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Gelanxinning capsule improves coronary microvascular dysfunction by inhibiting inflammation and restoring endothelial function

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Abstract. – OBJECTIVE: Gelanxinning capsule (GXSC) is a Chinese medicine to cure coronary artery disease (CAD) and a compound of *Pueraria lobata*, hawthorn extract, and gypenosides. However, whether GXSC could improve coronary microvascular dysfunction (CMD) is unknown. We aimed to demonstrate the therapeutic effect of GXSC on CMD and its underlying mechanisms in CAD patients.

PATIENTS AND METHODS: This was a single-center, randomized control trial. A total of 78 patients diagnosed by selective coronary angiography (CAG) participated in this study. Patients' demographics, medical history, medications, and results of laboratory testing were collected. The index of microcirculatory resistance (IMR) and coronary flow reserve (CFR) were obtained by CAG and single-photon emission computed tomography (SPECT) separately. Fasting blood samples were obtained on the morning following the admission day. Concentrations of several molecules of inflammation, endothelial function, and coronary microvascular function were measured by ELISA. Patients were followed-up two months after discharge and fasting blood samples were also acquired.

RESULTS: All patients were randomly divided into 2 groups: GXSC, 38 (48.7%), and control, 40 (51.3%). The intergroup comparison revealed no significant differences with respect to all baseline variables. As for inflammation biomarkers, proinflammatory NOD-like receptor thermal protein domain associated protein 3 (NLRP3) and interleukin (IL)-1 were significantly decreased in GXSC compared with the control group (0.71±0.08 *vs.* 1.04±0.07, $p<0.01$ and 7.16±0.59 *vs.* 10.93±1.04, $p<0.01$). Anti-inflammatory adropin was increased in the GXSC group (7.75±0.59 *vs.* 5.71±0.68, $p=0.03$). As for indexes of endothelial function, the concentrations of syndecan (SDC) 1, SDC4 and heparan sulphates (HS) were significantly downregulated in 2 months GXSC treatment (3.31±0.28 *vs.* 4.85±0.43, $p<0.01$, 3.79±0.56 *vs.* 5.69±0.68, $p=0.03$ and 21.31±2.79 *vs.* 35.18±4.11 $p<0.01$). In addition, the level of SIRTUIN 1 (SIRT1), which is a vascular protective protein, was upregulated in GXSC group (5.63±0.30 *vs.* 4.22±0.37, $p<0.01$). As for molecules of coronary microvascular function, endocan, soluble urokinase plasminogen activator receptor (suPAR), and growth differentiation factor (GDF)-15 were significantly decreased consistently in GXSC compared with the control group (0.09±0.01 *vs.* 0.19±0.03, $p<0.01$, 4.44±0.40 *vs.* 5.73±0.40, $p=0.03$ and 2.08±0.17 *vs.* 2.69±0.18, $p=0.02$).

CONCLUSIONS: In conclusion, GXSC could improve CMD by inhibiting inflammation and restoring endothelial function. GXSC might be an effective drug in CAD patients without obstructive epicardial coronary arteries but suffering from angina.

Key Words:
Gelanxinning capsule, Chinese medicine, Coronary microvascular dysfunction, Non-obstructive coronary arteries, Inflammation, Endothelial dysfunction.

Introduction

Coronary artery disease (CAD) remains one of the leading causes of morbidity and mortality worldwide[1]. It has been well-established that atherosclerotic plaques and coronary arterial stenosis resulting from them are the main culprits for CAD and revascularization therapy could reduce ischemic symptoms and improve overall prognosis[2]. Recently, growing evidence[3] is likely to break this routine cognition. For example, some patients present with symptoms and/or signs of myocardial ischemia but coronary angiography (CAG) shows no significant artery stenosis. Therefore, exploring the underlying mechanisms of the development and progression of CAD is still urgently needed.

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During the last few years, coronary microvascular dysfunction (CMD) was proposed to explain the above phenomenon defined as ischemia with non-obstructive coronary arteries (INOCA). CMD refers to structural and/or functional abnormalities of coronary microcirculation which reduce coronary blood flow and result in the clinical manifestations of myocardial ischemia ultimately[4,5]. Although the pathogenesis of CMD is unclear yet, systemic inflammation and endothelial dysfunction might play an important role in its pathophysiology[6,7]. The management of CMD has formed lately including lifestyle modification, risk factor control and medical therapy, however, INOCA still bothers a large number of patients especially women[3,8]. So, developing drugs targeted for CMD and its derived INOCA has great significance.

More and more evidence[9-12] has indicated that traditional Chinese medicine could have an effect on preventing and treating CMD through multiple signal pathways. Gelanxinning capsule (GXSC) is a Chinese medicine to cure CAD and a compound of *Pueraria lobata*, hawthorn extract, and gypenosides[13]. Gao et al[14] have reported that GXSC could play its therapeutic effect against CAD by regulating lipid metabolism. However, whether GXSC could improve CMD is unknown. In the present study, we aimed to demonstrate the therapeutic effect of GXSC on CMD and its underlying mechanisms in CAD patients.

Patients and Methods

Study Design and Participants

This was a prospective single-center, randomized control trial. From July 2021 to September 2022, a total of 78 patients diagnosed by selective CAG participated in this study at the Cardiology Department of Shaanxi Provincial People's Hospital. The inclusion criteria were as follows: (1) patients aged between 18 and 85; (2) patients who were able to understand the purpose of the study and signed the informed consent voluntarily; (3) patients who had selective CAG and were ruled out coronary artery stenosis; (4) patients who had angina, chest tightness, shortness of breath and/or other atypical symptoms of myocardial ischemia; (5) patients who had the measurement of the index of microcirculatory resistance (IMR) (<25) and coronary flow reserve (CFR) (<2.0).

The exclusion criteria were as follows: (1) patients who had chronic obstructive pulmonary diseases, dilated cardiomyopathy and/or hypertrophic myocardiopathy; (2) patients who had infectious diseases; (3) those with liver dysfunction (alanine aminotransferase and/or aspartate aminotransferase <200 U/L), and/or renal dysfunction (glomerular filtration rate <59 ml/min); (4) those with left ventricular ejection fraction (LVEF) <50% by echocardiography; (5) patients who had severe arrhythmias; (6) patients with a history of allergies to adenosine triphosphate (ATP) and/or other contraindication; (7) those with poor medication compliance; (8) those with malignant tumors and reduced life expectancy (<1 year).

All included patients were divided into treatment group (odd) and control group (even) through a random number table. All participants took aspirin 100 mg qd, atorvastatin 20 mg qd and metoprolol sustained-release tablets 47.5 mg qd. The treatment group took GXSC 2 pills tid in addition.

Initially, a total of 82 individuals were recruited, and finally, 78 participants were included after screening for eligibility. The study flow chart is shown in Figure 1.

This study complied with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of the Shaanxi Provincial People's Hospital, Xi'an, Shaanxi, China (No. SPPH-LLBG-17-3.2). CTRN2023090089. Written informed consent was obtained from all study participants.

Data Collection

The collected data included patients' demographics, medical history, medications, and results of laboratory testing. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. The CAG and single-photon emission computed tomography (SPECT) procedures and the acquisition of IMR and coronary flow reserve (CFR) have been published previously[15,16]. Fasting blood samples were obtained from the peripheral vein of each patient on the morning following the admission day. Concentrations of adropin, interleukin (IL)-1, NOD-like receptor thermal protein domain associated protein 3 (NLRP3), soluble urokinase plasminogen activator receptor (suPAR), syndecan (SDC), heparan sulphates (HS), growth differentiation factor (GDF)-15, endocan, SIRTUIN 1 (SIRT1) in the patients' serum samples were measured by using manufactured ELISA kits (Wuhan Fine Biotech Co., Ltd., Wuhan, China and Thermo Fisher Scientific, Waltham, MA, USA) following the manufacturer's instructions.

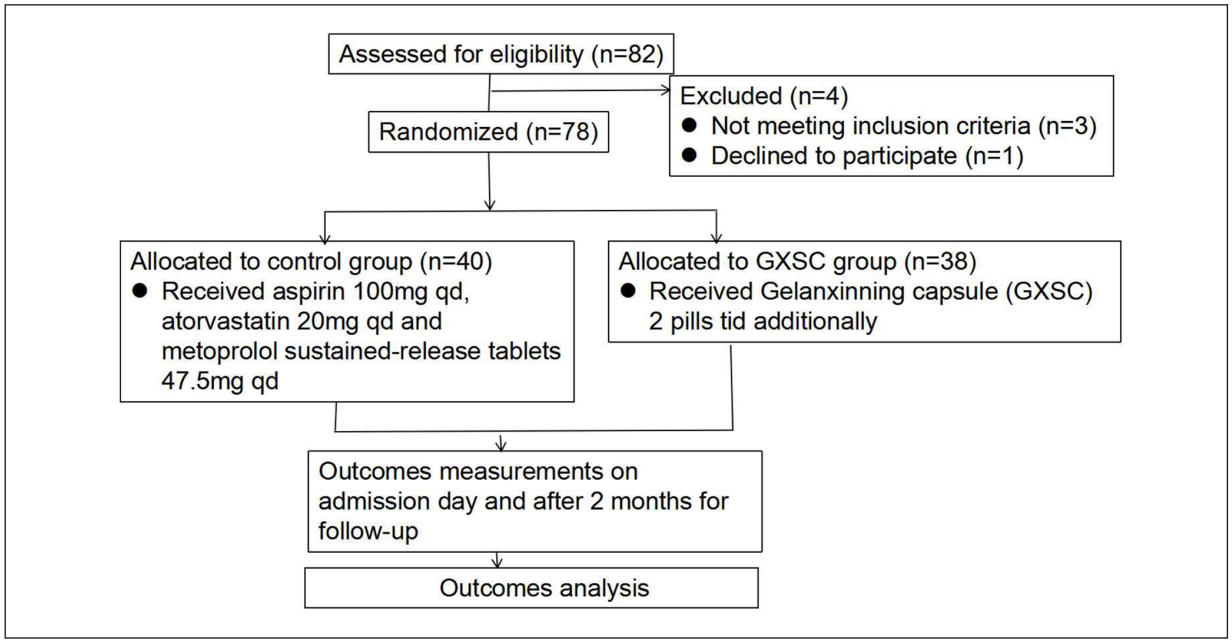

Figure 1. Study flow chart.

Follow-Up

Patients were followed up by face-to-face interviews by well-trained cardiologists two months after discharge and fasting blood samples were also acquired.

Statistical Analysis

Continuous variables were presented as the mean±standard deviation (SD) or median (lower quartile, upper quartile). The Kolmogorov-Smirnov test was used to assess the normality of continuous variables distribution. Student's *t*-test and Mann-Whitney U test were used for the comparison of continuous variables as appropriate. Categorical variables were presented as frequencies (percentages). The χ^2 test was used to analyze the differences between categorical variables. All computations were performed with SPSS software v. 22.0 (IBM Corp., Armonk, NY, USA). A statistically significant difference was defined at $p<0.05$ using a two-tailed test.

Results

Clinical Characteristics of the Study Population

A total of 78 patients were included in this analysis. All patients were randomly divided into 2 groups: GXSC in 38 (48.7%) and control in 40 (51.3%). The main baseline characteristics of these 2 groups are shown in Table I. Intergroup comparison revealed no significant differences between the groups with respect to all baseline variables including demographics, medical history, medications, and results of laboratory testing.

GXSC Decreased Inflammatory Levels

Levels of inflammation biomarkers were determined before and after treatment in GXSC and control group respectively. Results are shown in Figure 2 and the detailed data are provided in **Supplementary Table I.** After 2 months of treatment, inflammasome NLRP3 and its downstream effector molecular IL-1 were significantly decreased in GXSC compared with the control group (0.71±0.08 *vs.* 1.04±0.07, $p<0.01$ and 7.16±0.59 *vs.* 10.93±1.04, $p<0.01$) (Figure 2A and 2B). Besides, as we can see in Figure 2C, the level of adropin, which played an anti-inflammation role, was increased in the GXSC group (7.75±0.59 *vs.* 5.71±0.68, $p=0.03$).

GXSC Reduced Endothelial Dysfunction

Indexes of endothelial function were tested in GXSC and in the control group. The components of endothelial glycocalyx were investigated. The concentrations of SDC1, SDC4 and HS were significantly down-regulated in 2 months of GXSC treatment (3.31±0.28 *vs.* 4.85±0.43, $p<0.01$,

Table I. Characteristics of patients with coronary microvascular dysfunction according to whether receiving Gelanxinning capsule.

Variable	GXSC n = 38	Control n = 40	*p*-value
Age (years)	60.8 ± 11.3	61.9 ± 8.1	0.64
Males (%)	33 (86.8)	35 (87.5)	1.00
BMI (kg/m^2)	24.2 ± 3.5	24.8 ± 3.7	0.55
Smoking (%)	20 (52.6)	18 (45.0)	0.50
Alcohol (%)	7 (18.4)	6 (15.0)	0.69
Medical history			
Hypertension (%)	21 (55.3)	20 (50.5)	0.64
Diabetes mellitus (%)	10 (26.3)	16 (40.0)	0.20
Stroke (%)	5 (13.2)	12 (30.0)	0.07
Medication			
Aspirin (%)	37 (97.4)	38 (97.4)	1.00
β-Blockers (%)	35 (92.1)	39 (97.5)	0.57
Statin (%)	38 (100.0)	39 (97.5)	1.00
RAAS inhibitors (%)	27 (71.1)	29 (72.5)	0.89
Laboratory test			
ALT (U/L)	21.0 (14.0, 36.5)	21.5 (17.0, 35.7)	0.69
AST (U/L)	21.0 (18.0, 26.0)	22.5 (18.3, 28.7)	0.63
Albumin (g/L)	43.3 (40.3, 46.6)	46.2 (42.9, 47.5)	0.13
TC (mg/dL)	3.2 (2.6, 3.5)	3.5 (3.2, 4.1)	0.33
TG (mg/dL)	1.1 (0.9, 1.7)	1.1 (0.9, 1.8)	0.71
HDL-C (mg/dL)	1.1 ± 0.2	1.1 ± 0.3	0.35
LDL-C (mg/dL)	1.7 (1.3, 2.4)	1.6 (1.4, 2.2)	0.81
BUN (mmol/L)	5.8 (5.1, 6.6)	6.2 (5.4, 7.9)	0.28
Cre (umol/L)	70.5 ± 14.6	69.5 ± 24.0	0.85
UA (umol/L)	343.2 (293.5, 399.2)	281.5 (102.0, 394.7)	0.08

Data are presented as mean±SD, median (lower quartile, upper quartile) or number (%). GXSC, Gelanxinning capsule; BMI, body mass index; RAAS, renin–angiotensin–aldosterone system; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BUN, blood urea nitrogen; Cre, creatine; UA, uric acid.

3.79±0.56 *vs.* 5.69±0.68, p=0.03 and 21.31±2.79 *vs.* 35.18±4.11 p<0.01) (Figure 3 and **Supplementary Table II**). In addition, the level of SIRI1, which is a vascular protective protein, was up-regulated in the GXSC group (5.63±0.30 *vs.* 4.22±0.37, p<0.01) (Figure 3D and **Supplementary Table II**).

GXSC Improved CMD

Molecules of coronary microvascular function including endocan, suPAR and GDF-15 were measured in GXSC and control group. These three molecules above were significantly decreased consistently in GXSC compared with the control group (0.09±0.01 *vs.* 0.19±0.03, p<0.01,

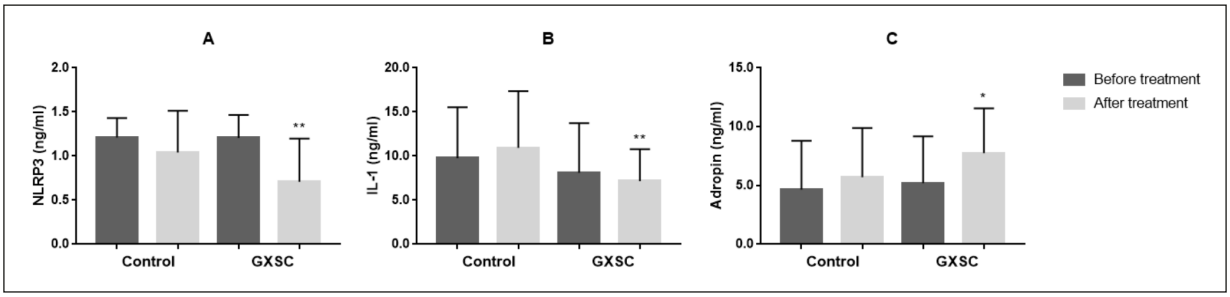

Figure 2. Inflammation biomarkers of patients with coronary microvascular dysfunction according to whether they received Gelanxinning capsule. **A**, NLRP3; (**B**) IL-1; (**C**) Adropin. *p<0.05 and **p<0.01 *vs.* the control group after treatment. GXSC, Gelanxinning capsule; NLRP3, NOD-like receptor thermal protein domain associated protein 3; IL, interleukin.

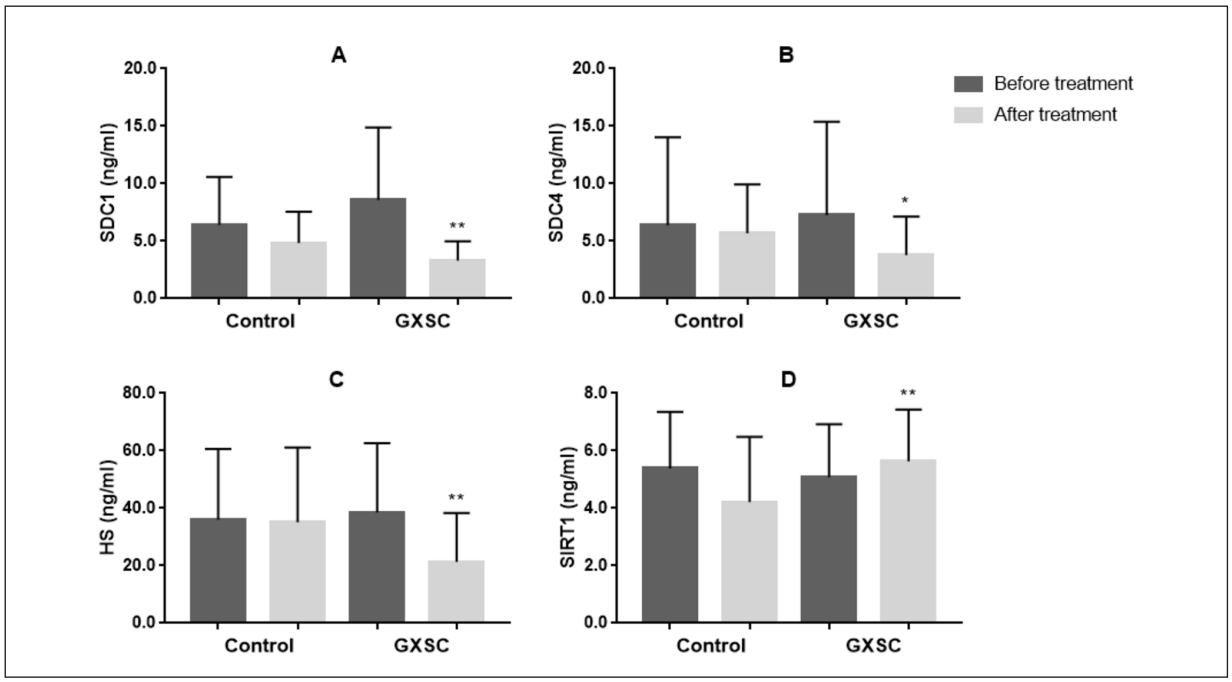

Figure 3. Indexes of endothelial function of patients with coronary microvascular dysfunction according to whether they received Gelanxinning capsule. **A**, SDC1; (**B**), SDC4; (**C**), HS; (**D**), SIRT1. *p<0.05 and **p<0.01 *vs.* the control group after treatment. GXSC, Gelanxinning capsule; SDC, syndecan; HS, heparan sulphates; SIRT1, SIRTUIN 1.

4.44±0.40 *vs.* 5.73±0.40, p=0.03 and 2.08±0.17 *vs.* 2.69±0.18, p=0.02) (Figure 4 and **Supplementary Table III**).

Discussion

Although many traditional Chinese medicines have been indicated to prevent and treat CMD, whether GXSC could improve CMD and its underlying mechanisms are still unknown. Our current study first reported that GXSC could improve CMD and this good effect might be achieved by inhibiting inflammation and restoring endothelial function.

Firstly, we tested whether the inflammation level was changed with GXSC. It has been generally acknowledged[6,7] that inflammation was the cornerstone in the development of CMD. NLRP3 is one of the inflammasomes, which is a high-molecular-weight protein complex and acts as an important component of the innate immune system and mediates a highly inflammatory state. Besides, the activation of NLRP3

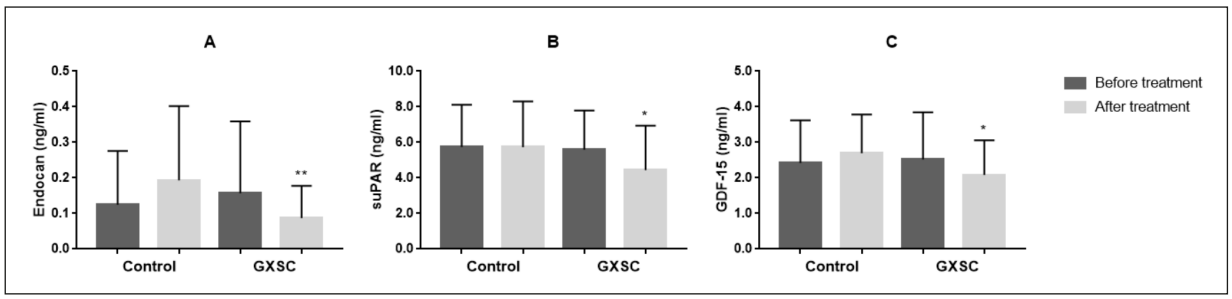

Figure 4. Molecules of coronary microvascular function of patients with coronary microvascular dysfunction according to whether they received Gelanxinning capsule. **A**, endocan; (**B**), suPAR; (**C**), GDF-15. *p<0.05 and **p<0.01 *vs.* the control group after treatment. GXSC, Gelanxinning capsule; suPAR, soluble urokinase plasminogen activator receptor; GDF-15, growth differentiation factor-15.

inflammasome induces the production of pro-inflammatory cytokines such as IL-1. In addition, inflammation and oxidative stress induced by NLRP3 inflammasome and leukocyte adhesion and extravasation induced by pro-inflammatory cytokines would lead to endothelial dysfunction[17]. A few studies have shown[18,19] that the NLRP3 inflammasome signaling pathway was a therapeutic target of cardiac microvascular endothelial cell injury. In the present study, serum levels of NLRP3 and its downstream IL-1 decreased after the treatment with GXSC, which was consistent with previous studies[18,19] (Figure 1). These results indicated that the activation of NLRP3 and IL-1 signaling pathway was crucial in CMD's pathogenesis and that GXSC could probably reduce CMD by inhibiting these pro-inflammatory effects. On the contrary, adropin is an emerging peptide and has many roles in the body, including improving coronary blood flow and inhibiting inflammation[20]. As we can see in Figure 1, adropin was up-regulated in the GXSC group. These findings together yielded that GXSC played an anti-inflammation role in patients with CMD.

Secondly, indexes reflecting endothelial function were also researched. Endothelial dysfunction is another crucial pathogenesis of CMD[7]. The endothelial glycocalyx, which is composed of SDC, HS, and hyaluronan mainly, was recognized as a vasoprotective barrier[21]. Previous studies[22-26] have shown the relationship between the reduced level of glycocalyx and microcirculation dysfunction. In our current research, the levels of SDC1, SDC4 and HS were increased significantly in the GXSC group compared with the control group (Figure 2A, 2B and 2C). Besides, SIRT1 is a histone deacetylase and has been recognized[27,28] as a beneficial protein that can protect vasculature and reduce the risk of cardiovascular diseases. Previous studies[9,27,28] have shown that lower SIRT1 was associated with CMD and therapeutic modulation of SIRT1 restored endothelial function by contrast. We also found that the concentration of SIRT1 increased significantly after GXSC treatment (Figure 2D). These consistent results indicated that restoring endothelial function might be beneficial in CMD and molecules above could become powerful therapeutic targets.

Lastly, molecules that have been associated with CMD were tested to explore whether CMD was improved. Endocan is a predictor of endothelial dysfunction and has been related to microvascular angina[29]. suPAR was reported[30] to be an independent predictor of coronary microvascular function. GDF-15 is a cytokine that is produced from tissue injury and inflammatory states[31]. Several researchers[32,33] have built bridges between GDF-15 and CMD. These three molecules mentioned above were increased significantly in the GXSC group, which reflected that CMD was improved after GXSC treatment (Figure 3).

In addition, evidence[34] showed that *Salvia miltiorrhiza* Bunge is the most commonly used traditional Chinese medicine for the clinical treatment of CMD. Modern pharmacological studies[34] have shown that *Salvia miltiorrhiza* Bunge has anti-inflammatory, antioxidant, anti-atherosclerotic, anti-coagulant, and anti-thrombotic effects, which regulate blood lipids, increase coronary blood flow, improve microcirculation, and protect vascular endothelial function. Danhong injections are composed of *Salvia miltiorrhiza* Bunge and *Carthamus tinctorius* L. Modern research[35] has found that Danhong injections can protect against cardiomyocyte injury, inhibit cardiomyocyte apoptosis, and improve the cell survival rates of myocardial cells. In addition, safranal, an active ingredient extracted from saffron, exerts a protective effect on the cardiovascular system. Wang et al[36] reported that safranal could increase the viability of H9c2 cardiac myoblasts and alleviate H/R-induced H9c2 cardiac myoblast injuries *via* the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/glycogen synthase kinase-3beta (GSK3β) signaling pathway. Huangqi (*Astragalus mongholicus* Bunge) and danghui [*Angelica sinensis* (Oliv.) Diels].

Astragalus mongholicus Bunge and *Angelica sinensis* (Oliv.) Diels are commonly used as couplet medicine in the clinical treatment of CMD. Modern pharmacological studies in literature have shown that *Astragalus mongholicus* Bunge-*Angelica sinensis* (Oliv.) Diels improved blood circulation, had anti-inflammation and antioxidation effects, and protected the vascular endothelium. By promoting the expression of endothelial nitric oxide synthase (eNOS) and phosphorylation of protein kinase B (PKB/Akt), *Astragalus mongholicus* Bunge-*Angelica sinensis* (Oliv.) Diels can promote nitric oxide (NO) release and diastolic blood vessels, which protect the endothelium. It can also inhibit the apoptosis of vascular endothelial cells by inhibiting inducible NOS (iNOS) expressions, improving the expressions of local inflammatory response factors in blood vessels, and inhibiting intimal hyperplasia due to endothelial injury[37].

To the best of our knowledge, we first reported that GXSC could improve CMD, which might be resulted from the inhibition of the inflammation and the restored endothelial function.

Limitations

The current study has several limitations. First, our study was a single-center, and the sample size was small, so the results still need to be confirmed in a multi-center study with a larger sample size. Secondly, we only performed coronary microvascular function tests once when all participants were included due to the expensive cost. Although indexes of coronary microvascular function were improved significantly, the better test results at the end of the study could be more convincing. Thirdly, specific mechanisms that show how GXSC plays a therapeutic role through inflammation and endothelial function pathways still need to be further studied in basic research.

Conclusions

GXSC can improve CMD by inhibiting inflammation and restoring endothelial function. GXSC might be an effective drug in CAD patients without obstructive epicardial coronary arteries but suffering from angina.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest..

Ethics Approval

This study complied with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of the Shaanxi Provincial People's Hospital, Xi'an, Shaanxi, China (No. SPPH-LLBG-17-3.2).

Informed Consent

Written informed consent was obtained from all study participants.

Authors' Contribution

M.D., B.H. and G.C. conceived and designed the study. H.J., Y.W., H.Z., R.J., C.L., J.Z. and S.J. performed the study. W.F., M.D. and G.C. analysed the data and wrote the paper. All authors read, critically revised, and approved the final manuscript.

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