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Original Article

Clinical effect and changes of ET-1, FMD and NO levels in the treatment of acute cerebral infarction with acanthopanax injection

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Abstract: Objective: To explore clinical efficacy of acanthopanax injection for the treatment of acute cerebral infarction and its effect on the changes in endothelin-1 (ET-1), flow-mediated vasodilation (FMD) and nitric oxide (NO) levels. Methods: A total of 120 patients with acute cerebral infarction were selected for prospective study. The patients with conventional treatment regimen were the control group while the observation group was treated acanthopanax injection in addition to the treatment given to the control group. Both groups contained 60 patients. After 14 days of treatment, we observed the clinical effects and measured ET-1, NO, FMD, serum C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), National Institute of Health stroke scale (NIHSS), Mini-mental state examination (MMSE) and Montreal Cognitive Assessment (MoCA) in both groups. Results: The total effective rate of the observation group was higher than that of the control group (P=0.020). The improvement of ET-1, FMD, NO, CRP, TNF-α and IL-6 in the observation group was superior to that of the control group (P<0.05). The scores of NIHSS, MMSE and MoCA in the observation group were better than those of the control group (P<0.05). Conclusion: The treatment of acute cerebral infarction with acanthopanax injection may enhance the clinical efficacy, improve vascular endothelial function, reduce inflammation and nerve damage, and improve cognitive function.

Keywords: Acanthopanax injection, acute cerebral infarction, clinical efficacy, endothelin-1, flow-mediated vasodilation, nitric oxide, endothelial function

Introduction

Acute cerebral infarct (ACI) is the stenosis or occlusion of the craniocerebral arteries due to various causes, resulting in insufficient blood supply to the brain, and the occurrence of cerebral tissue ischemia and hypoxia, which ultimately leads to serious damage to the function of the brain [1, 2]. There are approximately 2 million new cases of ACI in China each year, and the annual incidence is on the rise. About 75% of these patients have acute onset, and 30% of ACI patients are elderly [3, 4]. ACI has a high mortality and a disability rate, accounting for approximately 11.4-14.5% of deaths occurring in a year [5, 6]. ACI has become the leading cause of death in China [7]. For the treatment of ACI, the current clinical practice mainly uses the basic therapeutic principles of anticoagulation, thrombolysis, antiplatelet aggregation, and fibrinogen reduction [8]. However, the clinical efficacy was not significantly better after applying the above treatment [9]. According to past research, a series of pathophysiological changes can occur during the development of cerebral infarction, such as the aggravation of oxidative stress, the damage of vascular endothelial cells, the increase of blood viscosity and so on. Various factors are involved in the development of cerebral infarction, resulting in poor clinical efficacy after conventional treatment [10]. Acanthopanax injection is a Chinese patented medicine that benefits the liver, kidneys, and bones. It has anti-inflammatory and anti-tumor properties and improves myocardial ischemia [11-13]. In recent years, studies have found that it also has an effect on ACI treatment and may reduce brain tissue damage [14]. The mechanism of acanthopanax injection for treatment for ACI is not yet clear.

Previous studies have found that the inflammatory response is one of the important pathological alterations of ACI. Inflammation can induce oxidative stress and is also an important factor in promoting thrombosis and exacerbating neurological impairment [15]. Inflammation leads to tissue ischemia and hypoxia, which leads to vascular endothelial damage and accelerates the occurrence of vascular remodeling [16]. Vascular endothelial function damage is the initiating factor leading to vascular remodeling. With the aggravation of vascular endothelial damage, vascular remodeling occurs. Vascular remodeling is the basis for the occurrence of cardiovascular and cerebrovascular diseases, and it is also an important factor to promote its further aggravation [17, 18]. Endothelial function can be reflected by endothelin-1 (ET-1) and nitric oxide (NO) indicators [19]. Flow-mediated vasodilation (FMD) is also an indicator of endothelial function assessed with ultrasound equipment [20]. Studies have found that the use of acanthopanax injection can improve vascular endothelial function in patients with ACI, and inflammatory factors can aggravate endothelial injury [16, 21]. This study further investigated the effect of acanthopanax injection on vascular endothelial function along with its effect on inflammatory factors and cognitive function. This study has provided more clinical evidence for the treatment of ACI with acanthopanax injection.

Materials and methods

Clinical data

This study was approved by the Ethics Committee of The First People's Hospital of Taizhou. A prospective study was performed on 120 patients with ACI admitted to the Department of Neurology in The First People's Hospital of Taizhou from January 2017 to June 2020. According to a random number table, the patients were divided into groups with a conventional treatment regimen that were used as the control group while the observation group was treated acanthopanax injection. Both groups contained 60 patients. The participants or their families included in this study signed an informed consent form.

Inclusion criteria

(1) Patients who met the diagnostic criteria for ACI in 2014 Chinese guidelines for the diagnosis and treatment of acute ischemic stroke [22]. (2) Patients whose age was between 18-76 years; (3) Patients who were diagnosed with ACI at the beginning; (4) Patients with a score of 5-15 in the National Institute of Health stroke scale (NIHSS) upon admission [23]. (5) Patients who had treatment time for ACI within 4.5 hours after onset; (6) Patients with scores of Mini-mental state examination (MMSE) ≥24 points and Montreal Cognitive Assessment (MoCA) <26 points upon admission.

Exclusion criteria

(1) Patients who were allergic to acanthopanax injection drugs; (2) patients who had a history of craniocerebral trauma, epilepsy, or cerebrovascular disease; (3) patients who were unable to cooperate with cognitive function assessment; (4) patients who had combined cardiopulmonary insufficiency; (5) patients who had combination of malignant tumors; (6) patients who had psychiatric disorders affecting cognition; (7) patients who were breastfeeding or pregnant; (8) patients with recent onset of angina or myocardial infarction.

Methods

Control group: The treatment of both groups of patients was based on the ACI treatment plan in the 2014 Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke, which includes monitoring of vital signs, regular oxygen inhalation, monitoring and control of blood pressure, blood sugar, anti-coagulation, thrombolysis, anti-platelet aggregation, the fibrinogen reduction, stable plaque and so on [22].

Observation group: In addition to controlling treatment, the observation group received an intravenous injection of acanthopanax injection (Heilongjiang Baoqinglong Biotechnology Co., Ltd., China) of which the dosage was 400 mg added to normal saline or 250 mL of 5% glucose, given once a day for 14 days.

Outcome measures

Main outcome measures: After treatment, the clinical efficacy was assessed according to NIHSS criteria: categorized as cured, significant improvement, improvement and no change [23]. Efficiency = (recovery + significant improvement + improvement)/total cases * 100%.

At the time of admission and after 14 days of treatment, the patients had 5 mL of venous blood collected in two tubes for each patient at 8 o'clock in the morning. The content of ET-1, inflammatory factors serum C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) were determined by serum ELISA using a fully automatic multifunctional enzyme lab (Thermo, USA). The above kits are all from Shanghai Enzyme Bio Limited Company (China). The content of NO was determined by the micro colorimetric method using a kit from Beijing Solable Technology Co., Ltd., China. FMD was measured using color Doppler ultrasound (Siemens Acuson S3000): the internal diameter of the brachial artery was measured at the end of diastole, and three consecutive measurements were averaged and recorded as D. The patient was then pressurized at the elbow joint for about 300 mmHg for 4 minutes, after which the pressure was quickly relieved. The internal diameter of the brachial artery was measured again at the end of diastole after 15 seconds, and three consecutive measurements were averaged and recorded as E. The formula was calculated as FMD= (E-D)/D * 100%.

Secondary outcome measures: NIHSS standard was used to evaluate the degree of nerve injury before and after treatment. The score ranged from 0 to 42, and the higher the score, the more serious the nerve injury. In this score system, 0-1 points were normal, 2-4 points were mild injury, 5-15 points were moderate injury, 16-20 points were moderate-severe injury, and 21 points or more were severe injury [23].

Before and after treatment, MMSE and MoCA were used for cognitive assessment. The total scores of the MMSE and MoCA scoring systems were both 30 points, the lower the score, the worse the cognitive function [24].

Statistical indicators

SPSS 17.0 statistical software was used for analysis. The continuous variables all conformed to a normal distribution, expressed as mean ± standard deviation ($\bar{x}$ ± sd). The comparison between groups at the same time was conducted by the independent-samples t test, comparison within the group before and after treatment was done with a paired-samples t test. The count data was tested by Pearson's chi-square, and expressed as chi-square. $P< 0.05$ was considered statistically significant.

Results

Comparison of general information

There was 1 case of sudden death in the observation group and 2 patients with myocardial infarction in the control group. A total of 3 patients withdrew from the study. There is no difference between the general information and baseline data of the two groups of patients ($P>0.05$), as shown in **Table 1**.

Comparison of the treatment efficacy

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

Comparison of ET-1, FMD and NO before and after treatment

Compared to the pre-treatment period, the levels of ET-1, FMD and NO were improved in both groups. The degree of improvement was better in the observation group ($P<0.05$), as shown in **Table 3**.

Comparison of inflammatory factors before and after treatment

After treatment, the levels of CRP, TNF-α and IL-6 of the two groups of patients were lower than those before treatment, and the decrease in the observation group was higher than that in the control group ($P<0.05$), as shown in **Table 4**.

Comparison of NIHSS scores before and after treatment

Compared with those before treatment, the NIHSS scores of the two groups of patients decreased after treatment, and the decrease of the observation group was better than that of the control group ($P<0.05$), as shown in **Table 5**.

Comparison of MMSE and MoCA scores before and after treatment

The MMSE and MoCA of the observation group after treatment were significantly improved compared with those before treatment, and the MMSE and MoCA of the observation group

Table 1. Comparison of general information and baseline data

Items	Observation group (n=59)	Control group (n=58)	χ^2/t	P
Gender (Male/Female)	33/26	29/29	0.413	0.520
Age (years)	68.3±7.3	67.8±6.2	0.399	0.691
Education (years)	12.7±3.8	11.9±4.2	1.095	0.276
BMI (kg/m^2)	24.92±3.45	24.78±4.16	0.198	0.843
Time from onset to admission (h)	3.15±0.79	3.22±0.69	0.510	0.611
Stroke site			1.331	0.722
Brain stem	7	5		
Brain lobe	13	10		
Cerebellum	6	9		
Basal ganglia	33	34		
Comorbid disease				
Hyperlipidemia			0.073	0.787
Yes	33	31		
No	26	27		
Hypertension			1.047	0.306
Yes	39	33		
No	20	25		
Coronary heart disease			0.422	0.516
Yes	19	22		
No	40	36		
Obesity			0.698	0.404
Yes	20	24		
No	39	34		
Hyperhomocysteinemia			0.664	0.415
Yes	43	46		
No	16	12		
Hyperuricemia			1.255	0.263
Yes	37	42		
No	22	16		

Note: BMI: body Mass Index.

Table 2. Comparison of the efficacy of the two groups of patients

Items	Observation group (n=59)	Control group (n=58)	χ^2	P
Cured	6 (10.17)	3 (5.17)	8.222	0.042
Significant improvement	28 (47.46)	16 (27.59)		
Improvement	14 (23.73)	17 (29.31)		
No change	11 (18.64)	22 (37.93)		
Total efficiency (%)	48 (81.36)	36 (62.07)	5.373	0.020

were better than the control group after treatment (P<0.05), as shown in **Table 6** and **Figure 1**.

Discussion

Vascular endothelial disorder is the initiating factor of atherosclerosis, and it has a promoting effect on systemic inflammatory factors. After the increase of inflammatory factors, it can aggravate vascular endothelial damage and produce a vicious circle [25]. Vascular endothelial disorders exert a crucial part in the occurrence and development of ACI. Some studies reveal that endothelial cell damage was one of the most important factors to induce ACI [26]. ET-1 can reflect the vascular endothelial contractile function and promote the release of

Table 3. Comparison of ET-1, FMD and NO between two groups of patients before and after treatment

Items	Before treatment		After treatment	
	Observation group (n=59)	Control Group (n=58)	Observation group (n=59)	Control Group (n=58)
ET-1 (pg/L)	9.65±3.46	9.59±3.76	3.76±1.31$^{**,\#\#\#}$	5.66±1.43*
FMD (%)	11.47±2.32	11.76±2.65	5.28±2.44$^{***,\#\#\#}$	8.92±2.69***
NO (mmol/L)	1.78±0.84	1.76±0.89	3.97±1.65$^{***,\#\#\#}$	2.59±1.23***

Note: Before and after treatment in the same group, *P<0.05, **P<0.01, ***P<0.001; compared with the control group after treatment, $^{\#\#\#}$P<0.001. ET-1: endothelin-1; NO: nitric oxide; FMD: flow-mediated vasodilation.

Table 4. Comparison of inflammatory factors between two groups of patients before and after treatment

Items	Before treatment		After treatment	
	Observation group (n=59)	Control Group (n=58)	Observation group (n=59)	Control Group (n=58)
CRP (mg/L)	6.67±1.98	6.82±1.73	4.79±1.55$^{**,\#\#\#}$	5.66±1.49*
TNF-α (μg/mL)	123.92±18.65	123.92±18.21	86.92±14.94$^{***,\#\#\#}$	104.18±16.54***
IL-6 (μg/mL)	351.37±37.02	352.98±37.76	275.23±26.92$^{***,\#\#\#}$	318.92±31.45***

Note: Before and after treatment in the same group, *P<0.05, **P<0.01, ***P<0.001; compared with the control group after treatment, $^{\#\#\#}$P<0.001. CRP: C-reactive protein; TNF-α: tumor necrosis factor-α; IL-6: interleukin-6.

Table 5. Comparison of NIHSS scores of two groups of patients before and after treatment

Items	NIHSS (points)
Before treatment	
Observation group (n=59)	9.5±3.4
Control group (n=58)	9.7±3.6
T	0.309
P	0.758
After treatment	
Observation group (n=59)	4.7±1.4$^{\#}$
Control group (n=58)	5.6±1.6$^{\#}$
T	3.243
P	0.002

Note: $^{\#}$was the same group after treatment compared with before treatment, with statistical difference P<0.05. NIHSS: National Institute of Health stroke scale.

inflammatory factors [27]. Some studies have found a large increase in ET-1 in patients with acute myocardial infarction and high levels of ET-1 are prone to thrombosis in the body [28, 29]. Reduced NO production can lead to endothelial cell damage, and studies have revealed that increasing the NO content in the blood vessel wall is beneficial to improve endothelial function [30, 31]. FMD is an indicator showing the endothelial diastolic function of blood vessels. Its value is relevant to the content of NO in the blood, which can indicate the degree of endothelial cell damage [32, 33]. Previous studies revealed that the use of acanthopanax injection to treat ACI could improve vascular endothelial function [21]. In this study, it was found that treatment with acanthopanax injection reduced ET-1, FMD and increased NO levels, suggesting that acanthopanax injection could reduce endothelial cell damage. Inflammation can increase endothelial cell damage, whereas endothelial cell damage can also promote the production of inflammatory factors, both of which form a vicious circle. Under the mediation of various inflammatory factors, it can induce the oxidative stress response and result in oxidative stress damage for the brain tissue. Previous studies have revealed that monitoring CRP, TNF-α and IL-6 can reflect the degree of neurological damage and brain tissue damage in patients with ACI to a certain extent [34, 35]. Another study illustrated that acanthopanax injection improved cerebral ischemia and perfusion injury in rats. It can improve vascular endothelial function, inhibit inflammation and oxidative stress responses, and reduce tissue cell apoptosis [36]. Acanthopanax polysaccharide can effectively regulate the production of various cytokines by inhibiting the expression of chemokines and adhesion factors, as well as the inhibition of key enzyme activities during the development of inflammation. Thereby it can affect the recruitment, adhesion and exudation of leukocytes to the site of inflammation, and subsequently achieve

Table 6. Comparison of cognitive scores of two groups of patients before and after treatment

Items	MMSE (points)	MoCA (points)
Before treatment		
Observation group (n=59)	25.56±1.24	22.52±1.99
Control group (n=58)	25.41±1.18	22.25±2.38
T	0.670	0.666
P	0.504	0.507
After treatment		
Observation group (n=59)	27.87±0.93#	23.76±2.06#
Control group (n=58)	25.74±1.82	22.25±2.17
T	7.991	3.861
P	<0.001	0.002

Note: #was the comparison before and after treatment within the same group, and statistical difference was P<0.05. MMSE: Mini-mental state examination; MoCA: Montreal Cognitive Assessment.

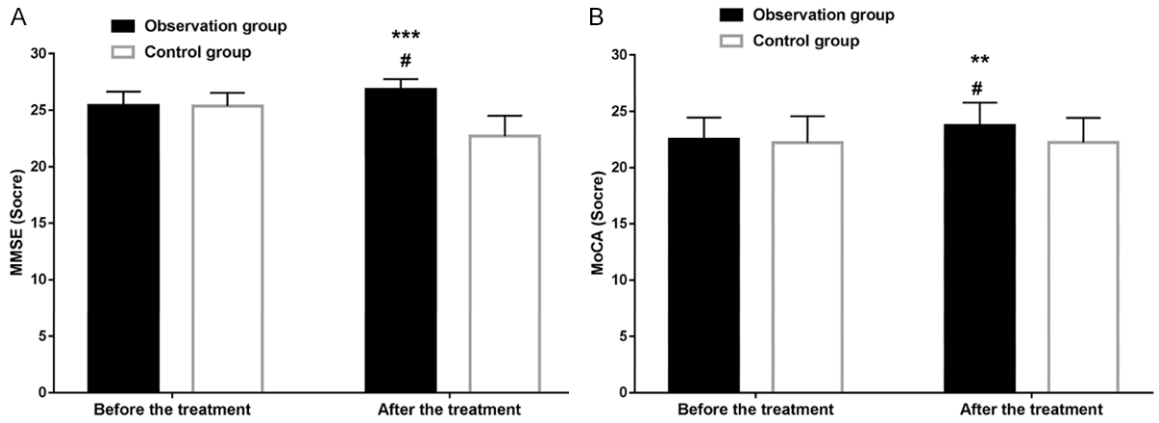

Figure 1. Comparison of cognitive scores after treatment. A. Comparison of MMSE scores; B. Comparison of MoCA scores. MMSE: Mini-mental state examination; MoCA: Montreal Cognitive Assessment. Compared with control group; **P<0.01; ***P<0.001; compared with before treatment, #P<0.05.

anti-inflammatory effects [37, 38]. This study demonstrated that the level of inflammatory factors in ACI patients after treatment with acanthopanax injection is relevant to the anti-inflammatory effect of the drug, while the improvement of endothelial cell function by acanthopanax injection was relevant to the decrease of inflammatory cytokine release. Studies have revealed that acanthopanax injection can alleviate the repair of ischemia-reperfusion tissue, inhibit the production of free radicals, inhibit the oxidation reaction to produce NO, and reduce neurological damage induced by cerebral ischemia and hypoxia. Inflammation and vascular endothelial injury can exasperate the nerve function injury of patients, and the inflammatory factors released by endothelial injury can aggravate endothelial injury and make nerve injury worse [39]. The NIHSS score was quantified by relevant indicators to provide a reliable basis for the degree of neurological impairment [21]. MMSE and MoCA ae common evaluation tools reflecting patients' cognitive function [24]. In the present study, differences were found in the observation group using acanthopanax injection to reduce neurological damage and improve cognitive function compared to the control group, which is consistent with the above findings.

The sample size of this study was small, ant it can be expanded for a multicenter randomized controlled study in future research. In the present study, the efficacy of different doses of acanthopanax injection was not studied, and the observation period was so short, so that other rehabilitation indicators of cerebral infarction could not be observed, thus longer follow-up time is required in further studies.

In summary, the treatment of ACI with acanthopanax injection can improve the clinical efficacy. It can improve vascular endothelial function, relieve inflammation, reduce nerve damage, and improve cognitive function, which is worthy of further clinical application and research.

Disclosure of conflict of interest

None.

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References

[1] Arba F, Inzitari D, Ali M, Warach SJ, Luby M and Lees KR; Imaging Collaboration STIR/VISTA. Small vessel disease and clinical outcomes after IV rt PA treatment. Acta Neurol Scand 2017; 136: 72-77.

[2] GBD 2017 causes of death collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories 1980-2017: a systematic analysis for the global burden of disease study 2017. Lancet 2018; 392: 1736-1788.

[3] Wahlgren N, Moreira T, Michel P, Steiner T, Jansen O, Cognard C, Mattle HP, van Zwam W, Holmin S, Tatlisumak T, Petersson J, Caso V, Hacke W, Mazighi M, Arnold M, Fischer U, Szikora I, Pierot L, Fiehler J, Gralla J, Fazekas F and Lees KR; ESO-KSU, ESO, ESMINT, ESNR and EAN. Mechanical thrombectomy in acute ischemic stroke: consensus statement by ESO-Karolinska Stroke Update 2014/2015, Supported by ESO, ESMINT, ESNR and EAN. Int J Stroke 2016; 11: 134-147.

[4] Juan Didier PG, Edgardo Jorge EV and Martinez HR. Epidemiology of ischemic strokes in elderly. Int J Stroke 2016; 11: NP54.

[5] Teh WL, Abdin E, Vaingankar JA, Seow E, Sagayadevan V, Shafie S, Shahwan S, Zhang YJ, Chong SA, Ng LL and Subramaniam M. Prevalence of stroke, risk factors, disability and care needs in older adults in Singapore: results from the Wi SE study. BMJ Open 2018; 8: e020285.

[6] Gan Y, Wu J, Zhang SC, Li LQ, Yin X, Gong YH, Herath C, Mkandawire N, Zhou YF, Song XY, Zeng XZ, Li WZ, Liu QY, Shu C, Wang ZH and Lu ZX. Prevalence and risk factors associated with stroke in middle-aged and older chinese: a community-based cross-sectional study. Sci Rep 2017; 7: 9501.

[7] GBD 2016 couses of death collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: asystematic analysis for the global burden of disease study 2016. Lancet 2017; 390: 1151-210.

[8] Chen B, Zhang F, Li QY, Gong AH and Lan Q. Protective effect of Ad-VEGF-bone mesenchymal stem cells on cerebral infarction. Turk Neurosurg 2016; 26: 8-15.

[9] Zhang D, Wu JR, Liu S, Zhang XM and Zhang B. Salvianolate injection in the treatment of unstable angina pectoris: a systematic review and meta-analysis. Medicine 2016; 95: e5692.

[10] Wang FJ, He QS, Wang JX, Yuan Q, Guo H, Chai LJ, Wang SX, Hu LM and Zhang Y. Neuroprotective effect of salvianolate lyophilized injection against cerebral ischemia in type1 diabetic rats. BMC Complement Altern Med 2017; 17: 258.

[11] Jin XN, Zou YX, Zhai J, Liu J and Huang B. Refractory mycoplasma pneumoniae pneumonia with concomitant acute cerebral infarction in a child: a case report and literature review. Medicine 2018; 97: e0103.

[12] Hwang E, Kim GW, Song KD, Lee HK and Kim SJ. The enhancing effect of acanthopanax sessiliflorus fruit extract on the antibacterial activity of porcine alveolar 3D4/31 macrophages via nuclear factor Kappa B1 and lipid metabolism regulation. Asian-Australas J Anim Sci 2019; 32: 1776-1788.

[13] Meng QL, Pan JZ, Liu YJ, Chen L and Ren YY. Anti-tumour effects of polysaccharide extracted from acanthopanax senticosus and cell-mediated immunity. Exp Ther Med 2018; 15: 1694-1701.

[14] Wang HQ, Li DL, Du ZY, Huang MT, Cui XX, Lu YJ, Li CY, Woo SL, Conney AH, Zheng X and Zhang K. Antioxidant and anti-inflammatory properties of Chinese Ilicifolius Vegetable (Acanthopanax Trifoliatus (L) Merr) and its reference compounds. Food Sci Biotechnol 2015; 24: 1131-1138.

[15] Atik I, Kozaci N, Beydilli I, Avcı M, Ellidağ H and Keşaplı M. Investigation of oxidant and antioxidant levels in patients with acute stroke in the emergency service. Am J Emerg Med 2016; 34: 2379-2383.

[16] Planas-Rigol E, Terrades-Garcia N, Corbera-Bellalta M, Lozano E, Alba MA, Segarra M, Espígol-Frigolé G, Prieto-González S, Hernández-Rodríguez J, Preciado S, Lavilla R and Cid MC. Endothelin-1 promotes vascular smooth muscle cell migration across the artery wall: Amechanism contributing to vascular remodelling and intimal hyperplasia in giant-cell arteritis. Ann Rheum Dis 2017; 76: 1624-1634.

[17] Xiao L and Tong XY. Advances in molecular mechanism of vascular remodeling in pulmonary arterial hypertension. J Zhejiang Univ (Med Sci) 2019; 48: 102-110.
[18] Mahmoud AD, Ballantyne MD, Miscianinov V, Pinel K, Hung J, Scanlon JP, Iyinikkel J, Kaczynski J, Tavares AS, Bradshaw AC, Mills NL, Newby DE, Caporali A, Gould GW, George SJ, Ulitsky I, Sluimer JC, Rodor J and Baker AH. The human-specific and smooth muscle cell-enriched Lncrna SMILR promotes proliferation by regulating mitotic CENPF mRNA and Drives cell-cycle progression which Can Be targeted to limit vascular remodeling. Circ Res 2019; 125: 535-551.
[19] Su J, An XR, Li Q, Li XX, Cong XD and Xu M. Improvement of vascular dysfunction by argirein through inhibiting endothelial cell apoptosis associated with ET-1/Nox4 signal pathway in diabetic rats. Sci Rep 2018; 8: 12620.
[20] Matsui S, Kajikawa M, Maruhashi T, Hashimoto H, Kihara Y, Chayama K, Goto C, Aibara Y, Yusoff FM, Kishimoto S, Nakashima A, Noma K, Kawaguchi T, Matsumoto T and Higashi Y. New assessment of endothelial function measured by short time flow-mediated vasodilation: comparison with conventional flow-mediated vasodilation measurement. Int J Cardiol 2018; 265: 24-29.
[21] Chen JB, Zheng DR, Wang SY and Kong GH. Effect of Ciwujia injection on endothelial function in patients with acute cerebral infarction. Jiangxi J Tradit Chin Med 2019; 11: 45-47.
[22] Chinese Society of Neurology and Neurology Cerebrovascular Disease Study Group of the Chinese Medical Association. Guidelines for diagnosis and treatment of acute ischemic stroke in China 2014. Chin J Neurol 2015; 48: 246-257.
[23] Lyden P. Using the national institutes of health stroke scale: a cautionary tale. Stroke 2017; 48: 513-519.
[24] Ciesielska N, Sokolowski R, Mazur E, Podhorecka M, Polak-Szabela A and Kędziora-Kornatowska K. Is the montreal cognitive assessment (MoCA) test better suited than the Mini-Mental State Examination (MMSE) in Mild Cognitive Impairment (MCI) detection among people aged over 60? meta-analysis. Psychiatr Pol 2016; 50: 1039-1052.
[25] Godo S and Shimokawa H. Endothelial functions. Arterioscler Thromb Vasc Biol 2017; 37: e108-e114.
[26] Maeshima S, Okamoto S, Okazaki H, Mizuno S, Asano N, Tsunoda T, Maeda H, Masaki M and Sonoda S. Hemorrhagic transformation in patients with cerebral infarction referred to a rehabilitation hospital. Interv Neurol 2015; 4: 69-74.
[27] Mayyas F, Baydoun D, Ibdah R and Ibrahim K. Atorvastatin reduces plasma inflammatory and oxidant biomarkers in patients with risk of atherosclerotic cardiovascular disease. J Cardiovasc Pharmacol Ther 2018; 23: 216-225.
[28] Abdel Rahman MF, Hashad IM, Abou-Aisha K, Abdel Maksoud SM and Gad MZ. Assessment of the link between endothelin K198n Snp, endothelin concentration and acutemyocardial infarction in Egyptians. Clin Exp Pharmacol Physiol 2017; 44: 132-134.
[29] Liu M, Liang T, Zhang PY, Zhang Q, Lu L and Wang ZL. hs CRP and ET-1 Expressions in patients with No-Reflow phenomenon after percutaneous coronary intervention. Pak J Med Sci 2017; 33: 920-925.
[30] Yuyun MF, Ng LL and Ng GA. Endothelial dysfunction, endothelial nitric oxide bioavailabilit, tetrahydrobiopterin, and 5-methyltetrahydrofolate in cardiovascular disease. Where are we with therapy? Microvasc Res 2018; 119: 7-12.
[31] Münzel T and Daiber A. Role of endothelial and macrophage tetrahydrobiopterin in development and progression of atherosclerosis: BH4 puzzle solved? Cardiovasc Res 2018; 114: 1310-1312.
[32] Moreno B, de Faria AP, Ritter AMV, Yugar LBT, Ferreira-Melo SE, Amorim R, Modolo R, Fattori A, Yugar-Toledo JC, Coca A and Moreno H. Glycated hemoglobin correlates with arterial stiffness and endothelial dysfunction in patients with resistant hypertension and uncontrolled diabetes mellitus. J Clin Hypertens (Greenwich) 2018; 20: 910-917.
[33] Kabutoya T, Hoshide S and Kario K. Integrated flow-mediated vasodilation response predicts cardiovascular events in elderly patients with cardiovascular risk factors: the Japan morning surge-home blood pressure study. J Am Soc Hypertens 2018; 12: 340-345, e2.
[34] Chen LL, Yang QH, Ding R, Liu D and Chen ZJ. Carotid thickness and atherosclerotic plaque stability, serum inflammation, serum MMP-2 and MMP-9 were associated with acute cerebral infarction. Exp Ther Med 2018; 16: 5253-5257.
[35] Lu WJ, Zeng LL, Wang Y, Zhang Y, Liang HB, Tu XQ, He JR and Yang GY. Blood micro RNA-15a correlates with IL-6, IGF-1 and acute cerebral ischemia. Curr Neurovasc Res 2018; 15: 63-71.
[36] Chen RH, Wang Q, Li J, Li ZF, Feng YL and Yang SL. Protective effect of acanthopanax senticosus extract on cerebral ischemia-reperfusion injury in rats. Tradit Chin Drug Res Clin Pharmacol 2020; 31: 37-42.
[37] Liu M, Li SS, Wang XX, Zhu YF, Zhang JJ, Liu H and Jia L. Characterization, anti-oxidation and

anti-inflammation of polysaccharides by hypsizygus marmoreus against LPS-induced toxicity on lung. Int J Biol Macromol 2018; 111: 121.
[38] Meng QL, Liu YJ, Cui WY and Pan JZ. Study on anti-inflammatory effect of acanthopanax senticosus polysaccharide. Lishizhen Med Mater Med Res 2019; 30: 2621-2623.
[39] Lorenzen N, Nielsen SB, Yoshimura Y, Vad BS, Andersen CB, Betzer C, Kaspersen JD, Christiansen G, Pedersen JS, Jensen PH, Mulder FAA and Otzen DE. How epigallocatechin gallate can inhibit alpha-synuclein oligomer toxicity in vitro. J Biol Chem 2014; 289: 21299-21310.