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The beneficial effects of the herbal medicine Di-huang-yin-zi (DHYZ) on patients with ischemic stroke: A Randomized, Placebo controlled clinical study

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ABSTRACT

Objectives: This study aimed to investigate the safety and therapeutic efficacy of herbal drug, Di Huang Yin Zi (DHYZ), in patients affected by ischemic stroke.
Methods: In this double blind, placebo-controlled study, a total of 100 patients with recent (less than 30 days) ischemic stroke were randomized to receive DHYZ or placebo for 12 weeks. Both groups also received rehabilitation therapy during the study period. As there were 13 dropouts, a total of 45 patients on DHYZ and 42 on placebo were available for analysis. The Fugl-Meyer Assessment (FMA) and Barthel index (BI) were assessed before treatment and at 4-week intervals.
Results: We observed that the FMA score and BI were increased, in both groups at week 4, 8 and 12 compared with the baseline. Furthermore, significantly better FMA score was observed in patients treated with DHYZ at week 8 and 12 (both $P<0.05$). BI was significantly higher in DHYZ group than in placebo group at weeks 12 ($P<0.05$). At week 12, the 95% Confidence Intervals (CI) of mean difference of FMA and BI also indicated that the differences between two groups were statistically significant. Compared to placebo, DHYZ produced significantly greater improvement in FMA grade at week 12 (44.4% versus 23.8%, $\chi^2=4.09$, $P<0.05$).
Conclusions: DHYZ showed good efficacy, safety and tolerability in patients affected by ischemic stroke. We conclude that DHYZ may be a useful therapeutic option in patients with ischemic stroke.
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Contents

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1. Introduction

Stroke is the major cause of disability worldwide, and the high incidence of post-stroke disability brings a heavy burden to patients and their caregivers.[1] This problem might be aggravated greatly in the next two decades due to the aging of population,[2] especially in the developing countries.

Rehabilitation therapy may prevent sequelae or improve functional status after stroke,[3] so patients with stroke are often transferred for rehabilitation when clinically stable. But still approximately 50% of the stroke patients need long-term care even they receive regular rehabilitation therapy.[4] Many patients are dissatisfied with the poor recovery and seek for alternative therapy to improve the physical functions[5] in recent years.

Alternative therapies, including herbal medicine, acupuncture/acupressure, and moxibustion[6] are used by 42–80% of stroke patients in China.[7,8] The chronic symptoms following a stroke such as spasticity, changed muscle tone, motor neuron excitability, and ankle plantar flexor spasticity can be alleviated after acupuncture treatment.[9–13] In Japan, herbal remedies have also been used for post-stroke patients with cold sensation and numbness.[14] However, most alternative medications in stroke treatment are of unproven benefit.[15] For example, neuroAid (MLC601), a traditional Chinese medication was shown to induce neurogenesis and stimulate the development of axonal and dendritic network in an in vitro model.[16] However, a multicenter, double-blind, placebo-controlled experiment with a randomized sample of 1100 patients with ischemic stroke has statistically shown that MLC601 no better than placebo.[17] More experiments are needed to be done to better define the role of an alternative therapy in the treatment of post-stroke patients.

Di-Huang-Yin-Zi (DHYZ) is a traditional Chinese decoction that has been used for neurological disorders since Song Dynasty (approximately 900 years ago). Previous clinical experiment has shown that DHYZ significantly improve neurological function in spinal-cord-injured patients compared to placebo,[18] and thus it may be beneficial for post-stroke rehabilitation. However, there are no reported studies of its use in post-stroke treatment. This double-blind, randomized, placebo-controlled clinical study presented here investigated the efficacy and safety of DHYZ on the recovery of ischemic stroke.

2. Patients and methods

2.1. Study setting

This double-blind, placebo-controlled clinical trial was conducted at the Chang-Guo Hospital of Shandong province, China, between September 2010 and August 2013. The study protocol was approved by the Medical Ethical Committee of Chang-Guo Hospital in conformity with the Declaration of Helsinki and its subsequent amendment.

A total of 100 patients with a recent ischemic stroke were recruited to the study (Fig. 1), and the treatment period lasted 12 weeks. All participants signed an informed consent document before entering the study. Each patient was evaluated by a neurologist specialized in clinical and rehabilitation assessment.

Inclusion criteria for this study were: age between 40 and 72 years, a recent (<30 days) ischemic stroke in anterior cerebral circulation. In addition, CT scan or MRI was applied to confirm diagnosis of ischemic stroke and exclude hemorrhagic stroke.

Exclusion criteria: infarction of the basilar artery system, treatment with thrombolytic, ischemic stroke combined with hemorrhage, a Mini-Mental State Examination score <23, seizure, history of previous stroke, severe aphasia, Severe dysphagia, pneumonia, urinary tract infections, atrial fibrillation, deep vein thrombosis.

2.2. Preparation of DHYZ and placebo

DHYZ is a combination of 13 herbal drugs. The quality of the constituent herbs was in accordance with the standards set out in the Pharmacopoeia of the People's Republic of China, 2000 edition.[19]

The content of known chemical constituents in a tablet of DHYZ derived from 3 g crude herbal mixture was evaluated by high-performance liquid chromatography with electrochemical detection (Table 1). The shelf life of DHYZ is 1 year. The placebo and DHYZ were prepared by Jinan Pharmaceutical (Jinan, Shandong, China) as described by Zhang et al.[20] The water extract of the crude herbal materials was processed as described in the Pharmacopoeia of the People's Republic of China, 2000 edition.[19]

The resulting powder was formed into tablets, each tablet containing 3 g of the crude herbal mixture. The main ingredients of placebo are medical starch, edible caramel pigment (correcting color agent), bitter agent (the flavoring agent), both the placebo and herbal tablets were identical in shape, size, color and taste. Furthermore, to minimize the effect of the distinctive smell of herbal preparations on double blinding, the herbal tablets and placebo were all contained in blister packs made from plastic film and aluminium foil, with six tablets in each blister pack. The packs were distributed to the patients by a physician who was not involved in the study. The study investigators and patients were not aware of the identity of the administered medications.

2.3. Study procedures

A physician who was not involved in patient evaluation performed a computer-generated randomization procedure by using SPSS 15.0 software. The participants, based on the severity of the disease, age, gender were randomly allocated to two different treating groups in a 1:1 ratio.

The DHYZ and placebo treatments were commenced when the patients were transferred to the ward of rehabilitation centre. All patients were treated with rehabilitation under the standard regimen as needed including antiplatelet, liplowering, antihypertensive, and antidiabetic medications. On top of rehabilitation and standard treatment, patients involved in this study received either DHYZ (18 g, twice daily) or placebo (18 g, twice daily) for 12 weeks.

During the study period, patients also received inpatient rehabilitation therapy consisting of 2 h of individual physiotherapy and 2 h of occupational therapy on 6 days each week.

2.4. Patient evaluation

Patients were assessed at baseline and after 4, 8 and 12 weeks' treatment with DHYZ or placebo. The motor function scores of patients were assessed by the Fugl-Meyer assessment (FMA) scale. The maximum score is 66 points for the upper extremity, 34 points for the lower extremity. Patients were categorized into 3 grades according to their baseline FMA score at initiation of this trial: severe (0–50), moderate (50–84), and mild (85–99).[21]

Activities of daily living (ADL), which was scored by Barthel index.[22] (Range 0–100; the higher the score, the greater the independence in ADL), was also assessed. Besides the neurological evaluation, all patients underwent electrocardiogram, blood routine, urine routine, renal function test, liver function test, electrolytes, prothrombin time (PT), and partial thromboplastin time (PTT) at first and every 4 weeks.

Side effects and tolerability were assessed by recording adverse events at each visit. All adverse events – reported, elicited, or observed – were recorded on the case report form, including the

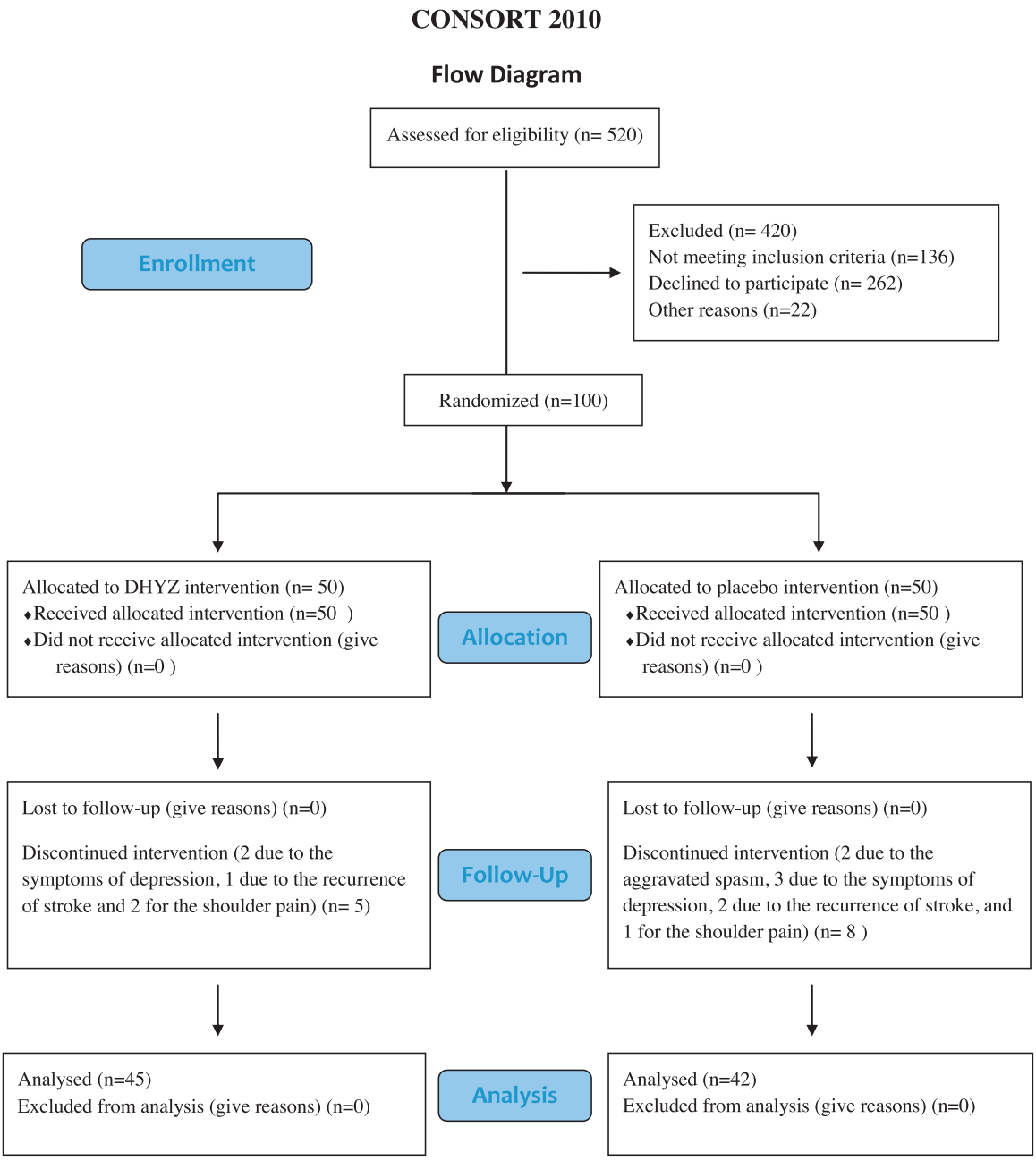

Fig. 1. CONSORT 2010 Flow Diagram.

date and time of onset, duration, severity, relationship to study drug, and action taken.

2.5. Statistical analysis

Results of FMA and BI at each measured point were expressed as the mean ±SD and assessed by the *t*-test; furthermore, if the value zero is excluded from the 95% CI of mean difference (FMA and BI), the results also means that the differences between groups are statistically significant.

The difference in the percentage of patients showing an improved FMA grade was assessed by the X^2-test. A *P*-value of <0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS® software version 15.0 (SPSS Inc., Chicago, IL, USA).

3. Results

As there were 13 dropouts (5 patients in DHYZ group and 8 in placebo group), a total of 45 patients on DHYZ and 42 on placebo were available for analysis (Fig. 1). General baseline characteristics of the patients who complete the trial are shown in Table 2.

No serious side effects were observed, although 6 patients in the DHYZ group complained of nausea for several days, but this side effect disappeared later, and 5 patients in the placebo group reported nausea. The drug-induced nausea was attenuated by massage, and no patient in both groups left the study owing to side effects of medication.

FMA scores at weeks 4, 8 and 12 were significantly higher than at week 0 in both groups (all $P < 0.05$). There were no significant differences in motor scores between the DHYZ and placebo groups at weeks 4; however, the scores at week 8 and 12 were significantly

Table 1
The formulation of DHYZ.

Full scientific name	*Herbal materials*	*%*	*Chemical constituent*	*mg/tablet*
Radix Rehmanniae preparata	Dry root	17	Catalpol	6.2
Radix Aconiti Lateralis Preparata (Zhi-Fuzi)	Dry root	4.3	Aconitine	0.16
Cortex Cinnamomi	Dry bark	4.3	Cinnamic aldehyde	3.1
Radix Ginseng	Dry root	8.5	Ginsenoside	6.6
Fructus Corni	Dry sarcocarp	6.4	Ursolic acid	5.4
Ramulus Loranthi	Dry stem with leaf	8.5	Oleanolic acid	3.8
Poria cocos Wolf	Dry sclerotium	8.5	Pachyman	114.8
Rhizoma Alismatis	Dry root	6.4	Alismol	0.23
Cortex Eucommiae	Dry bark	6.4		
Angelica Sinensis	Dry root	8.5	Ferulic acid	13.8
Radix Ophiopogonis.	Dry root	8.5	Ophiopogonin	18.4
Fructus Schisandrae Chinensis	Dry fruit	10.6	Schizandrin B	1.1
Glycyrrhiza uralensis Fisch	Dry root	2.1	Glycyrrhizic acid	0.53

Table 2
Baseline characteristics of patients with ischemic stroke treated with DHYZ or placebo.

Characteristic	DHYZ (n=45)	Placebo (n=42)
Age, years	60.7±12.2	58.1±10.7
M/F	30/15	28/14
Stroke onset to randomization, days	14.9±5.7	16.8±7.2
Stroke onset to first dose, days	15.9±7.7	17.8±7.2
Previous history of cerebrovascular event		
TIA	3(6.67%)	2 (4.76%)
Ischemic stroke	5 (11.11%)	4(9.52%)
Medical history of:		
Hypertension	36(80%)	32(76.19%)
Diabetes	15(33.33%)	13(30.95%)
Hyperlipidemia	24(53.33%)	20(47.61%)
Myocardial infarction	1(2.22%)	1(2.38%)
Angina cordis	1(2.22%)	2(4.76%)
FMA grade		
Severe(0–50)	18(40%)	13(30.95%)
Moderate(50–84)	27(60%)	29(60.05%)
Baseline FMA score	48.0±12.4	51.0±13.8
Baseline BI	44.1±11.9	46.2±11.4

Data presented as mean ± SD or *n* of patients. DHYZ – Di HuangYi Zi; BI – Barthel Index; FMA – Fugl-Meyer assessment.

higher (both $P < 0.05$) in the DHYZ group than in the placebo group; and the 95% CI of FMA mean difference also indicated that the differences between two groups were statistically significant(Table 3)

BI score increased significantly from baseline values during the treatment period (all $P < 0.05$). In addition, at weeks 12 the scores were significantly higher ($P < 0.05$) in the DHYZ group than in the placebo group; and the 95% CI of BI mean difference between two groups was also statistically significant (Table 4).

At week 12, 20 patients (44.4%) in DHYZ group showed improved FMA grade (12 from grade severe to moderate, and 8 from grade moderate to mild) and 10 patients (23.8%) in the placebo group had improved FMA grades (6 from grade severe to moderate, and 4 from grade moderate to mild); the difference between two groups

Table 3
FMA score of patients with ischemic stroke treated with DHYZ or placebo (mean, the 95% CI of mean and mean difference).

Weeks of treatment	DHYZ (n=45)	Placebo (n=42)	mean difference and 95% CI of mean difference
0	48.0(44.3, 51.7)	51.0(46.7, 55.3)	3.0 (- 1.5, 8.5)
4	56.4(52.7, 60.1)	57.6(53.7, 61.5)	1.2 (- 4.0, 6.4)
8	67.0(63.0, 71.0)	60.0(56.0, 64.0)	7.0 (1.6, 12.4)
12	71.8(67.6, 75.0)	65.3(61.1, 69.5)	6.5 (0.7, 12.3)

At week 8 and 12, the 95% CI of mean differences indicated that the differences between two groups were statistically significant.

Table 4
BI score of patients with ischemic stroke treated with DHYZ or placebo (mean, the 95% CI of mean and mean difference).

Weeks of treatment	DHYZ (n=45)	Placebo (n=42)	mean difference and 95% CI of mean difference
0	44.1(40.5, 47.7)	46.2(42.6, 49.8)	2.1(- 2.8, 7.0)
4	52.0(48.4, 55.6)	55.7(52.5, 58.9)	3.7(- 1.0, 8.4)
8	64.2(60.9, 67.5)	61.9(59.1, 64.7)	2.3(- 1.9, 6.5)
12	74.6(71.6, 77.6)	70.1(66.9, 73.3)	4.5(0.3, 8.7)

At week 12, the 95% CI of mean difference indicated that the difference between two groups was statistically significant.

in the percentage of patients showing an improved FMA grade was statistically significant ($\chi^2 = 4.09$, $P < 0.05$).

There were no significant differences in the results of blood routine, urine routine, liver function, renal function, electrocardiogram, prothrombin time (PT), and partial thromboplastin time (PTT) in both groups of patients before and after treatment.

4. Discussion

The concept of rehabilitation pharmacology proposes that conventional physical, occupational, or speech therapy might be augmented if coupled with pharmacotherapy.[23] In this placebo controlled study, we focused on motor function and ADL to obtain more specific and reliable data, and the results of this study suggest that DHYZ may have a role in rehabilitation of ischemic stroke patients.

4.1. DHYZ may facilitate angiogenesis and increase blood flow in the ischemia region

Angiogenesis is a process wherein new blood vessels are formed, and some insults such as ischemia can induce angiogenesis and vascular remodeling.[24] Through immunohistological analysis and mRNA studies, it was confirmed that angiogenesis was initiated within 48 h after ischemia occurred and last for up to a few weeks in rodent animal model.[25–28]

Radix Ginseng[29] and Angelica Sinensis[30] could facilitate the process of angiogenesis and induce neurogenesis. Radix Ginseng was also observed to suppress the formation of thrombin in blood coagulation.[31] Radix Angelica Sinensis significantly improved cognitive function which was impaired by repetitive cerebral ischemia–reperfusion.[32] Radix Aconiti Lateralis Preparata was reported to have vasodilatory and diuretic effects in patients with left ventricular failure.[33] Cinnamaldehyde, one of the major ingredient in Cortex Cinnamomi, was shown to have the vasorelaxant effects.[34] Radix Rehmanniae Preparata has been reported to improve peripheral microcirculation in various chronic diseases by facilitating blood flowing.[35] Furthermore, its neuroprotective effects against neuronal and cognitive impairments induced by cerebral ischemia were also been confirmed.[36] Poria cocos was proved to have protective effect against brain ischaemia–reperfusion injury.[37]

On the whole, some ingredients of DHYZ may have enhanced angiogenesis, and new blood vessels increased the blood flow in the affected region,[38] thus further improving the exchange of oxygen and stimulated the neurogenesis.

4.2. The inhibitory effects of DHYZ against free radical in the ischemia region

There is strong evidence for the early occurrence of oxygen free radical formation and cell membrane lipid peroxidation in central nervous system injury.[39] Free radicals are regarded to play a role in mediating ischemic neuronal damage, and in particular, reperfusion injury. A somewhat novel therapy to ischemic stroke is the use of free radical quenching agents.[40]

Several herbs in DHYZ have been reported to have inhibitory effects on the generation of oxygen free radicals, including Radix Ginseng,[41] Radix Aconiti Lateralis Preparata,[41] Cortex Cinnamomi,[42–44] Radix Rehmanniae Preparata,[45] Fructus Corni,[46] Poria cocos,[47] Radix Angelica Sinensis[48] and Radix Glycyrrhizae.[48] Furthermore, Fructus Corni has also been found to protect vascular endothelial cells from oxidant injury,[49] while Glycyrrhiza uralensis Fisch has a promising role in the amelioration of ischaemia–reperfusion injury by acting as an antioxidant and oxygen -radical-scavenging agent.[50]

These studies show that some ingredients of DHYZ may be useful for the removal of pathologically produced free radicals associated to the ischemic damage.

4.3. The anti-apoptotic effect of DHYZ in the ischemia region

Apoptosis occurs in days after the stroke and a larger number of apoptotic cells could be identified in the ischemic penumbra.[51] In

the rat model, electro-acupuncture demonstrated to have exerted anti-apoptotic effect on cerebral ischemia–reperfusion injury.[52] Radix Ginseng may exert a protective effect against apoptosis in PC12 neuronal cells.[53]

Poria cocos may protect nerve cells by suppressing apoptosis induced by amyloid β.[54] Radix Angelica Sinensis has a protective effect against cytotoxicity induced by hydrogen peroxide since it improves cellular antioxidant defence and inhibits the mitochondrial apoptotic pathway.[55] Radix Glycyrrhizae has been shown to cause a cytoprotective effect against arsenite-induced cell death by the inhibition of caspase-3.[56] Thus, the therapeutic effect of DHYZ might be associated with an anti-apoptotic mechanism in the ischemic area.

Other ingredients of DHYZ may also be beneficial to patients with ischemic stroke. For example, Ramulus Loranthi was proved to promote the activation of macrophages, suggesting that it may possess the potential to regulate immune responses.[57] Cortex Eucommiae may increase central nervous system excitability in mice.[58] We can infer that DHYZ have protective effect on brain-ischemia-induced damages through the actions of multiple components toward multiple targets.

The major strength of our study is that it is a well-designed study, conducted in a blinded, placebo-controlled manner. Nevertheless, compared to another trial of MLC601, which involved 1100 patients with ischemic stroke and statistically showed that MLC601 was no better than placebo,[17] there are some limitations in this study: (1) it is only a first trial with a relatively low number of subjects (2) it is not a multicenter study. The different components and mechanisms of action of DHYZ may account for the difference in the curative efficacy between DHYZ and MLC601; but, further confirmation of this study in larger studies is still required.

Furthermore, many questions remained to be answered, for instance, what the interactions of DHYZ with other drugs are, how long the duration of treatment should be, and whether it can be used for the patients with hemorrhagic stroke, etc. More clinical trials are needed to be performed to evaluate the safety and efficacy of DHYZ on stroke.

5. Conclusion

Traditional Chinese medicine is widely used in China and other Asian countries; but even in China, many rehabilitation physicians have strong reservations about its benefits and it is not a necessary part of standard rehabilitation. This trial provides evidence that the potential mechanism DHYZ involved with blood flow increasment, anti-apoptotic and anti-free radical in the ischemia region. This study will provide useful information that DHYZ may be an effective adjuvant therapy for patients with ischemic stroke.

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References

1. American Heart Association. 2009 Update at-a-Glance, Heart Disease and Stroke Statistics. Dallas: American Heart Association; 2009: 14-16.
2. Donnan GA, Fisher M, Macleod M, et al. Stroke. *Lancet*. 2008 May 10;371(9624):1612–1623.
3. Chou YC, Liao CC, Su LT, et al. Stroke rehabilitation is associated with a reduction in dementia risk: a population-based retrospective cohort study. *J Rehabil Med*. 2012;44(4):319–324.
4. Woo J, Ho SC, Yu LM, et al. Impact of chronic diseases on functional limitations in elderly Chinese aged 70 years and over: a cross-sectional and longitudinal survey. *J Gerontol A Biol Sci Med Sci*. 1998;53(2):M102–6.
5. Lee GB, Charn TC, Chew ZH, et al. Complementary and alternative medicine use in patients with chronic diseases in primary care is associated with perceived quality of care and cultural beliefs. *Fam Pract*. 2004;21:654–660.
6. Wu B, Liu M, Liu H, et al. Meta-analysis of traditional Chinese patent medicine for ischaemic stroke. *Stroke*. 2007;38:1973–1979.
7. Wei JW, Huang Y. ChinaQUEST Investigatorset et al. Current management of intracerebral haemorrhage in China: a national, multi-centre, hospital register study. *BMC Neurol*. 2011;11:16.
8. Huang Y, Wang JG. ChinaQUEST Investigatorset et al. Age and gender variations in the management of ischaemic stroke in China. *Int J Stroke*. 2010;5:351–359.
9. Wayne PM, Krebs DE, Macklin EA, et al. Acupuncture for upper-extremity rehabilitation in chronic stroke: a randomized sham-controlled study. *Arch Phys Med Rehabil*. 2005;86(12):2248–2255.
10. Mukherjee M, McPeak LK, Redford JB, et al. The effect of electro-acupuncture on spasticity of the wrist joint in chronic stroke survivors. *Arch Phys Med Rehabil*. 2007;88(2):159–166.
11. Zhao JG, Cao CH, Liu CZ, et al. Effect of acupuncture treatment on spastic states of stroke patients. *J Neurol Sci*. 2009;276(1–2):143–147.
12. Park J, White AR, James MA, et al. Acupuncture for subacute stroke rehabilitation: a Sham-controlled, subject- and assessor-blind, randomized trial. *Arch Intern Med*. 2005;165(17):2026–2031.
13. Wei YC, Sun MF, Chang KC, et al. Pilot scheme of health policy in stroke adjuvant acupuncture therapy for acute and subacute ischemic stroke in taiwan. *Evid Based Complement Alternat Med*. 2011;2011:689813.
14. Fujita K, Yamamoto T, Kamezaki T, et al. Efficacy of keishibukuryogan, a traditional Japanese herbal medicine, in treating cold sensation and numbness after stroke: clinical improvement and skin temperature normalization in 22 stroke patients. *Neurol Med Chir (Tokyo)*. 2010;50(1):1–5.
15. Bell IR. Adjunctive care with nutritional, herbal, and homeopathic complementary and alternative medicine modalities in stroke treatment and rehabilitation. *Top Stroke Rehabil*. 2007;14(4):30–39.
16. Heurteaux C, Gandin C, Borsotto M, et al. Neuroprotective and neuroproliferative activities of NeuroAid (MLC601, MLC901), a Chinese medicine, in vitro and in vivo. *Neuropharmacology*. 2010;58(7):987–1001.
17. Chen CL, Young SH, Gan HH, et al. Chinese medicine neuroaid efficacy on stroke recovery: a double-blind, placebo-controlled, randomized study. *Stroke*. 2013;44(8):2093–2100.
18. Li YL, Li LT, Yu M, et al. Beneficial effects of the herbal medicine Di Huang Yin Zi in patients with spinal cord injury: a randomized, placebo-controlled clinical study. *J Int Med Res*. 2012;40(5):1715–1724.
19. State Pharmacopoeia Commission of the People's Republic of China: Pharmacopoeia of the People's Republic of China. Beijing: Chemical Industry Press, 2000.
20. Zhang ZJ, Kang WH, Tan QR, et al. Adjunctive herbal medicine with carbamazepine for bipolar disorders: a double-blind, randomized, placebo-controlled study. *J Psychiatry Res*. 2007;41:360–369.
21. Fugl-Meyer AR. Post-stroke hemiplegia assessment of physical properties. *Scand J Rehabil Med Suppl*. 1980;7:85–93.
22. DeJong G, Branch LG, Corcoran PJ. Independent living outcomes in spinal cord injury: multivariate analyses. *Arch Phys Med Rehabil*. 1984;65(2):66–73.
23. Feeney DM. Rehabilitation pharmacology: noradrenergic enhancement of physical therapy. In: Ginsberg MD, Bogousslavsky J, eds. *Cerebrovascular Disease: Pathophysiology, Diagnosis and Management*. Oxford, UK: Blackwell Science; 1998:620–636.
24. Beck H, Plate KH. Angiogenesis after cerebral ischemia. *Acta Neuropathol*. 2009;117(5):481–496.
25. Arai K, Jin G, Navaratna D, et al. Brain angiogenesis in developmental and pathological processes: neurovascular injury and angiogenic recovery after stroke. *FEBS J*. 2009;276(17):4644–4652.
26. Hayashi T, Noshita N, Sugawara T, et al. Temporal profile of angiogenesis and expression of related genes in the brain after ischemia. *J Cereb Blood Flow Metab*. 2003;23(2):166–180.
27. Marti HJ, Bernaudin M, Bellail A, et al. Hypoxia-induced vascular endothelial growth factor expression precedes neovascularization after cerebral ischemia. *Am J Pathol*. 2000;156(March (3)):965–976.
28. Beck H, Acker T, Wiessner C, et al. Expression of angiopoietin-1, angiopoietin-2, and tie receptors after middle cerebral artery occlusion in the rat. *Am J Pathol*. 2000;157(Nov (5)):1473–1483.
29. Leung KW, Ng HM, Tang MK. Ginsenoside-Rg1 mediates a hypoxia-independent upregulation of hypoxia-inducible factor-1α to promote angiogenesis. *Angiogenesis*. 2011;14(Dec (4)):515–522.
30. Wang H, Zhang Y, Xia T, etc. Synergistic promotion of blood vessel regeneration by astragaloside IV and ferulic acid from electrospun fibrous mats. *Mol Pharm*. 2013;10(6):2394–2403.
31. Nakajima S, Uchiyama Y, Yoshida K, et al. The effects of Ginseng Radix Rubra on human vascular endothelial cells. *Am J Chin Med*. 1998;26:365–373.

32. Lin Z, Yan Y, Zhu D, et al. Protective effects of FBD ?an experimental Chinese traditional medicinal formula on memory dysfunction in mice induced by cerebral ischemia-reperfusion. *J Ethnopharmacol*. 2005;97:477–483.
33. Chen HC, Hsieh MT, Chang SS, et al. Long-termreno-cardiovascular effects of orally administered Aconiti Tuberin humans. *Am J Chin Med*. 1990;18:25–33.
34. Yanaga A, Goto H, Nakagawa T, et al. Cinnamaldehyde induces endotheliumdependent and -independent vasorelaxant action on isolated rat aorta. *Biol Pharm Bull*. 2006;29:2415–2418.
35. Kubo M, Asano T, Shiomoto H, et al. Studies on Rehmanniae Radix. I. Effect of 50% ethanolic extract from steamed and dried Rehmanniae Radix on hemorheology in arthritic and thrombosic rats. *Biol Pharm Bull*. 1994;17:1282–1286.
36. Yun YJ, Lee B, Hahm DH, et al. Neuroprotective effect of Palmul-Chongmyeong-Tang on ischemia-induced learning and memorydeficits in the rat. *Biol Pharm Bull*. 2007;30:337–342.
37. Li TJ, Qiu Y, Mao JQ, et al. Protective effects of Guizhi-Fuling-Capsules on rat brainischemia/reperfusion injury. *J Pharmacol Sci*. 2007;105:34–40.
38. Jiang Q, Zhang ZG, Ding GL. Investigation of neural progenitor cell induced angiogenesis after embolic stroke in rat using MRI. *Neuroimage*. 2005;10:698–707.
39. Demopoulos HB, Flamm ES, Pietronigro DD, et al. The free radical pathology and the microcirculation in the major central nervous system disorders. *Acta Physiol Scand Suppl*. 1980;492:91–119.
40. Green AR, Ashwood T. Free radical trapping as a therapeutic approach to neuroprotection in stroke: experimental and clinical studies with NXY-059 and free radical scavengers. *Curr Drug Targets CNS Neurol Disord*. 2005;4(2):109–118.
41. Zheng SY, Sun J, Zhao X, et al. Protective effect of Shen-Fu on myocardial ischemia-reperfusion injury in rats. *Am J Chin Med*. 2004;32:209–220.
42. Toda S. Inhibitory effects of aromatic herbs on lipid peroxidation and protein oxidative modification of mice brain homogenate by copper in vitro. *Phytother Res*. 2001;15:541–543.
43. Yokozawa T, Chen CP, Tanaka T. Direct scavenging of nitric oxide by traditional crude drugs. *Phytomedicine*. 2000;6:453–463.
44. Shimada Y, Yokoyama K, Goto H, et al. Protective effect of Keishi-bukuryo-gan and its constituent medicinal plants against nitric oxide donor-induced neuronal death in cultured cerebellar granule cells. *Phytomedicine*. 2004;11:404–410.
45. Koo BS, Kim YK, Park KS, et al. Attenuating effect of a traditional Korean formulation, Paeng-Jo-Yeon-Nyeon-Baek-Ja-In-Hwan (PJBH), on hydrogen peroxide-induced injury in PC12 cells. *Phytother Res*. 2004;18:488–493.
46. Peng Q, Wei Z, Lau BH. Fructus Corni enhances endothelial cell antioxidant defenses. *Gen Pharmacol*. 1998;31:221–225.
47. Wu SJ, Ng LT, Lin CC. Antioxidant activities of some common ingredients of traditional Chinese medicine, Angelica sinensis, Lycium barbarumand Poria cocos. *Phytother Res*. 2004;18:1008–1012.
48. Li H, Wang Q. Evaluation of free hydroxy radical scavenging activities of some Chinese herbs by capillary zone electrophoresis with amperometric detection. *Anal Bioanal Chem*. 2004;378:1801–1805.
49. Peng Q, Wei Z, Lau BH. Fructus Corni attenuates oxidative stress in macrophages and endothelial cells. *Am J Chin Med*. 1998;26:291–300.
50. Yokozawa T, Liu ZW, Chen CP. Protective effects of Glycyrrhizae radixextract and its compounds in a renal hypoxia (ischemia)–reoxygenation(reperfusion) model. *Phytomedicine*. 2000;6:439–445.
51. Nagy Z, Simon L, Bori Z. Regulatory mechanisms in focal cerebral ischemia. New possibilities in neuroprotective therapy. *Ideggyogy Sz*. 2002;55(Mar 20 (3–4)):73–85.
52. Xue X, You Y, Tao J, et al. Electro-acupuncture at points of Zusanli and Quchi exerts anti-apoptotic effect through the modulation of PI3K/Akt signaling pathway. *Neurosci Lett*. 2014;558(Jan 13):14–19.
53. Kim EH, Jang MH, Shin MC, et al. Protective effect of aqueous extract of Ginseng radix against 1-methyl-4-phenylpyridinium-induced apoptosis in PC12 cells. *Biol Pharm Bull*. 2003;26:1668–1673.
54. Park YH, Son IH, Kim B, et al. Poria cocoswater extract (PCW) protects PC12 neuronal cells from -amyloid-induced cell death through antioxidant and antiapoptotic functions. *Pharmazie*. 2009;64:760–764.
55. Yu Y, Du JR, Wang CY, et al. Protection against hydrogen peroxide-induced injury by Zligustilide in PC12 cells. *Exp Brain Res*. 2008;184:307–312.
56. Kim SC, Park SJ, Lee JR, et al. Cytoprotective activity of Glycyrrhizae radix extract against arsenite-induced cytotoxicity. *Evid Based Complement Alternat Med*. 2008;5:165–171.
57. Shin HY, Chang IA, Zhang WJ, et al. Immune stimulatory effects of Loranthi ramulus on macrophages through the increase of NO and TNF-α. *Immunopharmacol Immunotoxicol*. 2009;31:370–376.
58. Jian ZH, Chen CC, Lu HY, et al. Effects of Jiawey Siwu on rat activity. *Am J Chin Med*. 2001;29:509–516.