Pharmacological effects of *Radix Angelica Sinensis* (*Dang-qui*) on cerebral infarction

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Abstract

Dang-qui, the dried root of Angelica Sinensis, is a Chinese herb used to enrich blood, promote blood circulation, modulate the immune system, as an emollient and laxative for chronic constipation of the aged and debilitated, and treat female menstrual disorders. Dang-gui and its active ingredients had been proved effective on cerebral infarction in many researches. Dang-gui treats cerebral infarction type of stroke is through its anti-arthrosclerosis and anti-hypertension effect to prevent the occurrence of cerebral infarction, and through its anti-platelet aggregation, anti-inflammation and anti-oxidation to reduce cerebral infarction size and improve neurological deficit score. Therefore, Dang-qui is mediated via multiple pathways including anti-atherosclerosis, improving microcirculation, anti-platelet aggregation, anti-inflammatory, and increasing anti-oxidant system activity to improve cerebral infarction.

Key words: Angelica Sinensis (Dang-gui); Angelica polysaccharides; Z-Ligustilide; Ferulic acid; Cerebral infarction.

Review

Background

Dang-Gui, the dried root of *Angelica Sinensis*, is one of most common use Chinese herbs. According to Traditional Chinese medicine recordings, Dang-gui has the action of enrich blood and promoting blood circulation and is used to treat blood deficiency pattern and to treat menstruction disorders such as dysmenorrheal, irregular menstruction cycle [1]. Wilasrusmee et al. (2002) find that Dang-gui (105 μg/ml) increases average [^{3}H] thymidine incorporation counts per minute from 8524.6 to 16007.3 (87%) plays as an immunostimulatory role in mitogen-stimulated murine lymphocytes in vitro [2], and is also as an emollient and laxative for chronic constipation of the aged and debilitated [1]. Angelan is a purified polysaccharide component of Angelica Nakai of Umbelliferae includings Dang-qui. Angelan (100 μg/ml) may increase the expression of cytokines in splenocytes. Angelan may rapidly enhance and maintain thereafter production of interleukin-6 (IL-6) and interferon-γ(IFN-γ) of activated macrophage, helper T cells and natural killer cells, whereas the increase of IL-2 is gradually, and IL-4 increase is affected only a few hrs [3]. The polysaccharide component (AP) of Dang-qui (75 mg/kg) orally at 6 and 1 hr prior to acetaminophen administration may decrease serum alanine transferase (ALT) concentration from 831.6 to 146.6 (U/ml), and also may decrease the concentration of

hepatic malondialdehyde (MDA) in mice with acetaminophern-induced hepatic injury, whereas the AP (50 mg/kg or 75 mg/kg) cannot affect ALT, nitric oxide synthase (NOS) and glutathione concentration in mice or rat with carbon tetrachloride (CCl_4)-induced liver damage [4]. Therefore, AP of Dang-qui is a selective protection to liver.). The crude water-soluble polysaccharide (ASP) component of Dang-qui can be separated into the three main fraction of ASP1 (neutral polysaccharide), and ASP2 and ASP3 (acid polysaccharide). The pretreatment with ASP3 fraction of ASP at 200 mg/kg/day for 7 day may increase peripheral leucocytes counts to 85.7%, and also may increase lymphocytes counts to 99.14% compared to control in 3.0 Gy gamma irradiated mice. In addition, pretreatment with ASP3 at 50 mg/kg, and at 200 mg/kg may produce inhibition rate of peripheral lymphocytes apoptosis is 11.50 and 44.78%, respectively, compared to control at 12 hr after irradiation in mice [5], suggesting that ASP3 component of Dang-qui may modulate apoptosis process and plays a radio-protective effect.

The chemical constituents of the Dang-gui extract are classified into essential oil and water soluble parts, including lipid compounds, phenolic compounds, carbohydrates, organic acids, and other constituents [6]. The most active ingredients are polysaccharides, Z-Ligustilide (3-butylidene-4,5-dihydrophthalide) and ferulic acid (4-hydroxy-3-methoxycinnamicacid). This article aims to provide an overview of

the the effects and mechanisms in how does Dang-gui reduce cerebral infarction size and neurological deficit. We searched the databases including Medline, PubMed, Cochrane Library and Chinese language database namely China National Knowledge Infrastructure between 1990 and 2010, using Angelica Sinensis, Dang-gui, Angelica polysaccharides, Z-Ligustilide, Ferulic acid, and ischemic stroke as keywords.

Pharmacology

Vasodilation and improving microcirculation

Nitric oxide (NO) is synthesized by NOS, and the three different isoforms include endothelial NOS (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS). Although nNOS and eNOS are induced by different condition, their activation needs intracellular Ca2+ for binding calmodulation [7, 8]. eNOS is considered as neuro-protection due to its vasodilative effect [8]. Hypertension and lack endothelium-derived relaxing factor activity is finds in eNOS knockout mice. In addition, the cerebral infarction size is larger in eNOS mutant mice with middle cerebral artery occlusion (MCAo) model. Therefore, eNOS has a vasodilatation effect and increase blood flow plays as neuro-protection [9]. Dang-qui can increase the formation of NO to cause relaxation of endothelium, and it also can mediate the inhibition of calcium influx to cause directly smooth muscle relaxation [10]. Sodium

of ferulic acid can increase the generation of NO to inhibit platelet aggregation of endothelial cells and proliferation of smooth muscle, and also can prevent leucocytes adhesion to endothelium in hyperlipid diet-treated rabbit [11]. Therefore, Dang-qui enhances the generation of NO cause vasodilatation acts a neuroprotection..

Ligustilide (3-butylidene-4,5-dihydrophthalide), a component of Dang-qui, at 4-8 μg/ml may inhibit the spontaneous contraction of isolated rat uterus, and this effect is dose-dependent. In addition, Ligustilide also may inhibit prostaglandin F-2α, oxytocin, acetylcholine chloride, and potassium depolarization-induced uterine contraction, therefore, suggesting that Ligustilide has a modulator function to uterus and plays a non-specific anti-spasmodic effect [12]. Ligustilide can enhance the recovery of conjunctival capillary and venue diameter to 92.4% and 85% of original diameter at 30 min after dextran T500 administration in rabbit, and also can increase the number of opened capillary and can increase blood flow speeds, therefore, suggesting Ligustilide can improve microcirculation [13]. To sum up, Ligustilide can inhibit constriction of smooth muscle and plays an anti-spasmodic effect to enhance blood flow and to improve microcirculation.

Ferulic acid is the main organic acids component of Dang-qui. Ferulic acid (10^{-3} mol/L) can relax phenylephrine-induced contraction of aorta ring in spontaneous hypertension rat (SHR), whereas these effect of ferulic acid can be partially blocked

by removing the endothelium of aorta or by N^G-nitro-L-arginine methyl ester (L-NAME, 10-4 mol/L) pretreatment of the aorta [14]. Ferulic acid (10^{-3} mol/L) can reduce the production of thromboxane B_2 in aorta ring of spontaneous hypertensive rat (SHR) [14]. Ferulic acid (10^{-4} mol/L) also can significantly reduce the generation of NADPH-dependent production of superoxide anion [14], and ferulic acid also can enhance acetylcholine-induced vasodilatation, whereas hydroxyhydroquinone (HHQ) can mediate via superoxide anion inhibit this potentiate effect of ferulic acid [14]. Taken together, the mechanisms of ferulic acid reducing blood pressure in SHR possibly involves to: 1) eNOS; 2) through the inhibition of thromboxane B_2 to relax aorta ring; 3) reactive oxygen species (ROS) scavenging activity to increase the availability of NO in endothelial cell of aorta [14].

Anti-arthrosclerosis effects

Stroke divided into mainly tow type of cerebral infraction and cerebral hemorrhage, and 80% of stroke patient suffer from cerebral infarction [15]. The main cause of cerebral infarction includes thrombosis, embolism or systemic hemodynamic hypotension. Atherosclerotic change of large and small arteries is a major contributor of cerebral thrombosis. The etiology of atherosclerosis and stroke is related to inflammation and genetic factors. Ischemic cerebral infarction may be prevented

through anti-inflammation and treatment for vascular diseases, heart diseases and hypertension [16, 17, 18].

Atherosclerosis is a principal contributor to cerebral infarction, and the development of atherosclerosis is due to initial endothelium and smooth muscle of the arterial wall insult results in an excessive inflammatory-fibro-proliferative response. The process of atherosclerosis involves to a lot of growth factor, cytokine and vaso-regulatory factor such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGH), transforming growth factor-β (TGF-β), interleukin-1 (IL-1) and tumor necrosis factor –α (TNF-α) [19, 20]. Cytokine can play both pro- and anti-athrogenic role , for example, IL-1 and TNF-α can mediate via the production of monocyte chemoattractant protein-1 (MCP-1) to induce monocyte migrates directly into the intima. In contrast, cytokine also can induce a vasodilatory NO to regular vasomotor tone of artery; therefore, cytokine can influence initiation and progression of atherosclerosis process [20]. A study finds that nicotine mediates via the regulation of TGF-β1 and Basic fibroblast growth factor (bFGF) production and release to play a critical role in the development and progression of arteriosclerosis [21] . The reduction of TGB-β signaling cause the atherosclerotic change of vessel wall, and the increase of TGB-β signaling can plays as an athero-protective because the levels of TGF-β reduces in the atherosclerotic sites [22]. A study reports that bFGF in the early

stages of atherosclerosis can mediate via the regulation of interstitial collagenase expression to enhance smooth muscle migration and proliferation [23]. The morphology endothelial cell occurs damage is observed by electro-microscopy, and the levels of TGB-β reduces from 1959 to 1018 optical density, and the levels of bFGF increase from 1256 to 1488 optical density in the hyper-lipidemic serum treated human umbilical vein endothelial cells. Both Dang-qui (20 mg/ml) and its component of sodium ferulate (0.3 mg/ml) can reverse this damage of endothelial cells. Dan-qui can reverse this reduction of TGB-β to 1897, and also can reverse this increase of bFGF to 1120; Sodium ferulate can reverse this reduction of TGB-β to 1938, and also can reverse this increase of bFGF to 903. Taken together, both Dang-qui and its component of sodium ferulate have anti-atherogenic effect [24]. Yu et al.(2000) find that the levels of total cholesterol (TC, 0.95 vs 11.79 mmol/L), triglyceride (TG, 0.87 vs 3.52 mmol/L), high density lipoprotein cholesterol (HDLC, 0.46 vs 1.63 mmol/L) and low density lipoprotein cholesterol (LDLC, 0.52 vs 8.23 mmol/L) increased compared to normal control group in high lipid diet-treated rabbits. The levels of TG decrease to 1.68 mmol/L after 25% Dang-qui intra-venous administration for 4 weeks. The plaque area of thoracic aorta also reduces from 63.31% to 35.58% after Dang-qui treatment. In addition, Dang-qui also can reduce the increase of serum malonyldialdehyde (MDA) levels [25]. Similar study is reported that the plague area

of thoracic aorta is 23.2%, TG is 1.75 mmol/L in the sodium ferulated-treated group. In addition, the sodium ferulated also can increase the reduction of NO production [11]. Therefore, both Dang-qui and its component of sodium ferulate can inhibit the formation of atherosclerosis, and this effect of Dang-qui has relationship to its reducing TG and lipid peroxidation level, or increasing NO.

Anti-platelet aggregation effects

Anti-platelet agent such as Aspirin, Ticlopidine and Clopidogrel had been widely used to the prevention of secondary ischemic stroke [16, 26]. A Multicentre Acute Stroke Trial-Italy reports that administration of aspirin with 6 hrs of ischemic stroke onset can reduce mortality rate [26].

Dang-qui at 200 mg/ml and 500 mg/ml can inhibit ADP-induce rat platelet aggregation, and the inhibition rate is 30 and 75%, respectively. The inhibition rate is 48, 66 and 88%, respectively, in Dang-qui at 200, 300 and 500 mg/ml on collagen-induced rat platelet aggregation. The intravenous administration of Dang-qui 20 g.kg can produced an inhibition rate of 87.9% in ADP-induced platelet aggregation, and inhibition rate of 33.0% in collagen-induced platelet aggregation in rat [27]. Similar effect also is seen in sodium ferulate, intravenous administration of sodium ferulate at 0.2 g/kg can produce an inhibition rate of 38% in ADP-induced platelet

aggregation in rat, and sodium ferulate at 0.1g/kg can produce an inhibition rate of 81% in collagen-induced platelet aggregation [27]. Pretreatment with Z-Ligustilide (10 mg and 40 mg/kg) orally for three days can reduce wet weight of thrombus from 46.4 mg in the control to 19.5 mg and to 13.6 mg in the arteriovenous shunt rat model [28]. The maximal platelet aggregation is 6.8% in the 10 mg/kg group and 2.0% in the 40 mg/kg group (pretreatment with Z-Ligustilide orally three days in rat) are lower than 44.6% in the control group in ADP-induced platelet aggregation ex vivo [28], whereas Z-Ligustilide (10 mg/kg and 40 mg/kg) orally three days cannot like warfarin (1.0 mg/kg, p.o.) affect activated partial thromboplastin time (APTT) and prothrombin time (PT) in coagulation time test ex vivo [28]. To sum up, Dang-qui and its component of Z-Ligustilide have anti-platelet aggregation effect.

Anti-inflammatory effects

The pro-inflammatory cytokine such as IL-1β, TNF-α increase in transient MCAo rats [29, 30], and cytokine IL-1 can up-regular expression of adhesion molecule such as intercellular adhesion molecule-1 (ICAM-1), P-selectins and E-selectins expression in the endothelium [31, 32]. This adhesion molecular can facilitate activated leukocytes into the ischemic core [31, 32]. In addition, nuclear factor-κB (NF-κB) also is activated in the ischemic core [32]. Both the Sophora Japonica L. and paeoniflorin

can reduce cerebral infarction size and neurological deficit. The Sophora Japonica L also can reduce IL-1β [29], and paeoniflorin also can reduce IL-1β, TNF-α, ICAM-1 and leucocytes [30]. Therefore, anti-inflammation such as inhibition of pro-inflammatory cytokine and ICAM-1 plays a critical role in treating cerebral infarction.

Ferulic acid at 80 and at 100 mg/kg iv can reduce cerebral infarction size and neurological deficit, and also can inhibit ICAM-1 and NF-κB expression in transient MCAo rats, therefore, its anti-inflammatory action plays, at least, partly an important role in the therapeutic effect to cerebral infarct [33]. In addition, ferulic acid (100 mg/kg iv) can mediate its anti-inflammation to reduce the generation of 4-hydroxy-2-nonenal (4-HNE), 8-hydroxy-2'-deoxyguanosine (8-OHdG) and apoptosis in the reperfusion period after cerebral ischemia and provide a neuro-protection [32]. This neuro-protection of ferulic acid is through enhancing gamma-aminobutyric acid type B1 ($GABA_{B1}$) receptor expression to against p38 mitogen activated protein kinase (MAPK)-mediated NO-induced apoptosis [34]. Dang-qui reduce inflammatory cells infiltration, and also reduce TNF-α and TGF-ß1 mRNA expression and reduce TNF-α and TGF-ß1 positive cells in radiation-induced pneumonitis in mice [35]. Dang-qui polysaccharides (400 mg/kg and 800 mg/kg) can reduce TNF-α levels in the colon mucosa in intra-colon enema with

2,4,6-trinitrobenzene sulfonic acid (TNBS) and ethanol rat [36]. Taken together, both Dang-qui and its component of ferulic acid have anti-inflammation effect.

Anti-oxidative effects

ROS including superoxide anion, hydrogen peroxide, and hydroxyl radical is generated during the period after cerebral ischemia. These ROS can cause neuronal cells damage because they can affect mitochondria function, DNA repair and transcription factors results in apoptosis after cerebral ischemia [37, 8]. Recurrent studies find that superoxide dismutase 1 (SOD1), an endogenous antioxidant, block the early release of cytochrome c in mitochondria and reduce development of apoptosis in focal cerebral ischemic mice [38], and apolipoprotein E is through its anti-oxidation to against cerebral ischemia plays a neuro-protective effect in transient forebrain ischemia induced by bilateral common carotid artery occlusion (BCCAo) mice [39]. Anti-oxidant nutrients such as vitamin E, Ginkgo biloba extract reduces cerebral damage in rodent model with ischemia and reperfusion [40]. $GABA_B$ receptor agonist baclofen may play a neuro-protection through the inhibition of N-methyl-D-asparate (NMDA) receptor-mediated NO production in brain ischemic injury [41]. Ferulic acid (100 mg/kg iv.) enhances the expression of $GABA_{B1}$ at the reperfusion period of 3 and 24 hr after ischemia [34]. Z-ligustilide

reduces cerebral infarction size from 22.1% to 11.8% at 5 mg/kg i.p, and to 2.60% at 20 mg/kg i.p.. Z-ligustilide also can reduce MDA levels and can increase glutathione peroxidase (GSH-Px) and SOD activities in the ischemia–reperfusion brain tissues induced by BCCAo in mice [42]. To sum up, Dang-qui has anti-oxidation effect.

Effect on Dang-qui on cerebral infarction: basic and clinical study

Liu et al. (2004) reports that Dan-qui (25%, i.v.) has greater improvement in neuro-function scores and Barthel index score than compound salvia (78.7% vs 59.3%) in 1040 patients with acute cerebral infarction [43]. Dang-qui (5 g/kg, i.p.) can increase blood circulation and neuronal metabolism [44], and Dang-qui can reduce cerebral infarction size, neurological deficit, and can increase blood flow and SOD activity in MCAo rat model [45]. Z-ligustilide can reduce cerebral infarction size to 10.90% and 3.19% in 20 m/kg or 80 mg/kg orally, these reduce is greater than in the control that reduce cerebral infarction size to 21.08% in rat with MCAo model [46]. In addition, Z-ligustilide (10 mg/kg or 40 mg/kg orally) also can mediate via increasing choline acetyltransferase activity and inhibiting acetylcholinesterase to improve cognitive function in rats with hypo-perfusion [47]. Ferulic acid (80 mg/kg or 100 mg/kg i.v.) reduces cerebral infarction size and neurological deficit scores had been studied in our previous studies [33]. Taken together, Dang-qui can reduce

cerebral infraction size and also can improve neurological deficit scores; therefore it can be used to cerebral infarction type of stroke.

Conclusion

Dang-qui prevent and treat cerebral infarction is through multiple pathways including anti-arthrosclerosis, improving microcirculation, anti-platelet aggregation, anti-inflammatory and anti-oxidative effects (Table 1).

Abbreviations

IL : interleukin ; IFN-γ : interferon-γ ; AP : the polysaccharide component ; ALT : serum alanine transferase ; MDA : malondialdehyde ; NOS : nitric oxide synthase ; CCL_4 : carbon tetrachloride ; ASP : water-soluble polysaccharide ; NO : nitric oxide ; eNOS : endothelial nitric oxide synthase ; nNOS : neuronal nitric oxide synthase ;iNOS : inducible nitric oxide synthase ; MCAo : middle cerebral artery occlusion ; L-NAME : N^G-nitro-L-arginine methyl ester ; SHR : spontaneous hypertensive rat ; NADPH: nicotinamide adenine dinucleotide phosphate; HHQ : hydroxyhydroquinone ; ROS : reactive oxygen species ; VEGF : vascular endothelial growth factor ; FGH : fibroblast growth factor ; TGF-β: transforming growth factor-β; TNF-α: tumor necrosis factor –α; MCP-1: monocyte chemoattractant protein-1;

bFGF : basic fibroblast growth factor; TC: total cholesterol; TG: triglyceride; HDLC: high density lipoprotein cholesterol; LDLC: low density lipoprotein cholesterol; ADP: adenosine diphosphate; APTT: activated partial thromboplastin time; PT: prothrombin time; ICAM-1: intracellular adhesion molecule-1; NF-κB: nuclear factor-κB; 4-HNE: 4-hydroxy-2-nonenal; 8-OHdG : 8-hydroxy-2'-deoxyguanosine; $GABA_{B1:}$ gamma-aminobutyric acid type B1; MAPK: mitogen activated protein kinase; mRNA: messenger ribonucleic acid; SOD: superoxide dismutase; NMDA: N-methyl-D-asparate; GSH-Px: glutathione peroxidase; BCCAo: bilateral carotid artery occlusion.

Competing interests

The authors declare that they have no competing interests.

Author' contributions

YCW searched the literature, organized the data and wrote the manuscript. CLH analyzed the data and revised the manuscript . Both author authors read and approved the final version of the manuscript.

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Reference:

1. Hou TC. **Herbal extracts**, China Medical Scientific Technological Publishing Company, Beijing 2004, pp. 173-183. In Chinese

2. Wilasrusmee C, Kittur S, Siddiqui J, Bruch D, Wilasrusmee S, Kittur DS. **In Vitro immunomodulatory effects of ten commonly used herbs on murine lymphocytes**. J. Altern. Complement. Med, 2002, 8(4): 467–475.

3. Han SB, Kim YH, Lee CW, Park SM, Lee HY, Ahn KS, et al., **Characteristic immunostimulation by angelan isolated from Angelica gigas Nakai** . Immunopharmacology 1998, 40(1):39-48.

4. Ye YN, Liu ES, Li Y, So HL, Cho CC, Sheng HP, et al., **Protective effect of polysaccharides-enriched fraction from Angelica sinensis on hepatic injury.** Life Sci. 2001, 69:637.

5. Sun Y, Tang J, Gu X and Li D, Int. J. Biol. **Water-soluble polysaccharides from Angelica sinensis (Oliv.) Diels:Preparation, characterization and bioactivity.** Macromol.2005, 36(5):283-289.

6. Huang LF, Li BY, Liang YZ, Guo FQ and Wang YL. **Application of combined approach to analyze the constituents of essential oil from Dong Quai**. Anal. Bioanal. Chemist. 2004, 378(2):510–517.

7. Michel, T., Feron, O.. **Nitric oxide synthases: which, where, how, and why?** The Journal of Clinical Investigation 1997, 100:2146–2152.

8. Chan, P.H. **Reactive oxygen radicals in signaling and damage in the ischemic brain.** J. Cereb. Blood Flow. Metab.2001, 21(1):2–14.

9. Huang PL. **Neuronal and endothelial nitric oxide synthase gene knockout mice.** Braz J Med Biol Res 1999, 32(11):1353-1359.

10. Rhyu MR, Kim JH and Kim EY. **Radix Angelica elicits both nitric oxide–dependent and calcium influx–mediated relaxation in rat aorta.** J Cardiovasc Pharmacol 2005, 46(1):99-104.

11. Wang B, Ouyang J, Liu Y, et al. **Sodium ferulate inhibits atherosclerogenesis in hyperlipidemia rabbits.** J Cardiovasc Pharmacol. 2004, 43(4):549–554.

12. Du J, Bai B, Kuang X, Yu Y, Wang C, Ke Y, et al. **Ligustilide inhibits spontaneous and agonists- or K+ depolarization-induced contraction of rat uterus.** J Ethnopharmacol 2006, 108(1):54–8.

13. Shi LF, Zheng XM, Cai Z and Wu BS. **Comparison of influence of essential oil from Ligusticum chuanxiong Hort. on microcirculation in rabbit conjunctiva bulbar before and after decomposition of ligustilide**. Chin J Pharmcol Toxicol 1995,9:157–8.

14. Suzuki, A.,M. Yamamoto, H. Jokura, A. Fujii, I. Tokimitsu, T. Hase and I. Saito. **Ferulic acid restores endothelium-dependent vasodilation in aortas of spontaneously hypertensive rats.** Am.J.Hyper-tens. 2007, 20: 508–513.

15. Dietl M, Pohle R, Weingärtner M, Polgar R, Grässel E, Schwab S, Kolominsky-Rabas P. **Stroke etiology and long-term need of care in ischemic stroke patients.** Fortschr Neurol Psychiatr 2009, 77(12):714-719.

16. Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P. **Antithrombotic and thrombolytic therapy for ischemic stroke: American college of chest physicians evidence-based clinical practice guidelines.** Chest 8th edition. 2008, 133(6):630S-669S.

17. Mostaza JM, Martín-Jadraque R, Vicente I, San Martin MA, Lahoz C. **Patients at high risk of cerebrovascular disease: the REACH study.** Cerebrovasc Dis 2009, 27(supp1):77-81.

18. Liu LS, Caguioa ES, Park CG, Quek DKL, Saito I, Venketasubramanian N, Wong KSL, Reid JL: **Reducing stroke risk in hypertensive patients: Asian Consensus Conference recommendations.** Int J Stroke 2006, 1(3):150-157.

19. Ross R. **The pathogenesis of atherosclerosis: a perspective for the 1990s**. Nature 1993, 362:801-809.

20. Libby P, Sukhova G, Lee RT, et al. **Cytokines regulate vascular functions related to stability of the atherosclerotic plaque** .Journal of Cardiovascular Pharmacology 1995, 25 (Supp 2) :S9-S12 .

21. Cucina A, Corvino V, Sapienza P, et al. **Nicotine regulates basic fibroblastic growth factor and transforming growth factor beta-l production in endothelial cells.** Biochem Biophys Res Commun 1999, 257(2):306-312 .

22. Grainger DJ. **TGF-β and atherosclerosis in men.** Cardiovascular Research 2007, 74:213-222.

23. Kennedy SH, Rouda S,Q in H, et al. **Basic FGF regulates interstitial collagenase gene expression in human smooth muscle cells.** J Cell Biochem 1997, 65(1):32-41.

24. Wang BH, Ou-Yang JP, Wei L, Liu YM, Zheng HQ and Tu SZ. **Effects of Angel ica and Sodium Ferulate on the Expressions of TGFB1 and bFGF in the Endothelial Cells.** Liaoning Journal of Traditional Chinese Medicine 2001, 28(1):45-47. In Chinese

25. Yu Z, Ou-Yang JP, Liu YM, Zheng HQ, Yang JW, Tu SZ and Yang HL. **The Antiatherogenetic Effect of Angelica in Rabbits Aorta.** Chin J Arterioscler 2000, 8(1):46-48. In Chinese

26. Bednar MM, Gross CE: **Antiplatelet therapy in acute cerebral ischemia.** Stroke 1999, 30(4):887-893.

27. Yin ZZ, Zhang LY and Xu LN. **The effect of Dang-Gui (Angelica Sinensis) and its ingredient ferulic acid on rat platelet aggregation and release of 5-HT.** Acta Pharmaceutica Sinica 1980, 15(6):321-326. In Chinese

28. Zhang L, Du JR, Wang J,Yu DK, Chen YS, He Y and Wang CY: **Z-ligustilide extracted from Radix Angelica Sinensis decreased platelet aggregation induced by ADP ex vivo and arterio-venous shunt thrombosis in vivo in rats.** YAKUGAKU ZASSHI 2009, 127(7):855-859.

29. Lao CJ, Lin JG, Kuo JS, Lee Chao PD, Cheng CY, Tang NY and Hsieh CL. **Microglia, apoptosis and interlukin-1β expression in the effect of Sophora Japonica L. on cerebra; infarct induced by ischemia-reperfusion in rats.** Am. J. Chin. Med. 2005, 33(3):425-438.

30. Tang NY, Liu CH, Hsieh CT and Hsieh CL. **The anti-inflammation effect of Paeoniflorin on cerebral infarction induced by ischemia-reperfusion injury in Sprague-Dawley rats**. Am. J. Chin. Med. 2010, 38(1):51-64.

31. Yang GY, Mao Y, Zhou LF, Gong C, Ge HL and A.L. Betz. **Expression of intercellular adhesion molecule 1 (ICAM-1) is reduced in permanent focal cerebral ischemic mouse brain using an adenoviral vector to induce overexpression of interleukin-1 receptor antagonist.** Mol Brain Res 1999, 65(2): 143–150.

32. Cheng CY, Su SY, Tang NY, Ho TY, Chiang SY and Hsieh CL. **Ferulic acid provides neuroprotection against oxidative stress-related apoptosis after cerebra; ischemia/reperfusion injury by inhibiting ICAM-1 mRNA expression in rats.** Brain research 1209. 2008,136-150.

33. Cheng CY, Ho TY, Lee EJ, Su SY, Tang NY and Hsieh CL. **Ferulic acid reduces cerebral infarct through its antioxidative and anti-inflammatory effects following transient focal cerebral ischemia in rats.** Am J Chin Med 2008, 36(6):1105-1119.

34. Cheng CY, Su SY, Tang NY, Ho TY, Lo WY and Hsieh CL. **Ferulic acid inhibits nitric oxide-induced apoptosis by enhancing GABA $_{B1}$ receptor expression in transient focal cerebral ischemia in rats**. Am. J. Chin. Med. 2010, 31(8):889-899.

35. Xie CH, Zhang MS, Zhou YF, Han G, Cao Z, Zhou FX, Zhang G, Luo ZG, Wu JP, Liu H, Chen J and Zhang WJ. **Chinese medicine Angelica Sinensis suppresses radiation induced expression of TNF-α and TGF-ß1 in mice.** Onco Rep 2006,15:1429-1436.

36. Liu SP, Dong WG, Wu DF, Luo HS and Yu JP. **Protective effect of Angelica Sinensis polysaccharide on experimental immunological colon injury in rat.** World J Gastroenterol 2003, 9(12):2786-2790.

37. Siesjo, B.K. **Pathophysiology and treatment of focal cerebral ischemia Part II: Mechanisms of damage and treatment.** J. Neurosurg.1992, 77(3):337–354.

38. Fujimura M, Morita-Fujimura Y, Noshita N, Sugawara T, Kawase M and Chan PH. **The cytosolic antioxidant copper/zinc-superoside dismutase prevent the early release of mitochondrial cytochrome c in ischemic brain after transient focal cerebral ischemia in mice.** J. Neurosci 2000, 20(8):2817-2824.

39. Kitagawa K, Matsumoto M, Kuwabara K, Takasawa K, Tanaka S, Sasaki T, Matsushita K, Ohtsuki T, Yanagihara T and Hori M, 2002. **Protective effect of apolipoprotein E against ischemic neuronal injury is mediated through antioxidant action.** J. Neurosci. Res. 2002, 68(2):226–232.

40. Katsumi I, Hiroko N and Yukio Y. **Antioxidant nutrients and hypoxia/ischemia brain injury in rodents.** Toxicology 2003,189 (1–2):55–61.

41. Tuttolomondo A, Di Sciacca R, Di Raimondo D, Arnao V, Renda C, Pinto A and Licata G: **Neuron protection as a therapeutic target in acute ischemic stroke.** Curr Top Med Chem 2009, 9(14):1317-1334.

42. Kuang X, Yao Y, Du JR, Liu YX, Wang CY and Qian ZM. **Neuroprotective role of Z-ligustilide against forebrain ischemic injury in ICR mice.** BRAIN RESEARCH, 2006, 1102:145-153.

43. Liu YM, Zhang JJ, Jiang J, et al. **Observation on clinical effect of Angelica injection in treating acute cerebral infarction.** CJITWM 2004, 24(3):205-208. In Chinese

44. Liao WJ, Fan M, Yang YH, Yang WT and Liu ML. **Effects of Angelica sinensis injection on the neuronal metabolites and blood flow speed within reperfusion following the ischemic cerebral injury in rats** .Chin J Appl Physiol 2003, 19(3):209-212. In Chinese

45. Zhao XQ, Ji XM, Shi WJ et al. **Angelica against cerebral ischemia/reperfusion injury.** Chinese journal of coal industry medicine, 2009,12(11):1773-1774. In Chinese

46. Peng HY, Du JR, Zhang GY, Kuang X, Liu YX, Qian ZM, et al. **Neuroprotective effect of Z-ligustilide against permanent focal ischemic damage in rats.** Biol Pharm Bull 2007, 30:309–312.

47. Kuang X, Du JR, Liu YX, Zhang GY and Peng HY. **Postischemic administration of Z-Ligustilide ameliorates cognitive dysfunction and brain damage induced by permanent forebrain ischemia in rats.** Pharmacology, Biochemistry and Behavior, 2008, 88:213–221.

Table 1. Possible pharmacological actions of *Radix Angelica Sinensis* on cerebral infarction

pharmacological actions	**Related components**	**Possible mechanisms**
anti-arthrosclerosis effects	Dang-qui and sodium ferulate	reverse the reduction of TGB-β / reverse the increase of bFGF [24]
	Dang-qui	reduce the increase of serum malonyldialdehyde (MDA) levels [25]
	sodium ferulated	decrease the levels of triglyceride [11]
vasodilatation and improving microcirculation effects	Dang-qui	increase the formation of NO and mediate the inhibition of calcium influx [10]
	sodium ferulate	increase the generation of NO [11]
	Ligustilide	inhibit prostaglandin F-2α, oxytocin, acetylcholine chloride, and potassium depolarization-induced muscle contraction [12]
	Ligustilide	increase the number of opened capillary and the speed of blood flow [13]
	Ferulic acid	enhance acetylcholine-induced vasodilatation and reduce the production of thromboxane B_2 [14]
anti-platelet aggregation effects	Dang-qui and sodium ferulate	inhibit ADP-induced and collagen-induced platelet aggregation [27]
	Z-Ligustilide	inhibit ADP-induced platelet aggregation [28]
anti-inflammatory effects	Ferulic acid	inhibit ICAM-1 and NF-κB expression [33]
	Ferulic acid	enhance gamma-aminobutyric acid type B1 ($GABA_{B1}$) receptor expression [34]
	Dang-qui	reduce TNF-α and TGF-ß1 mRNA expression [35]
	Dang-qui polysaccharides	reduce TNF-α levels [36]
anti-oxidative effects	Ferulic acid	reduce the generation of NADPH-dependent production of superoxide anion [14]

	Ferulic acid	enhances the expression of $GABA_{B1}$ receptor expression [34]
	Z-ligustilide	reduce MDA levels and increase GSH-PX and SOD activities [42]