Am J Transl Res 2025;17(3):1756-1767
www.ajtr.org /ISSN:1943-8141/AJTR0160766

Original Article

Combined use of anti-platelet aggregation drugs and shujin huoluo decoction for diabetic peripheral vascular disease: enhanced therapeutic efficacy

Zhiqiang Li[1], Yang Yu[2], Baozhong Chen[3]

[1]First Affiliated Hospital of Heilongjiang University of Traditional Chinese Medicine, Harbin 150040, Heilongjiang, China; [2]Heilongjiang Open University, Harbin 150006, Heilongjiang, China; [3]Prescription Teaching and Research Department, School of Basic Medicine, Heilongjiang University of Traditional Chinese Medicine, Harbin 150040, Heilongjiang, China

Received September 26, 2024; Accepted February 17, 2025; Epub March 15, 2025; Published March 30, 2025

Abstract: Objective: To investigate the clinical effect of anti-platelet aggregation drugs combined with Shujin Huoluo Decoction (SJHLD, a decoction for relaxing muscles and activating collaterals) in the treatment of diabetic peripheral vascular disease. Methods: A total of 130 patients with diabetic peripheral vascular disease were retrospectively included in this study and divided into two groups. In the monotherapy group, 65 patients were treated with cilostazol (CTZ) monotherapy; in the combined group, 65 patients were treated with CTZ combined with SJHLD. The treatment efficacy, inflammatory indexes, blood glucose and lipid levels, ultrasound parameters, and hemorheology of the two groups were compared before and after treatment. Results: Both groups showed significant improvements in walking distance and skin temperature of the toes, with more pronounced changes observed in the combined group ($P < 0.05$). After treatment, inflammatory markers decreased notably in both groups ($P < 0.05$). Blood glucose and lipid levels decreased markedly, with a more substantial reduction in lipid levels observed in the combined group ($P < 0.05$). Lower limb arterial conditions improved markedly in both groups, with greater improvements seen in the combined group ($P < 0.05$). Additionally, the pulsatile index and blood flow velocity in the ankle-brachial and dorsalis pedis arteries increased markedly in both groups, with the combined group showing a greater improvement ($P < 0.05$). Hemorheology parameters also decreased significantly in both groups, with the combined group showing a more significant reduction ($P < 0.05$). The effective treatment rate was significantly higher in the combined group ($P < 0.05$). Conclusions: The combination of CTZ and SJHLD significantly improves lower limb function, ultrasound parameters, and blood flow, enhancing treatment efficiency in patients with diabetic peripheral vascular disease. This therapeutic approach offers valuable clinical guidance and warrants consideration for use in diabetic patients.

Keywords: Anti-platelet aggregation drugs, Shujin Huoluo Decoction, diabetic peripheral vascular disease, clinical curative effect

Introduction

Diabetes mellitus is a chronic disease with high heritability and strong environmental influences [1]. It is associated with high incidence and complications that are difficult to cure. It severely impacts patients' health, daily functioning, and social status [2, 3]. A family history of diabetes, work environment, age, economic level, excessive weight, elevated blood pressure, abnormal blood lipid levels, smoking and drinking, excessive diet, poor and irregular sleep quality, poor mood, and other related factors are all closely related to the incidence of diabetes [4, 5]. Diabetes disrupts metabolic functions, leading to systemic effects throughout the body [6-8]. Prolonged poor glycemic control can cause chronic degenerative changes, affecting organs such as the eyes, kidneys, and heart [9, 10].

Diabetic patients are also prone to vascular complications. Abnormal glucose levels increase the risk of dyslipidemia, leading to physiological changes and impaired blood vessel function, ultimately affecting all organs [11]. Diabetic peripheral vascular disease (DPVD) impairs blood flow to the lower limbs, potentially

https://doi.org/10.62347/NFKV1920

causing limb ischemia, and even gangrene in severe cases, significantly affecting patients' daily life and social interactions [12]. Pharmacological treatment is the primary method for managing DPVD, due to its ease of use and high patient compliance [13, 14]. Cilostazol (CTZ) is a widely used vasodilator that can greatly improve the vascular condition of patients' lower limbs and promote the early resumption of normal activities [15-17]. Shujin Huoluo Decoction (SJHLD, a decoction for relaxing muscles and activating collaterals), consisting of Astragalus membranaceus, Paeoniae, and other herbs, is used to strengthen qi, warm the channels, and activate blood circulation. It is commonly prescribed for DPVD and has demonstrated therapeutic benefits. Combination therapy is widely employed in clinical practice, as it enhances efficacy, provides a more comprehensive treatment, and reduces drug-related side effects [18-20].

In this study, 130 patients with DPVD were treated with different medication methods. The efficacy of subcutaneous injection of CTZ alone versus a combination of anti-platelet aggregation drugs and SJHLD was compared between groups before and after treatment. The inflammatory markers, blood glucose and lipid levels, ultrasound parameters, and hemorheology were assessed to analyze the treatment outcomes and provide guidance for the management and remission of DPVD.

Materials and methods

Case selection

This study retrospectively analyzed data from 130 patients treated for diabetic peripheral vascular disease between June 2021 and October 2021. The patients were divided into two groups: a monotherapy group (65 patients) treated with anti-platelet aggregation drugs alone, and a combined group (65 patients) treated with anti-platelet aggregation drugs combined with SJHLD. No remarkable differences were observed in basic information between groups, indicating comparability. This study was conducted with approval from the Ethics Committee of the First Affiliated Hospital of Heilongjiang University of Traditional Chinese Medicine.

Inclusion criteria: i) Complete medical records; ii) Patients able to communicate with healthcare providers; iii) No genetic disease; iv) First-time treatment; v) No contraindications for treatment.

Exclusion criteria: i) Difficulty in communication; ii) Presence of other malignant tumors; iii) Patients in pregnancy or lactation; iv) Recent use of medications that could interfere with study outcomes.

Intervention approaches

All patients received basic treatment, including medications to control blood glucose. After blood glucose and glycosylated hemoglobin (HbAlc) were stabilized, patients in the monotherapy group were treated with cilostazol (CTZ) (Shanghai Jichun Industrial Co., Ltd., SJ-JC14112) administered via subcutaneous injection in 2 mL of 0.9% normal saline (Shanghai Yaji Biotechnology Co., Ltd., HB-PT034), and patients in the combined group were additionally treated with SJHLD, in addition to CTZ, as is was delivered to the monotherapy group.

The formula of SJHLD (all herbs sourced from Shanghai Yubo Biotechnology Co., Ltd.) consisted of 15 g of medicinal cyathula root, 30 g of Salvia miltiorrhiza, 12 g of Angelica, 12 g of Ligusticum wallichii, 15 g of peach kernel, 15 g of leech, 20 g of lumbricus, 15 g of Liquidambaris Fructus, and 12 g of raw licorice. The herbs were decocted in water and administered orally as one dose per day. The preparation method of SJHLD decoction involved grinding the herbal ingredients into powder, mixing them according to weight ratios, soaking them in water for 1 hour, and then decocting the mixture twice. After each boiling, the mixture was cooked for 40 minutes. The filtrate was then mixed and allowed to precipitate for half a day. The supernatant was concentrated to 200 mL per unit dose, which was administered to patients. Each patient took 200 ml of the decoction daily, divided into two doses taken 1 hour apart after breakfast and dinner. The therapeutic effect was observed after two weeks of treatment.

Data collection

I. Patient demographics, including sex, age, diabetes history, hypertension, coronary heart disease, diabetic nephropathy, and diabetic neuropathy, were recorded.

Table 1. Comparison of general data between groups

Indicators	Monotherapy group (n=65)	Combined group (n=65)	t/χ^2	P
Gender (male/female)	34/31	35/30	0.031	0.861
Age (years old)	57.54±7.13	57.02±7.85	0.395	0.693
Medical history (years)	9.85±4.46	11.06±4.93	1.467	0.145
Hypertension (with/without)	22/43	25/40	0.300	0.584
Coronary heart disease (with/without)	10/55	8/57	0.258	0.612
Diabetic nephropathy (with/without)	12/53	9/56	0.511	0.475
Diabetic neuropathy (with/without)	6/59	4/61	0.433	0.510

II. Walking distance and toe skin temperature were measured before and after treatment.

III. Levels of inflammatory indexes (tumour necrosis factor [TNF]-α, interleukin [IL]-6, and C-reactive protein [CRP]) were measured using chemiluminescence.

IV. Blood lipid and glucose indexes, including fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TGs), and HbA1c, were determined.

V. Arterial diameter and blood flow in the femoral artery, popliteal artery, and dorsalis pedis artery were measured.

VI. Ultrasound indexes of lower extremity blood vessels, including ankle-brachial index (ABI), dorsalis pedis artery pulsatility index (DPAPI), resistive index (RI), and mean blood flow velocity in the dorsalis pedis artery, were compared before and after treatment. ABI was calculated using the following formula:

$$ABI = \frac{\text{Ankle artery pressure}}{\text{Brachial artery pressure}} \quad (1)$$

VII. Hemorheological indices.

VIII. The therapeutic effects were compared between the two groups. The therapeutic effects were categorized as follows: Cured: Lower limb blood flow was normal, and walking function was restored; Markedly Effective: Significant improvement in lower limb blood flow, with normal walking ability; Effective: Mild improvement in blood flow and walking function; Ineffective: No improvement in blood flow or walking function. The effective rate was calculated using the formula:

Efficiency = (Cured + Markedly effective + effective)/Total 100%. (2)

In this study, the primary outcomes included walking distance, toe skin temperature, lower limb arterial diameter and blood flow, ultrasound indexes, and therapeutic effects. Secondary outcomes included general data, inflammatory markers, blood lipids and glucose levels, and hemorheological indices.

Statistical methods

Data were recorded and summarized using Excel 2019, and statistical analysis was performed using SPSS 20.0. Measurement data are presented as mean ± standard deviation ($\bar{x} \pm s$), and comparisons between groups were made using the t-test. Count data are presented as percentages (%), with inter-group comparisons conducted using the χ^2 test. The difference was considered statistically significant at $P < 0.05$.

Results

Comparison of general data between the two groups before treatment

Table 1 presents the comparison of baseline data of patients with DPVD between the two groups. No significant differences were observed between groups in terms of gender, age, medical history, hypertension coronary heart disease, diabetic nephropathy, or diabetic neuropathy ($P > 0.05$), indicating comparability between the two groups.

Comparison of walking distance and toe skin temperature between the two groups before and after treatment

Before treatment, no statistical significances were found in the painless walking distance, maximum walking distance, or toe temperature between the two groups (all $P > 0.05$). After

treatment, both groups showed a significant increase in these measures ($P < 0.05$), with the combined group demonstrating a more pronounced improvement ($P < 0.05$), as shown in **Figure 1**.

Comparison of inflammatory indexes between the two groups before and after treatment

Before treatment, no significant differences were observed between the two groups in terms of TNF-α, IL-6, and CRP ($P > 0.05$). After treatment, both groups showed significant reductions in these inflammatory markers (all $P < 0.05$), with the combined group exhibiting significantly lower values than the monotherapy group ($P < 0.05$), as shown in **Figure 2**.

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

Before treatment, no significant differences were observed in blood lipid and blood glucose indicators between the two groups ($P > 0.05$). After treatment, both groups showed significant reductions in blood lipid and glucose levels ($P < 0.05$), with the combined group demonstrating significantly lower TC and TG levels compared to the monotherapy group ($P < 0.05$), as shown in **Figure 3**. However, there were no statistical differences in FBG and HbA1c levels between the two groups after treatment.

Comparison of lower limb artery conditions between the two groups before and after treatment

Before treatment, there were no significant differences in lower limb artery diameter and blood flow volume between the two groups ($P > 0.05$). After treatment, all these indices increased significantly in both groups ($P < 0.05$), with the combined group demonstrating a more pronounced improvement compared to the monotherapy group ($P < 0.05$), as shown in **Figure 4**.

Comparison of lower extremity vascular ultrasound parameters between the two groups before and after treatment

Before treatment, there were no significant differences in the ultrasound parameters of lower extremity blood vessels (ABI, DPAPI, RI, and blood flow velocity) between the two groups (all $P > 0.05$). After treatment, ABI, DPAPI, and blood flow velocity increased significantly, while IR decreased notably, in both groups (all $P < 0.05$), with the combined group showing more remarkable alterations than the monotherapy group (all $P < 0.05$), as shown in **Figure 5**.

Comparison of hemorheological indexes between the two groups before and after treatment

Before treatment, there were no significant differences in hemorheological parameters between the two groups ($P > 0.05$). After treatment, all these indices decreased significantly in both groups, with the combined group showing more substantial reductions compared to the monotherapy group ($P < 0.05$), as shown in **Figure 6**.

Comparison of clinical effect and treatment efficiency between the two groups

The combined group demonstrated a significantly higher overall effective rate than the monotherapy group (92.31% versus 80.00%, $P=0.042$), as shown in **Table 2**.

Discussion

The insulin secretion function in diabetic patients is often impaired, leading to metabolic dysfunction that can harm various tissues and organs of the whole body, and the probability of complications is high. There are many types of complications. This dysfunction increases the likelihood of complications, which are diverse, highly damaging, and difficult to treat, contributing to significant morbidity and high mortality rates [21, 22]. Studies have shown that the incidence of diabetes is higher among women in European and American countries, while in Asian countries, it is more prevalent in men [23]. Being overweight and obese are also risk factors for hypertension, as well as cardiovascular and cerebrovascular diseases [24]. Sedentary lifestyles and poor sleep quality further increase the risk of developing diabetes [25]. Additionally, both nicotine and alcohol negatively impact insulin sensitivity, and smokers and excessive drinkers are prone to elevated blood sugar levels and a higher risk of diabetes [26, 27]. Emotion can also affect the occurrence of diabetes. Long-term negative emo-

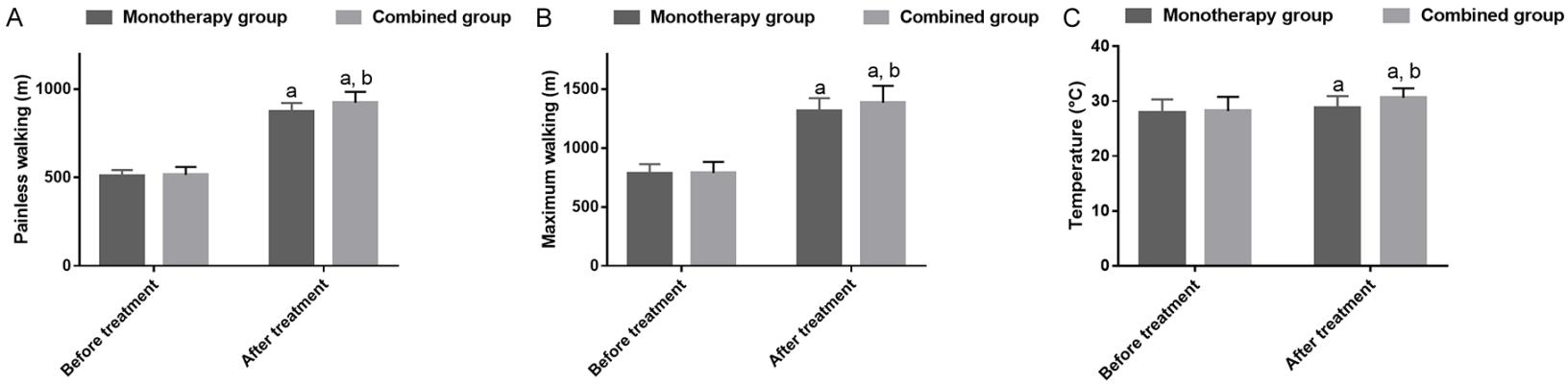

Figure 1. Comparison of walking ability and toe temperature between groups before and after treatment. A: Painless walking distance; B: Maximum walking distance; C: Toe temperature. a, $P < 0.05$, compared with before treatment; b, $P < 0.05$, compared with monotherapy group.

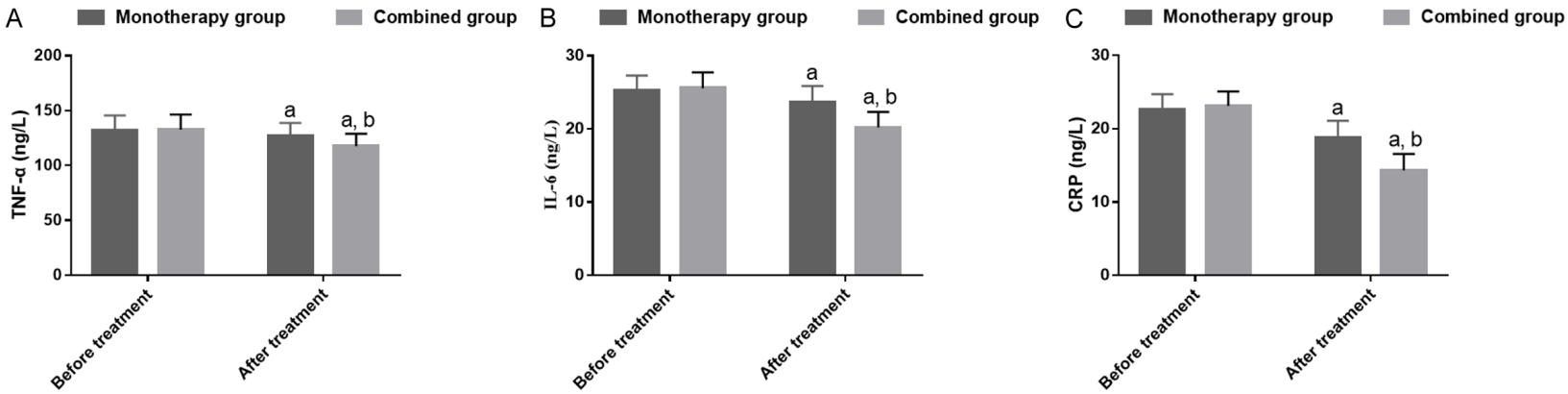

Figure 2. Comparison of inflammatory markers between groups before and after treatment. A: TNF-α; B: IL-6; C: CRP. TNF-α, tumour necrosis factor-α; IL-6, interleukin-6; CRP, C-reactive protein. a, $P < 0.05$, compared with before treatment; b, $P < 0.05$, compared with monotherapy group.

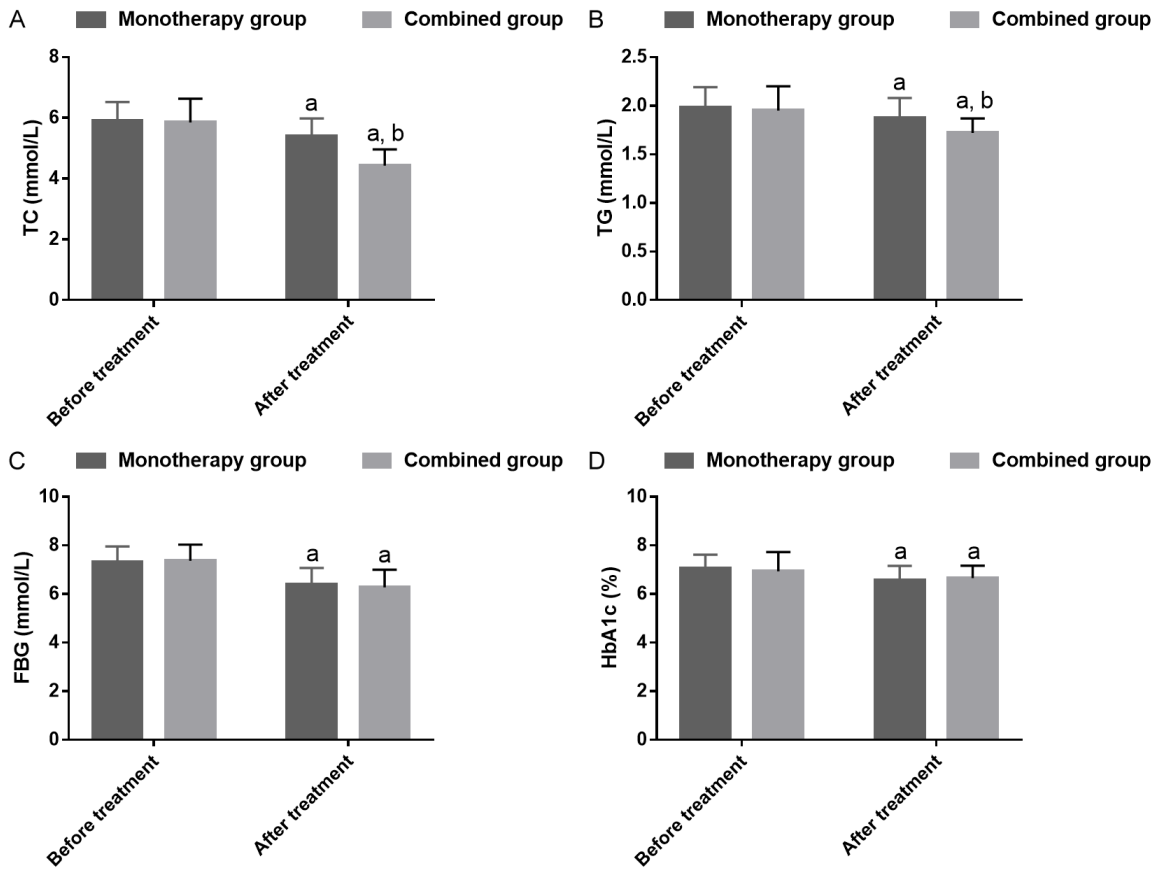

Figure 3. Comparison of blood lipid and glucose indices between groups before and after treatment. A: TC; B: TG; C: FBG; D: HbA1c. TC, total cholesterol; TG, triglyceride; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin. a, $P < 0.05$, compared with before treatment; b, $P < 0.05$, compared with monotherapy group.

tions can worsen metabolic disorders, disrupt blood sugar balance, and aggravate the condition. If patients fail to manage their diabetes effectively, the disease tends to progress, leading to severe metabolic disruptions, acute onset, and increased risks [28]. Abnormal glucose metabolism is often accompanied by lipid metabolism disorders, which can lead to vascular diseases, worsening the condition and complicating treatment [29, 30]. Active and stable drug therapy plays an important role in controlling DPVD and other complications. Rational drug use is an effective way to control and improve the condition. Combining drugs offers a comprehensive, systematic approach to treatment, significantly benefiting disease control and promoting faster patient recovery. The integration of traditional Chinese medicine with Western medicine has been shown to enhance overall efficacy, reduce complications, and improve both safety and effectiveness, making it highly valuable in the management of chronic diseases [31].

Anti-platelet drugs increase blood flow, dilate blood vessels, and enhance circulation. CTZ has both anti-platelet and vasodilatation effects, significantly improving intermittent claudication symptoms. It is widely used for treating DPVD with significant clinical effects [32]. Shujin Huoluo Decoction (SJHLD) promotes blood circulation, clears collaterals, and is beneficial for treating DPVD. Multidrug combination therapy offers a more effective treatment option, achieving better outcomes while minimizing adverse reactions and side effects [33].

Several studies support the combination of anti-platelet and anticoagulant drugs in treating diabetic patients. Bhatt et al. [34] found that combining aspirin with rivaroxaban could reduce the incidence of vascular lesions in dia-

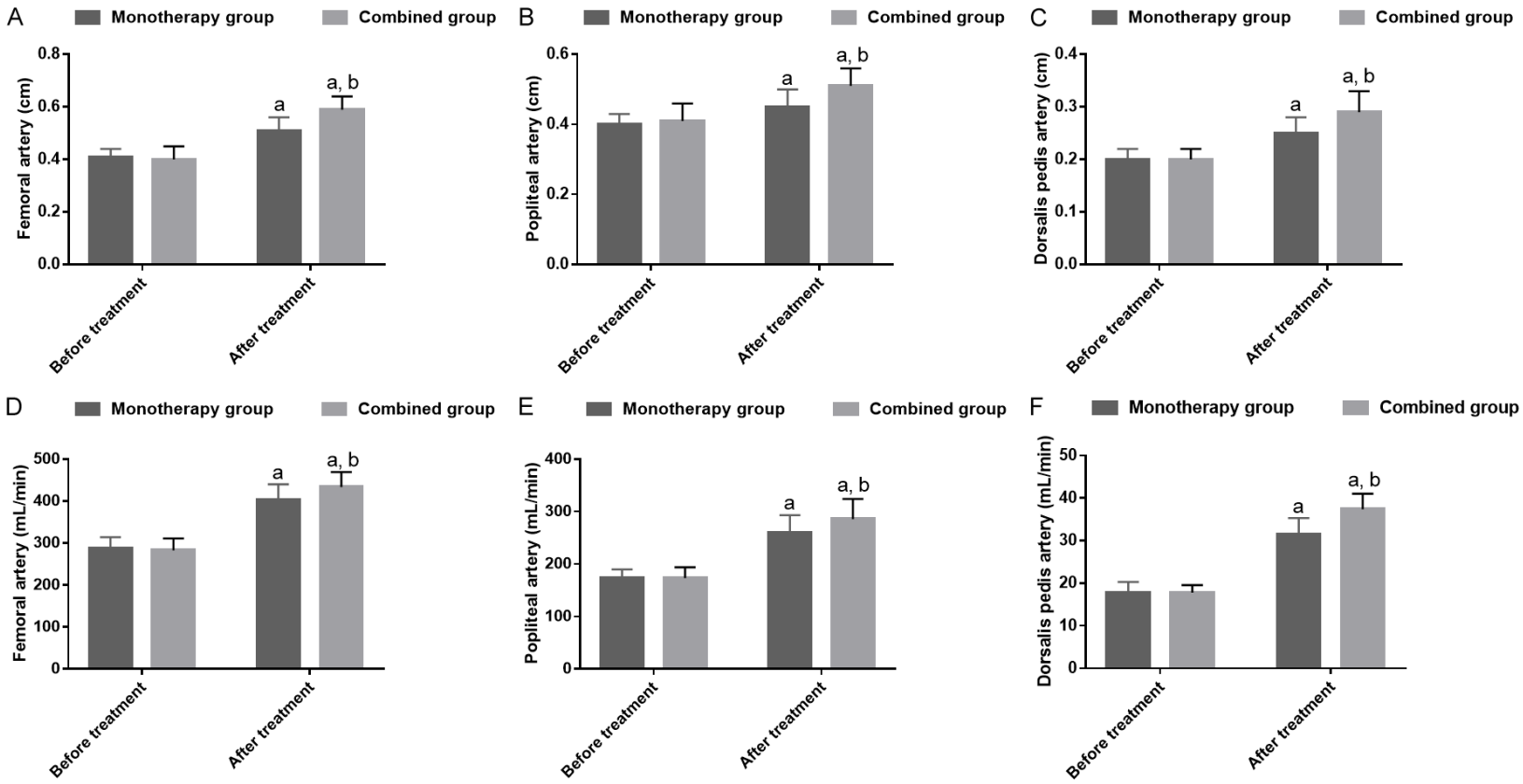

Figure 4. Comparison of artery diameter and blood flow in lower limbs between groups before and after treatment. A: Femoral artery diameter; B: Popliteal artery diameter; C: Dorsalis pedis artery diameter; D: Femoral artery blood flow; E: Popliteal artery blood flow; F: Dorsalis pedis artery blood flow. a, $P < 0.05$, compared with before treatment; b, $P < 0.05$, compared with monotherapy group.

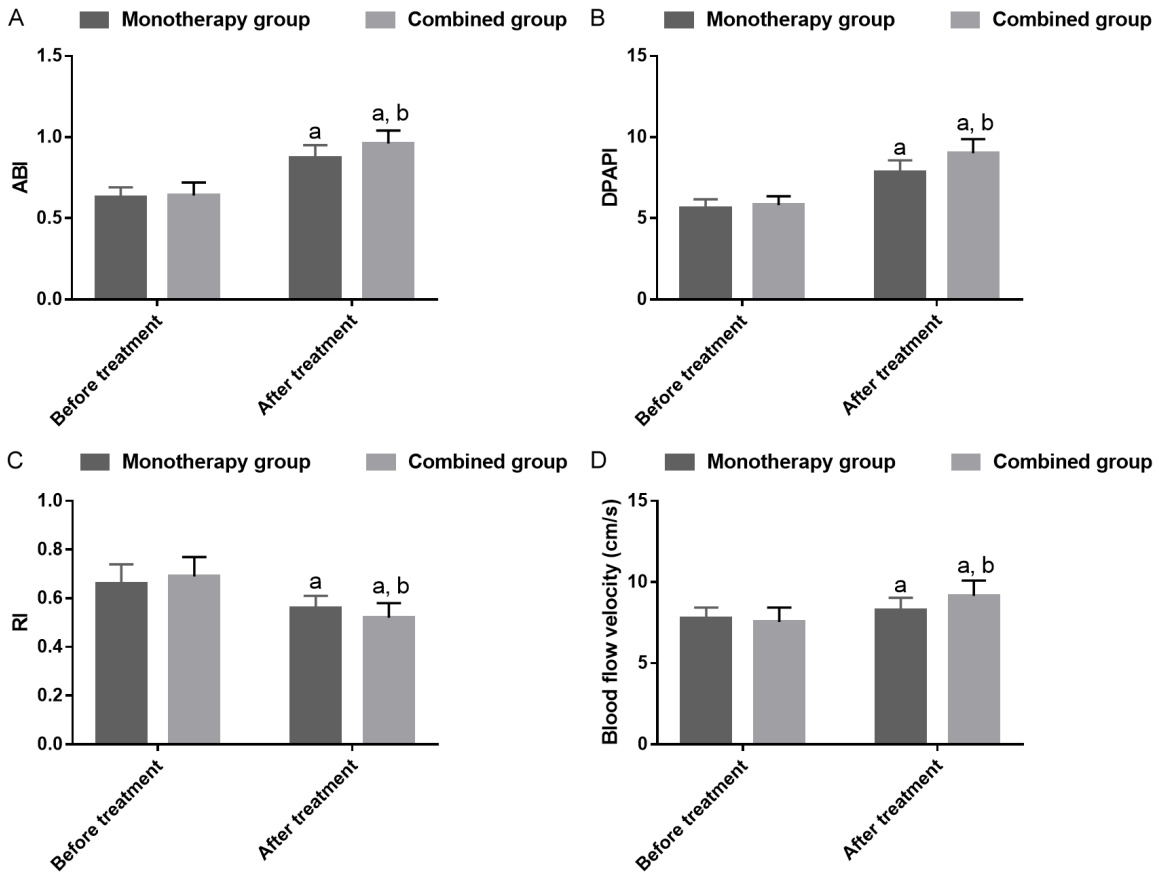

Figure 5. Comparison of lower extremity vascular ultrasound parameters between groups before and after treatment. A: ABI; B: DPAPI; C: RI; D: Mean blood flow velocity. ABI, ankle-brachial index; DPAPI, dorsalis pedis artery pulsatility index; RI, resistive index. a, $P < 0.05$, compared with before treatment; b, $P < 0.05$, compared with monotherapy group.

betic patients. Liu et al. [35] reported that the combination of aspirin, ticagrelor, and tirofiban substantially lowered the risk of adverse reactions in diabetic patients, demonstrating both safety and efficacy. Similarly, Kalantzi et al. [36] showed that combining CTZ with clopidogrel in type 2 diabetic patients with lower limb artery disease reduced ischemic events and improved intermittent claudication without increasing bleeding risks. In this study, we compared single-drug and combination treatments for DPVD. In addition to raising the toe temperature, CTZ combined with SJHLD greatly alleviated walking difficulties, enabling patients to walk a longer distance. This improvement can be attributed to the medicinal herbs in SJHLD: Angelica sinensis can nourish and promote blood circulation, Ligusticum wallichii can activate blood and qi, dispel wind, and relieve pain; Leech can promote blood circulation and prevents coagulation; Lumbricus can not only promote blood circulation and remove blood stasis but also dredge collaterals and alleviate pain; Liquidambaris Fructus clears heat, drains dampness, and promotes water flow, while Raw licorice can harmonize the herbs' effects and alleviate acute pain [37-39]. These synergistic activities help improve toe temperature and walking ability.

Compared with monotherapy, the combination therapy showed more pronounced effects in reducing inflammatory markers such as TNF-α, IL-6, and CRP, as well as improving blood lipid and glucose markers. Zhu Z et al. [40] observed that lumbrokinase, a bioactive agent from earthworm extract, has anti-inflammatory, antibacterial, antifungal, and hypoglycemic effects, contributing to the anti-inflammatory action of SJHLD. Other studies have shown that compounds like myrtenal and β-caryophyllene oxide from Liquidambaris Fructus can down-regulate

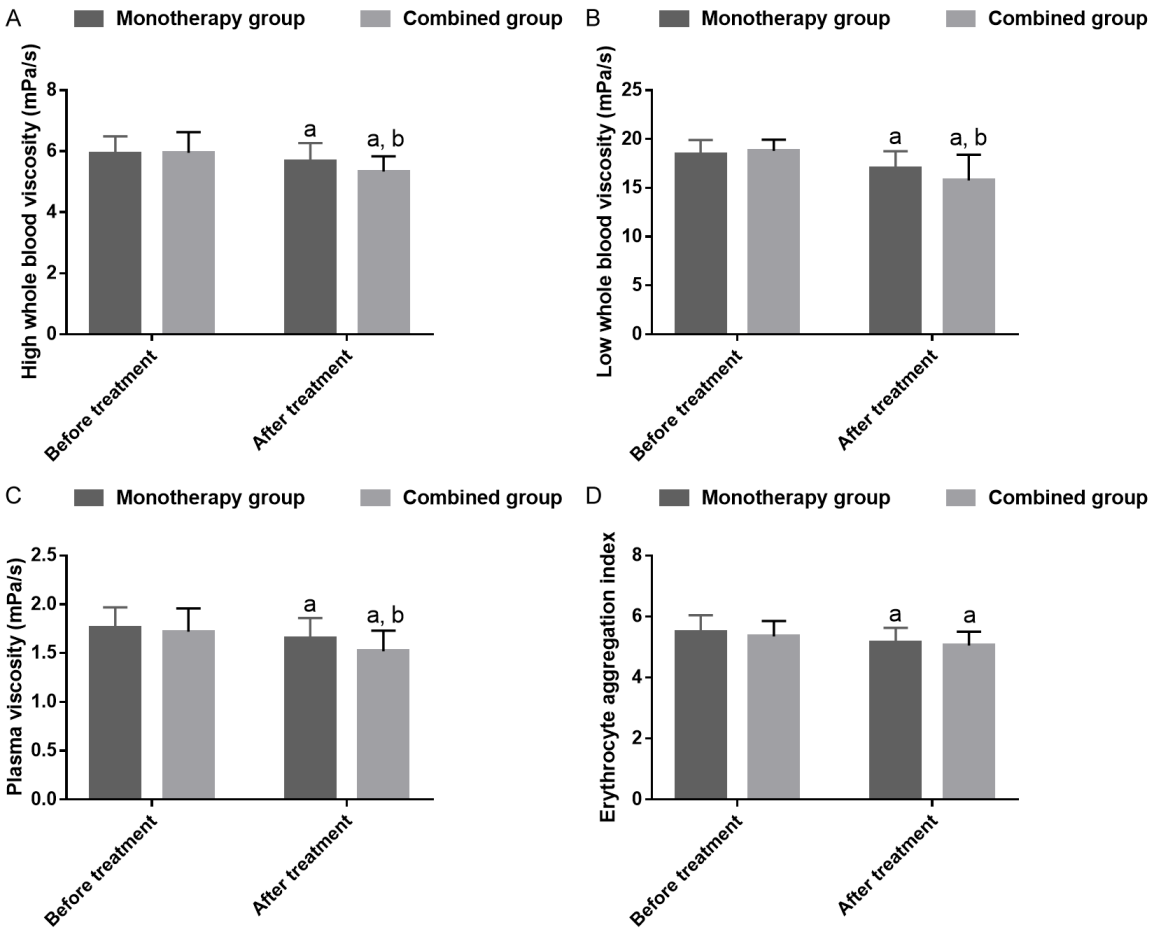

Figure 6. Comparison of hemorheological indices between groups before and after treatment. A: High whole blood viscosity; B: Low whole blood viscosity; C: Plasma viscosity; D: Erythrocyte aggregation index. a, $P < 0.05$, compared with before treatment; b, $P < 0.05$, compared with monotherapy group.

Table 2. Comparison of treatment efficacy between groups

Therapeutic effect	Monotherapy group (n=65)	Combined group (n=65)	χ^2	P
Cured	16 (24.62)	23 (35.38)		
Markedly effective	21 (32.31)	25 (38.46)		
Effective	15 (23.08)	12 (18.46)		
Ineffective	13 (20.00)	5 (7.69)		
Overall effective rate	52 (80.00)	60 (92.31)	4.127	0.042

serum inflammatory factors by inhibiting the NLRP3 inflammasome, explaining part of the anti-inflammatory effect of SJHLD [41]. Likewise, the combined therapy showed more advantages in improving lower limb physiology and function. It facilitated the restoration of normal blood flow, increased blood volume, prevented vascular occlusion, and positively impacted blood lipids, vascular lesions, and hemorheology. This is likely due to the blood-circulating and blood-stasis-dissipating effects of SJHLD. As for overall efficacy, the combined treatment group had a significantly higher effective rate compared to the monotherapy group. Similarly, Song G et al. [42] found that the combination of Chinese herbal footbaths (Gubu Decoction) and traditional Chinese medicine (Yiqi Huoxue Decoction) outperformed

conventional Western treatments for diabetic peripheral neuropathy, which aligns with our findings.

This study has several limitations. First, the sample size was relatively small, and the study design was from a single-center. Therefore, to enhance the generalizability of the findings, future research should focus on expanding the sample size and employing multi-center studies. Second, the treatment mechanisms of each herb were not fully explored. Additional research into the pharmacological effects and mechanisms of these herbs would deepen the understanding of how they contribute to the therapeutic outcomes. Third, the long-term prognosis was not analyzed. Further studies investigating the long-term benefits of the combination therapy would provide valuable insights into its sustained efficacy. These aspects will be addressed in future improvements to the study.

Conclusions

This study compared the therapeutic effects of CTZ monotherapy and CTZ combined with SJHLD in patients with diabetic peripheral vascular disease. The results indicate that the combination therapy offers superior safety, more targeted disease treatment, and faster functional recovery. Patients in the combined treatment group showed significant improvements in blood flow and walking ability, allowing for quicker return to normal activities. Therefore, the CTZ + SJHLD combination is a promising treatment with strong clinical potential, offering effective relief and improved outcomes for diabetic peripheral vascular disease patients.

Disclosure of conflict of interest

None.

Address correspondence to: Baozhong Chen, Prescription Teaching and Research Department, School of Basic Medicine, Heilongjiang University of Traditional Chinese Medicine, Harbin 150040, Heilongjiang, China. Tel: +86-0451-82193455; E-mail: chen3640@126.com

References

[1] Xiong J, Hu H, Guo R, Wang H and Jiang H. Mesenchymal stem cell exosomes as a new strategy for the treatment of diabetes complications. Front Endocrinol (Lausanne) 2021; 12: 646233.

[2] Redquest B, Ahmed S, Balogh R and Lunsky Y. Preventing and treating diabetes in Canadian adults with intellectual and developmental disabilities. Can J Diabetes 2020; 44: 205-210.

[3] Biondi B, Kahaly GJ and Robertson RP. Thyroid dysfunction and diabetes mellitus: two closely associated disorders. Endocr Rev 2019; 40: 789-824.

[4] Eizirik DL, Pasquali L and Cnop M. Pancreatic beta-cells in type 1 and type 2 diabetes mellitus: different pathways to failure. Nat Rev Endocrinol 2020; 16: 349-362.

[5] Cloete L. Diabetes mellitus: an overview of the types, symptoms, complications and management. Nurs Stand 2022; 37: 61-66.

[6] Ringholm L, Damm P and Mathiesen ER. Improving pregnancy outcomes in women with diabetes mellitus: modern management. Nat Rev Endocrinol 2019; 15: 406-416.

[7] Petrov MS. Post-pancreatitis diabetes mellitus: investigational drugs in preclinical and clinical development and therapeutic implications. Expert Opin Investig Drugs 2021; 30: 737-747.

[8] Alalawi F and Bashier A. Management of diabetes mellitus in dialysis patients: obstacles and challenges. Diabetes Metab Syndr 2021; 15: 1025-1036.

[9] R A and R N. Diabetes mellitus prediction and severity level estimation using owdann algorithm. Comput Intell Neurosci 2021; 2021: 5573179.

[10] Mott AK. Diabetes mellitus self-management to decrease the risk for chronic kidney disease. Nephrol Nurs J 2021; 48: 65-63.

[11] Liu G and Wang F. Macular vascular changes in pregnant women with gestational diabetes mellitus by optical coherence tomography angiography. BMC Ophthalmol 2021; 21: 170.

[12] Shita NG and Muluneh EK. Predictors of blood glucose change and vascular complication of type 2 diabetes mellitus patients in Felege Hiwot Referral hospital, North West Ethiopia. Sci Rep 2021; 11: 12974.

[13] Zhao X, Liu Y, Zhang W, Meng L, Lv B, Lv C, Xie G and Chen Y. Relationships between retinal vascular characteristics and renal function in patients with type 2 diabetes mellitus. Transl Vis Sci Technol 2021; 10: 20.

[14] Rababa'h AM, Mardini AN, Alzoubi KH, Ababneh MA and Athamneh RY. The effect of cilostazol on hippocampal memory and oxidative stress biomarkers in rat model of diabetes mellitus. Brain Res 2019; 1715: 182-187.

[15] Lee CY, Wu TC and Lin SJ. Long-term cilostazol treatment and predictive factors on outcomes of endovascular intervention in patients with diabetes mellitus and critical limb ischemia. Diabetes Ther 2020; 11: 1757-1773.

[16] Wahba MGF, Messiha BAS, El-Daly ME and Abo-Saif AA. Vardenafil and cilostazol can improve vascular reactivity in rats with diabetes mellitus and rheumatoid arthritis co-morbidity. Life Sci 2019; 229: 67-79.
[17] Gomaa AA, Farghaly HSM, Ahmed AM, El-Mokhtar MA and Hemida FK. Advancing combination treatment with cilostazol and caffeine for Alzheimer's disease in high fat-high fructose-STZ induced model of amnesia. Eur J Pharmacol 2022; 921: 174873.
[18] Manolis AA, Manolis TA, Melita H, Mikhailidis DP and Manolis AS. Update on cilostazol: a critical review of its antithrombotic and cardiovascular actions and its clinical applications. J Clin Pharmacol 2022; 62: 320-358.
[19] Hong S, Lee WJ and Park CY. Comparative study of ex vivo antiplatelet activity of aspirin and cilostazol in patients with diabetes and high risk of cardiovascular disease. Endocrinol Metab (Seoul) 2022; 37: 233-242.
[20] Colak B, Orhan A, Ece I, Yormaz S, Yilmaz H and Sahin M. Comparison of the effects of cilostazol and aspirin on wound healing in patients with diabetic foot ulcer and peripheral artery disease. Ann Ital Chir 2020; 91: 225-232.
[21] Arroyave F, Montano D and Lizcano F. Diabetes mellitus is a chronic disease that can benefit from therapy with induced pluripotent stem cells. Int J Mol Sci 2020; 21: 8685.
[22] Plows JF, Reynolds CM, Vickers MH, Baker PN and Stanley JL. Nutritional supplementation for the prevention and/or treatment of gestational diabetes mellitus. Curr Diab Rep 2019; 19: 73.
[23] Kharode I, Coppedge E and Antal Z. Care of children and adolescents with diabetes mellitus and hyperglycemia in the inpatient setting. Curr Diab Rep 2019; 19: 85.
[24] Robert AA and Al Dawish MA. The worrying trend of diabetes mellitus in Saudi Arabia: an urgent call to action. Curr Diabetes Rev 2020; 16: 204-210.
[25] Darenskaya MA, Kolesnikova LI and Kolesnikov SI. Oxidative stress: pathogenetic role in diabetes mellitus and its complications and therapeutic approaches to correction. Bull Exp Biol Med 2021; 171: 179-189.
[26] Anastasiou E, Farmakidis G, Gerede A, Goulis DG, Koukkou E, Kourtis A, Mamopoulos A, Papadimitriou K, Papadopoulos V and Stefos T. Clinical practice guidelines on diabetes mellitus and pregnancy: Iota. Pre-existing type 1 and type 2 diabetes mellitus. Hormones (Athens) 2020; 19: 593-600.
[27] Goyal RK, Cristofaro V and Sullivan MP. Rapid gastric emptying in diabetes mellitus: pathophysiology and clinical importance. J Diabetes Complications 2019; 33: 107414.
[28] Zhang Y, Bai R, Liu C, Ma C, Chen X, Yang J and Sun D. MicroRNA single-nucleotide polymorphisms and diabetes mellitus: a comprehensive review. Clin Genet 2019; 95: 451-461.
[29] Klein KR and Buse JB. The trials and tribulations of determining HbA(1c) targets for diabetes mellitus. Nat Rev Endocrinol 2020; 16: 717-730.
[30] Sun Y, Tao Q, Wu X, Zhang L, Liu Q and Wang L. The utility of exosomes in diagnosis and therapy of diabetes mellitus and associated complications. Front Endocrinol (Lausanne) 2021; 12: 756581.
[31] Jiang M, Zhang C, Cao H, Chan K and Lu A. The role of Chinese medicine in the treatment of chronic diseases in China. Planta Med 2011; 77: 873-881.
[32] Lee DH, Chun EJ, Oh TJ, Kim KM, Moon JH, Choi SH, Park KS, Jang HC and Lim S. Effect of cilostazol, a phosphodiesterase-3 inhibitor, on coronary artery stenosis and plaque characteristics in patients with type 2 diabetes: ESCAPE study. Diabetes Obes Metab 2019; 21: 1409-1418.
[33] Kim SK, Kim G, Choi BH, Ryu D, Ku SK and Kwak MK. Negative correlation of urinary miR-199a-3p level with ameliorating effects of sarpogrelate and cilostazol in hypertensive diabetic nephropathy. Biochem Pharmacol 2021; 184: 114391.
[34] Bhatt DL, Eikelboom JW, Connolly SJ, Steg PG, Anand SS, Verma S, Branch KRH, Probstfield J, Bosch J, Shestakovska O, Szarek M, Maggioni AP, Widimsky P, Avezum A, Diaz R, Lewis BS, Berkowitz SD, Fox KAA, Ryden L and Yusuf S; COMPASS Steering Committee and Investigators. Role of combination antiplatelet and anticoagulation therapy in diabetes mellitus and cardiovascular disease: insights from the COMPASS trial. Circulation 2020; 141: 1841-1854.
[35] Liu Y, Gao Y, Liu H, Chen Q, Ji J and Jia K. Therapeutic effects of triple antiplatelet therapy in elderly female patients with diabetes and acute myocardial infarction. Arq Bras Cardiol 2021; 116: 229-235.
[36] Kalantzi K, Tentolouris N, Melidonis AJ, Papadaki S, Peroulis M, Amantos KA, Andreopoulos G, Bellos GI, Boutel D, Bristianou M, Chrisis D, Dimitsikoglou NA, Doupis J, Georgopoulou C, Gkintikas SA, Iraklianou S, Kanellas K, Kotsa K, Koufakis T, Kouroglou M, Koutsovasilis AG, Lanaras L, Liouri E, Lixouriotis C, Lykoudi A, Mandalaki E, Papageorgiou E, Papanas N, Rigas S, Stamatelatou MI, Triantafyllidis I, Trikkalinou A, Tsouka AN, Zacharopoulou O, Zoupas

C, Tsolakis I and Tselepis AD. Efficacy and safety of adjunctive cilostazol to clopidogrel-treated diabetic patients with symptomatic lower extremity artery disease in the prevention of ischemic vascular events. J Am Heart Assoc 2021; 10: e018184.

[37] Wang Z, Li M, Bi L, Hu X and Wang Y. Traditional chinese medicine in regulating tumor microenvironment. Onco Targets Ther 2024; 17: 313-325.

[38] Zhang J, Meng H, Zhang Y, Zhang X, Shao M, Li C and Tu P. The therapeutical effect of Chinese medicine for the treatment of atherosclerotic coronary heart disease. Curr Pharm Des 2017; 23: 5086-5096.

[39] Zhang HX, Kang Y, Li N, Wang HF, Bao YR, Li YW, Li XZ, Jiang Z and Chen G. Triterpenoids from liquidambar fructus induced cell apoptosis via a PI3K-AKT related signal pathway in SMMC7721 cancer cells. Phytochemistry 2020; 171: 112228.

[40] Zhu Z, Deng X, Xie W, Li H, Li Y and Deng Z. Pharmacological effects of bioactive agents in earthworm extract: a comprehensive review. Animal Model Exp Med 2024; 7: 653-672.

[41] Li WX, Qian P, Guo YT, Gu L, Jurat J, Bai Y and Zhang DF. Myrtenal and beta-caryophyllene oxide screened from Liquidambaris fructus suppress NLRP3 inflammasome components in rheumatoid arthritis. BMC Complement Med Ther 2021; 21: 242.

[42] Song G, Zhuang J and Wang X. Clinical efficacy of Chinese herbal footbath plus traditional Chinese medicine decoction in diabetic peripheral neuropathy. Am J Transl Res 2023; 15: 2911-2917.