disorder in diabetic rats, resulting in a noticeable raise in the presence of significantly enriched communities, mainly in Proteobacteria, Bacteroidales, and their subordinate taxonomic levels; the significantly enriched communities in the Met group were Micrococcales, *Rothia*, etc. (Figure 13C). In summary, during the intervention of SDP, the abundance of flora in diabetic rats has changed noticeably at both the phylum and the genus level, and had a tendency to develop in the normal direction as a whole.

Analysis of the association between intestinal flora and lipids, glucose, and SCFAs in T2DM rats

The results are shown in Figure 14, at the genus level, *Frisingicoccus* and *Escherichia-Shigella* associated with body weight ($R < 0$, $P < 0.01$), norank_f_Lachnospiraceae, *UCG-005* and *Quinella* was positively associated with body weight ($R > 0$, $P < 0.05$); *UCG-003*, norank_f_Ruminococcaceae were negatively associated with INS ($R < 0$, $P < 0.01$). *Clostridium_sensu_stricto_1*, *Blautia*, unclassified_c_Clostridia, chirstensenellaceae_R-7_group, and *Turicibacter* were positively associated with INS ($R > 0$, $P < 0.01$). Unclassified_c_Clostridia were negatively associated with GHb ($R > 0$, $P < 0.01$), while Lachnospiraceae_NK4A136_group, norank_f_Oscillospiraceae, *Lactobacillus*, and *Quinella* were positively associated with GHb ($R < 0$, $P < 0.01$). Lachnospiraceae_NK4A136_group, unclassified_f_Ruminococcaceaee, and *Intestinimonas* were negatively associated with FBG ($R < 0$, $P < 0.01$). *Frisingicoccus* were positively correlated with FBG ($R > 0$, $P < 0.01$). Lachnospiraceae_NK4A136_group, *UCG-005* and *Intestinimonas* were negatively associated with HOMA-IR ($R < 0$, $P < 0.01$). *Frisingicoccus* were positively associated with HOMA-IR ($R > 0$, $P < 0.01$).

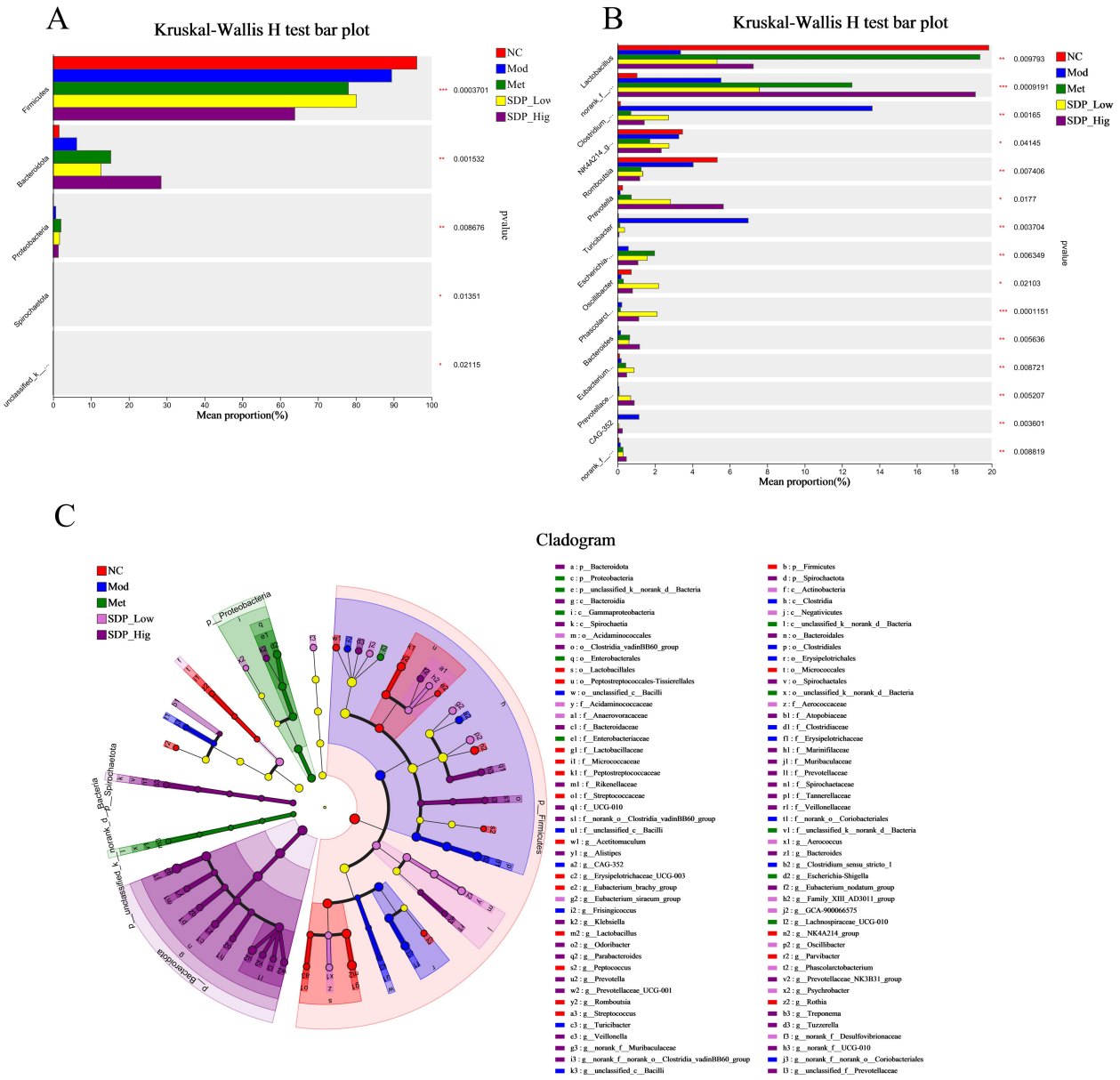

Figure 13 Comparative analysis of differences at the gut flora phylum level (A), genus level (B) and Lefse multilevel species difference discriminant analysis (C). NC, control group; Mod, model group; Met, positive group; SDP, the dichloromethane part of *Schisandra sphenanthera*.

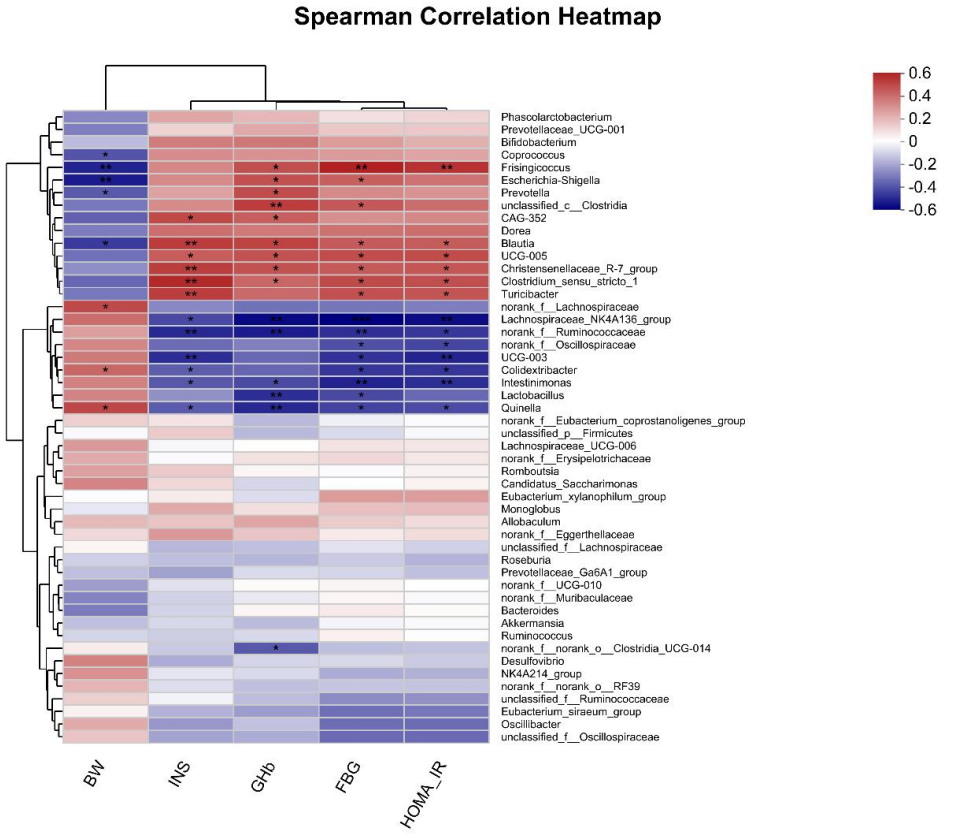

Figure 14 Correlation analysis of intestinal flora and blood glucose index. BW, body weight; GHb, glycated hemoglobin; INS, insulin; HOMA-IR, homeostatic model assessment for insulin resistance; FBG, fasting blood glucose.

The results are shown in Figure 15, intestinal flora correlates with blood lipid indexes at the genus level. *UCG-005* was negatively associated with HDL-C ($R < 0$, $P < 0.01$), Lachnospiraceae_NK4A136_ group was positively associated with HDL-C ($P < 0.01$). *UCG-003* were negatively associated with TG ($R < 0$, $P < 0.01$). *Bifidobacterium* and *Clostridium_sensu_stricto_1* were positively associated with TG ($R < 0$, $P < 0.05$). *Intestinimonas*, *UCG-003*, norank_ f_Oscillospiraceae, *Oscillibacter*, *Colidextribacter*, norank_f_Ruminococcaceae, and unclassified_f_Oscillospiraceae were negatively associated with TC ($R < 0$, $P < 0.01$), *Escherichia-Shigella* was positively associated with TC ($R > 0$, $P < 0.01$). *UCG-003*, Lachnospiraceae_NK4A136_group, norank_f_Oscillospiraceae, *Oscillibacter*, norank_f_Ruminococcaceae and *Colidextribacter* were negatively associated with LDL-C ($R < 0$, $P < 0.01$), Christensenellaceae_R-7_group and *Turicibacter* were positively associated with LDL-C ($R > 0$, $P < 0.05$).

The results are shown in Figure 16, association between gut microbiota and SCFAs at genus level, *Clostridium_sensu_stricto_1*, CAG-352, Christensenellaceae_R-7_group, *Prevotella*, and Prevotellaceae_UCG-001 were negatively associated with acetic acid (ACE) ($R < 0$, $P < 0.05$). *Lactobacillus* and norank_f_norank_o_Clostridia_UCG-014 were positively associated with ACE ($R > 0$, $P < 0.01$). *Clostridium_sensu_stricto_1*, CAG-352, Christensenellaceae_R-7_group, *Prevotella*, and Prevotellaceae_UCG-001 were negatively associated with propionic acid (PRO) ($R < 0$, $P < 0.05$). *Clostridium_sensu_stricto_1* and CAG-352 were negatively associated with butyric acid (BUT) ($R < 0$, $P < 0.01$). *Lactobacillus* was positively correlated with PRO and BUT ($R > 0$, $P < 0.01$).

Effect of SDP on SCFAs in T2DM rats

The levels of SCFAs in the fecal samples of T2DM rats were measured [19]. In comparison to the NC, the concentrations of ACE, PRO, and BUT in the diabetic Mod rats exhibited a noticeable diminution ($P < 0.05$), whereas the positive NC showed a notably higher level than the Mod ($P < 0.05$). Conversely, the SDP-Low and SDP-Hig demonstrated decreased levels of SCFAs, albeit insignificant ($P > 0.05$) (Figure 17).

Discussion

In the contemporary era, the holistic features of Chinese medicine can potentially serve as pivotal components in the administration of diabetes mellitus. Numerous studies have demonstrated the notable therapeutic efficacy of *S. sphenanthera* extract in T2DM. Nevertheless, the specific effect of SDP on alleviating diabetic symptoms and its influence on intestinal flora is still ambiguous. Thus, the objective of this research was to comprehensively investigate the biochemical indices and intestinal flora of diabetic rats following a six-week SDP treatment regimen.

Research conducted in clinical settings suggests a significant alteration in gut flora levels among individuals with T2DM compared to healthy individuals. This alteration typically manifests as a reduction in advantageous bacteria and a raise in potentially harmful bacteria [20, 21]. Diabetes causes changes in the plenitude of many genera at the genus level, like a notable rise in the abundance of *Lactobacillus* spp. Researches have found that the number of *Lactobacillus* spp. in the intestinal flora of diabetic patients is significantly higher than that of the healthy population, while *Prevotella* spp. is also significantly elevated in diabetic patients [22]. The significant inhibitory effect of SDP on these opportunistic pathogens suggests that SDP will be able to lower the risk of diabetic and inflammation that may be caused by these opportunistic pathogens, and may improve the dysbiosis of the intestinal flora caused by diabetes. During the intervention of SDP administration, the abundance of flora in diabetic rats was changed at phylum and genus level, with the abundance of many genera of bacteria regressed and an overall trend towards normal. These findings indicate that *Schisandra sphenanthera* has the capability to regulate the balance of intestinal flora, leading to potential improvements in diabetes.

Traditional Medicine Research 2025;10(1):3. https://doi.org/10.53388/TMR20240224002

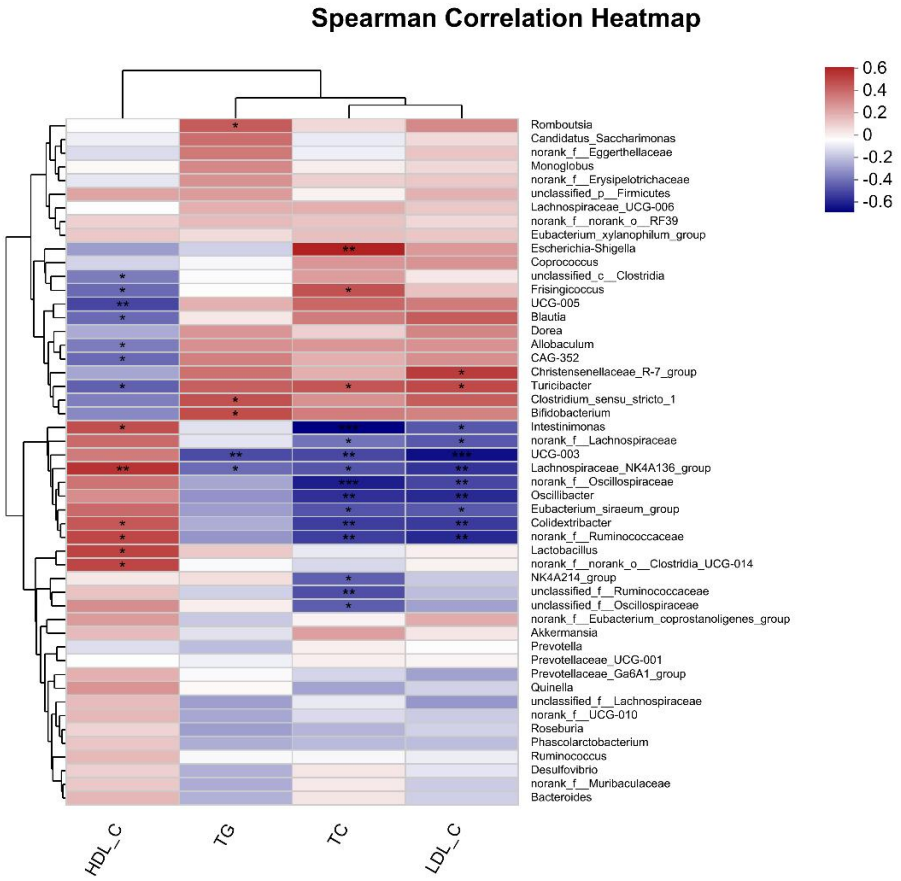

Figure 15 Correlation analysis of intestinal flora and blood lipid index. TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

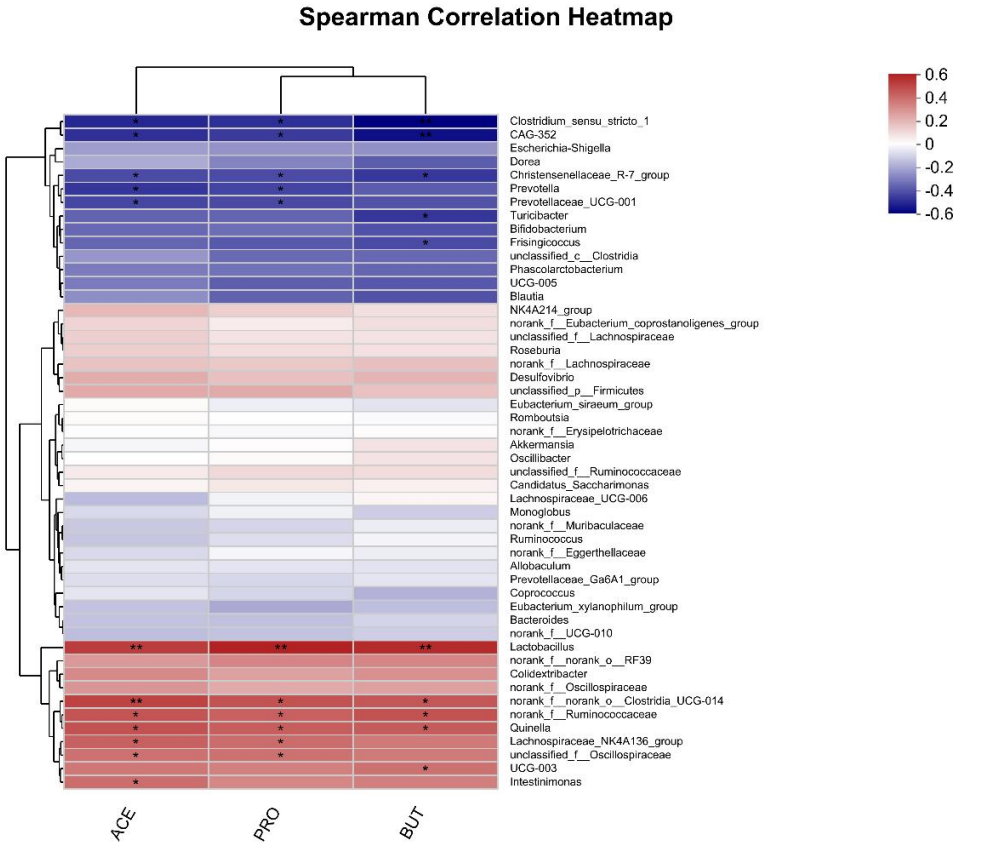

Figure 16 Correlation analysis of intestinal flora and short-chain fatty acid index. ACE, acetic acid; PRO, propionic acid; BUT, butyric acid.

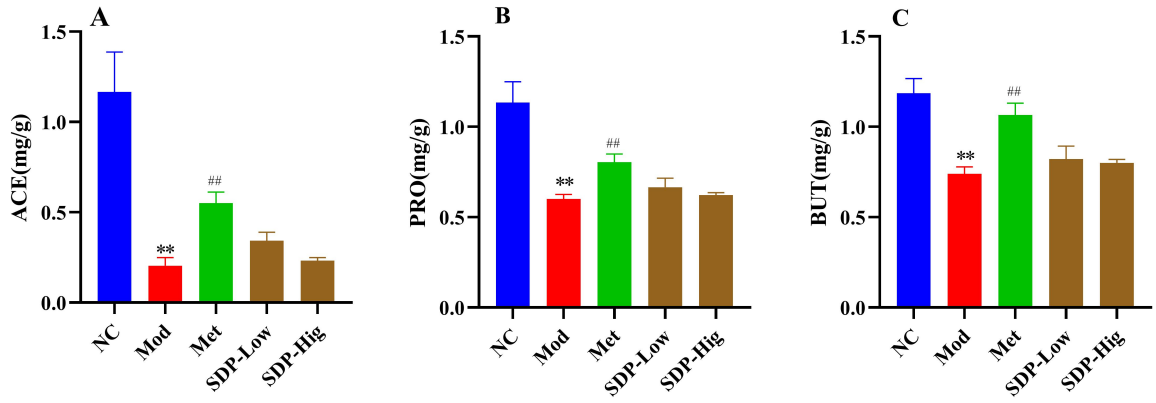

Figure 17 Content of SCFAs in each group of rats. (A) Acetic acid. (B) Propionic acid. (C) Butyric acid. Compared with NC, $^{**}P < 0.01$. Compared with Mod, $^{\#\#}P < 0.01$ ($n \geq 6$). NC, control group; Mod, model group; Met, positive group; SDP, the dichloromethane part of *Schisandra sphenanthera*; ACE, acetic acid; PRO, propionic acid; BUT, butyric acid.

SCFAs act as metabolites generated by the gut microbiota, and inadequate SCFA production is associated with T2DM. Among SCFAs, ACE, PRO, and BUT are the most abundant [23]. ACE, PRO, and BUT are closely related to diabetes, study finds [24]. The levels of ACE, PRO, and BUT were found to be markedly reduced in diabetic patients [25]. It is worth observing that ACE and PRO have been reported to have positive impacts on glucose tolerance [26]. G Protein-coupled receptor 43 (GPR43) and G Protein-coupled receptor 41 (GPR41) are receptors for SCFA. ACE and PRO can activate GPR41 and GPR43 receptors on the surface of intestinal epithelial cells, upregulate GPR43/41 activity in the intestine to promote glucagon-like peptide-1 (GLP-1) secretion, and then GLP-1 induces INS secretion, effectively regulating blood glucose metabolism. BUT could increase INS sensitivity, and it was able to increase oxidative capacity [27]. Compared to the NC, rats in the Mod had markedly lower levels of ACE, PRO, and BUT ($P < 0.05$), while the SPD-Hig and Met were markedly higher than the Mod. This suggests that SPD can increase the levels of SCFAs in T2DM rats and that increasing the content of the SCFAs could be a strategy for diabetes treatment [28, 29]. SCFAs have been shown to exert influence on pharmacodynamics, including the inhibition of gluconeogenesis and promotion of glycogen synthesis, thus impacting T2DM. SCFAs increased the adenosine monophosphate to adenosine triphosphate ratio, activating the AMPK signaling pathway, which subsequently reduced *glucose-6-phosphatase* gene expression, leading to the inhibition of gluconeogenesis [30]. It has been reported in the literature that when diabetic mice were fed diets containing ACE, the mice showed a rise in hepatic AMPK expression, a down-regulation of gluconeogenesis-related genes, and a reduction in blood glucose levels. Therefore, SCFA can reduce gluconeogenesis through the AMPK signalling pathway [31]. SCFA also acts on GPR41/GPR43 receptors on the surface of enteroendocrine cells L, prompting the release of GLP-1 with peptide YY (PYY), which leads to INS secretion and augmentation of glucose utilisation. Tolhurst demonstrated that colonic PYY expression was associated with reduced glucose tolerance in GPR41/GPR43 knockout mice [32]. Christiansen utilized rat colon as an enteroendocrine model to investigate SCFA perfusion effects. They observed a significant increase in GLP-1 secretion from the rat colon following intestinal luminal perfusion or vascular injection of acetate and butyrate [24]. Additionally, there was a moderate increase in PYY secretion under similar conditions.

Identification of the chemical constituents of SDP was conducted using GC-MS, complemented by literature and database analysis. The main components identified include lignans, fatty acids, and terpenoids containing oxygen derivatives, among others. Additionally, the content of eight lignans in SDP was determined using HPLC. The combined content of the eight lignan components in the SDP was measured at 39.236 μg/mg. Studies in the literature have shown that Schisandrol A improves oxidative/nitrosative stress, attenuates inflammation, and reduces apoptosis; it is protective against acetaminophen-induced liver injury and inhibits hepatic sinusoidal endothelial cell function and angiogenesis [33]. Schisandrin A and Schisandrin B significantly reduced MDA levels in diseased mice, attenuated renal tissue damage, and upregulated mRNA levels of nuclear factor erythroid-2 related factor 2 (Nrf2), HO-1, glutamate-cysteine ligase (GCLM), and SOD [34, 35]. Schisandrinol A can lower blood glucose, increase SOD, decrease MDA and increase GLUT-4 expression in mice with the mechanism of action of scavenging free radicals and reducing lipid peroxidation, protecting pancreatic islet cells from normal INS secretion and lowering blood glucose [36]. It is hypothesized that the antidiabetic effect exerted by SDP may be attributed to a lignan-like component.

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