



Research Article

# Application of Tongqiao Huoxue Decoction in the Treatment of Cerebrovascular Disease: A Review

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## Abstract

Tongqiao Huoxue Decoction (TONGQIAO HUOXUE DECOCTION) originated from the book "Medical Forest Correction" written by Wang Qingren in 1830. It is a prescription for activating blood circulation and dispersing stagnation, mainly for the faculties of the head and face. With more than one hundred years of clinical and experimental exploration by Chinese medicine researchers, the connotation of TONGQIAO HUOXUE DECOCTION has been enriched and developed. It can be used to treat many diseases, but it still focuses on head and face related diseases, especially cerebrovascular diseases. By collecting and sorting out the relevant literature on TONGQIAO HUOXUE DECOCTION, we systematically report the latest knowledge about TONGQIAO HUOXUE DECOCTION, mainly including the application of TONGQIAO HUOXUE DECOCTION in the treatment of cerebrovascular diseases and their secondary diseases.

## Introduction

Tongqiao Huoxue Decoction (TONGQIAO HUOXUE DECOCTION) is derived from Wang Qingren's "Medical Forest Correction", which consists of red peony root, peach kernel, safflower, ginger, chuanxiong, musk, green onion, and red dates. Wang believes that it has the effects of activating blood and removing blood stasis, dredging collaterals and relieving pain, and fragrant and resuscitating, which can improve the blood stasis syndrome of the blood vessels of the head, face and limbs. However, with the in-depth understanding of TONGQIAO HUOXUE DECOCTION by Chinese medicine

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researchers, the application of TONGQIAO HUOXUE DECOCTION has become more and more extensive. At present, TONGQIAO HUOXUE DECOCTION has been applied to Ischemic Stroke (IS) [1], Hemorrhagic Stroke (hemorrhagic stroke) [2], Vertebrobasilar artery extension and Dilatation (VBD) [3], Vascular Dementia (VD) [4] and Posterior Circulation Ischemic Vertigo (PCIV) [5] and other diseases. The purpose of this article is to summarize the latest knowledge about TONGQIAO HUOXUE DECOCTION, mainly including the application of TONGQIAO HUOXUE DECOCTION in the treatment of cerebrovascular diseases and their secondary diseases.

## Application of TONGQIAO HUOXUE DECOCTION in Cerebrovascular Diseases

### IS

China is one of the countries with the heaviest stroke burden in the world. The incidence of stroke disease is about 1.6%, of which IS accounts for 21.4% [6]. At present, the treatment of this disease is mainly through intravenous drug thrombolysis, arterial thrombolysis, non-stent mechanical thrombectomy and stent mechanical thrombectomy treatment [7]. Among them, the time of intravenous drug thrombolysis treatment is stricter (3~4.5h in acute cerebrovascular occlusion), and the recanalization rate of large artery occlusion is low, and the treatment effect is relatively poor. The cerebral infarction secondary to acute cerebrovascular occlusion is mostly caused by the formation of a large number of thrombi on the basis of cerebral artery stenosis. Even if the blood vessel is recanalized after simple thrombolysis, it will often leave obvious stenosis and be prone to re-occlusion [8]. And because thrombolytic drugs [9,10] easily cause intracranial hemorrhage, the incidence of intravenous thrombolysis is about 6.4%, and the incidence of arterial thrombolysis is close to 10%, which exacerbates the deterioration of the disease. Therefore, the treatment effect is not particularly ideal. Traditional Chinese medicine believes that the incidence of IS is closely related to blood stasis [11], so the treatment mainly starts with promoting blood circulation and removing blood stasis [12]. Among the 6 traditional Chinese medicine compounds for promoting blood circulation and removing blood stasis, the results of a network meta-analysis [13] show that TONGQIAO HUOXUE DECOCTION and BuyangHuanwu Decoction are effective. Liu Yali et al., [14] found that the improvement of the Montreal Cognitive (MoCA) score and the Ability of Daily Living (ADL) score of patients taking TONGQIAO HUOXUE DECOCTION was significantly better than that of the control group. Han Sufang [15] found that after TONGQIAO HUOXUE DECOCTION treatment, the patient's Nihemorrhagic Stroke S score was significantly lower than that of the control group. HuoQiwen et al., [16] also found that TONGQIAO HUOXUE DECOCTION can effectively reduce the expression of serum Copeptin and BNP and improve the perfusion of the infarct center and nearby tissues. All the above evidences show that TONGQIAO HUOXUE DECOCTION can effectively improve

the symptoms of IS and cerebral ischemia, and this has also been confirmed by evidence-based medicine [1]. Regarding the mechanism of TONGQIAO HUOXUE DECOCTION in the treatment of IS, there are currently several opinions, including inflammation [17], oxidative stress [18], autophagy [17], immunity [17] and apoptosis [17,19] and other functions.

### Hemorrhagic stroke

Hemorrhagic stroke is a disease caused by rupture of blood vessels that penetrates into the brain. It is associated with severe morbidity and high mortality [20]. It can be further divided into Intracerebral Hemorrhage (ICH) and subarachnoid hemorrhage (subarachnoid hemorrhage) [21]. Among them, ICH penetrates into the brain parenchyma, and Subarachnoid Hemorrhage penetrates into the subarachnoid space. There is no name for hemorrhagic stroke in the classics of traditional Chinese medicine. According to its symptoms, it is included in the categories of stroke, seizure syndrome, and true headache. Traditional Chinese medicine believes that the main causes of hemorrhagic stroke are wind, fire, phlegm, qi, blood, stasis, and deficiency. According to the different time of onset, "Chinese Medicine Internal Medicine" [22] divides hemorrhagic stroke into three stages: acute phase, recovery phase and sequelae phase. It is further divided into two categories: the meridian and the viscera for treatment based on syndrome differentiation. According to the order of onset time, Peng Weixian [23] subdivided hemorrhagic stroke into five periods: hyper acute, acute, subacute, recovery and sequelae. According to the pathological changes in each stage, it is proposed that the traditional Chinese medicine for promoting blood circulation and removing blood stasis can be used during the super-acute and acute phases while taking into account the symptoms and signs of the patient.

### Cerebral Hemorrhage (CH)

CH is defined as primary non-traumatic cerebral parenchymal hemorrhage, also known as spontaneous hemorrhage. In recent years, the incidence of CH has gradually increased among the Chinese population, especially among the middle-aged and elderly people [24,25]. CH has always been known for its high fatality rate and high disability rate [26]. In order to save the lives of patients and prevent the occurrence of disability, clinicians are required to deal with them as quickly as possible. Traditional Chinese medicine believes that the onset of CH is closely related to blood stasis, so TONGQIAO HUOXUE DECOCTION treatment is also feasible in this disease. GuohuaXi [27] believes that CH mainly occurs in the arteries, and NieZhiling [28] found that the main pathogenesis of CH is that long-term hypertension causes structural changes in the wall of deep perforating arteries, such as the growth of tiny aneurysms which rupture when blood pressure rises sharply. This indicates that the pathogenesis of hemorrhagic stroke is the change of blood vessel wall, and has nothing to do with the coagulation mechanism. Gao Huijuan et al., [29] observed the hemorheological indexes of 157 patients with CH and found that the indexes were significantly higher than those in the normal control group, suggesting that the blood of patients with CH was in a state of thick, sticky, coagulated and aggregated in the acute phase. Not only that, early studies [30-32] found that both acute CH and new ischemic lesions coexist. These factors lead to the destruction of the blood-brain barrier, cerebral edema, and hydrocephalus [33]. Different from the effects of anti-platelet

aggregation drugs such as aspirin, traditional Chinese medicines that promote blood circulation and remove blood stasis will not induce vascular endothelial cell damage while reducing the level of platelets [34,35]. On the contrary, it may also protect vascular endothelial cells [36,37], such as the peach kernel [38], safflower [39], red peony [40] and other traditional Chinese medicines in TONGQIAO HUOXUE DECOCTION. Therefore, Gao Niuniu [41] believes that Chinese medicine for promoting blood circulation and removing blood stasis can be used reasonably in hemorrhagic stroke. Chen Qingren et al., [42] divided 94 patients with acute CH into TONGQIAO HUOXUE DECOCTION combined with conventional western medicine group and conventional western medicine group. The results showed that the IL-6, TNF- $\alpha$  and Nihemorrhagic stroke S scores of the observation group were significantly lower than those of the control group, ESS score and Barthel index Both were significantly higher than the control group. This result is basically consistent with the result of JinYumei [43]. These evidences suggest that TONGQIAO HUOXUE DECOCTION has the effect of improving the symptoms of patients with CH, and this effect may be related to the reduction of brain inflammation.

### Subarachnoid Hemorrhage

Subarachnoid Hemorrhage is a special subtype of intracranial hemorrhage. It includes two types. One is primary Subarachnoid Hemorrhage, such as aneurysmal subarachnoid hemorrhage [44]. The other is secondary subarachnoid hemorrhage, such as secondary subarachnoid hemorrhage after brain trauma [45]. In general, basal acute subarachnoid hemorrhage is common in cerebral aneurysm rupture, and cortical acute subarachnoid hemorrhage is common in brain trauma [44]. Aneurysm rupture subarachnoid hemorrhage [46] and traumatic subarachnoid hemorrhage [47] are critical and critical illnesses in neurology. Scientists have long believed that cerebral vasospasm is the main cause of delayed nervous system deterioration after aneurysmal subarachnoid hemorrhage [48] and traumatic subarachnoid hemorrhage [49]. Although the essence of subarachnoid hemorrhage and CH is different, the understanding of them in Chinese medicine is the same. Recent studies have found that there is vasospasm in deep cerebral veins after subarachnoid hemorrhage [50]. In addition, subarachnoid hemorrhage can also lead to the formation of micro thrombosis and microvascular stenosis [51-53], which suggests that subarachnoid hemorrhage is likely to be complicated by ischemic events. Therefore, the use of traditional Chinese medicine for promoting blood circulation and removing blood stasis, such as TONGQIAO HUOXUE DECOCTION, is allowed. XiongJiarui et al., [54] found that Tongqiao Huoxue Decoction had a poor prevention and treatment effect on early-onset cerebral vasospasm after subarachnoid hemorrhage, but had a significant effect on delayed-onset cerebral vasospasm ( $P<0.05$ ). And the use of TONGQIAO HUOXUE DECOCTION does not increase the risk of bleeding in patients with subarachnoid hemorrhage [55]. Liu Changya et al., [56] found that the serum carbon monoxide and the mean blood flow Velocity of the Middle Cerebral Artery (VMCA) of the TONGQIAO HUOXUE DECOCTION group were higher than those of the control group, the serum endothelin vascular peptide, Serum Neurospecific Enolase (NSE) and serum Intracellular Adhesion Molecules -1 (ICAM-1) and Serum Interleukin-1 $\beta$  (IL-1 $\beta$ ) were lower than those of the control group, and the above differences were statistically significant ( $P<0.05$ ). This suggests that TONGQIAO HUOXUE DECOCTION can improve the symptoms of patients with

subarachnoid hemorrhage, and this is not only limited to primary subarachnoid hemorrhage, TONGQIAO HUOXUE DECOCTION is also effective for patients with secondary Subarachnoid hemorrhage [57]. The main reason for the onset of TONGQIAO HUOXUE DECOCTION [58] may be related to the relief of vascular spasm.

## Application of TONGQIAO HUOXUE DECOCTION in Secondary Diseases of Cerebrovascular Disease

### Post stroke Vascular Dementia (VD)

According to estimates by the World Health Organization [59], there were approximately 35.6 million people suffering from dementia worldwide in 2012, and this number is expected to triple by 2050. VD is a group of heterogeneous brain diseases, accounting for about 20% of dementia cases [60], and its cognitive impairment is mainly due to cerebrovascular diseases. The CA1 area of the hippocampus is one of the most sensitive areas of cerebral ischemia. It plays a very important role in the storage, consolidation and extraction of information, and is an important part of high-level neural activities such as learning and memory [61]. There is a significant loss of neurons in the CA1 area of the hippocampus after cerebral ischemia, and the loss of neurons in this area is closely related to the changes in the learning and memory ability of patients with VD [62]. This suggests that the ischemia and hypoxia of hippocampal CA1 area caused by cerebral microcirculation is closely related to the occurrence of VD. The 2019 Chinese Guidelines for the Diagnosis and Treatment of Vascular Cognitive Impairment [63] divides the severity of VD into mild vascular cognitive impairment (mild VCI) and severe Vascular Cognitive Impairment (major VCI). Phthalin and nimodipine are included in the recommended list of anti-platelet aggregation and microcirculation drugs. Chinese medicine believes that VD belongs to the category of “Dai Bing” in Chinese medicine, and its disease is located in the brain. “JingyueQuanshu” believes that “everyone who has blood stasis in the heart and brain can also make forgetful”, which shows that blood stasis is closely related to the occurrence of dementia. As a famous prescription for promoting blood circulation and removing blood stasis, TONGQIAO HUOXUE DECOCTION can be used for the treatment of VD. The latest clinical research [64] results show that TONGQIAO HUOXUE DECOCTION can significantly improve the living ability and cognitive function of patient’s with VD, and can significantly reduce blood lipids, Hcy levels and arteriosclerosis. Evidence-based medicine [65] found that TONGQIAO HUOXUE DECOCTION has a certain effect in the treatment of VD, and its effect is related to the course of treatment. Animal experimental studies [66] showed that TONGQIAO HUOXUE DECOCTION can reduce the ratio of LC3II/LC3I and Beclin1 protein in CA1 area of VD rats. TONGQIAO HUOXUE DECOCTION can reduce the content of AchE and increase the content of ChAT in the hippocampus of VD rats [67]. Its regulation of the central cholinergic system may be one of the reasons for promoting the recovery of learning and memory in rats. The therapeutic effect of TONGQIAO HUOXUE DECOCTION on VD rats may be related to the up-regulation of the Ca<sup>2+</sup>/CaMKII/CREB pathway [67]. YQHxD can also significantly increase the content of cAMP and PKA in the serum of VD rats [68], significantly reduce the apoptosis rate of neurons in the hippocampal CA1 area, and increase the end-field excitatory postsynaptic potential 1h after hippocampal High Frequency Stimulation (HFS) (fEPSP) [69]. These studies have provided clinical evidence for TONGQIAO HUOXUE DECOCTION treatment of VD.

### Post-Stroke Depression (PSD)

PSD is one of the most common complications of cerebrovascular disease. The main manifestations are depression, loss of interest, loss of appetite, fatigue, slow thinking, pessimism and despair after stroke, and even suicide attempts and behaviors [70]. In recent years, the incidence of PSD has increased year by year. A large sample study conducted in Italy [71] indicates that the incidence of PSD is about 36%, and the incidence of mild depression is about 80%. Related studies conducted in China have found that the incidence of PSD in patients is about 41.8% [72]. The specific pathogenesis of PSD is currently unclear. The main theories include elevated monoamine system [73], abnormal Hypothalamus-Pituitary-Adrenal (HPA) axis [74], rupture of the prefrontal-subcortical circuit [75], neuroplasticity and the neurotransmission of glutamate [76] and excess pro-inflammatory cytokines [77]. However, Chinese medicine’s understanding of PSD is not that complicated. Chinese medicine believes that PSD belongs to the category of “stagnation syndrome” and the pathogenesis is qi stagnation and blood stasis. The location of the disease is often in the brain and kidney [78] and the disease is mostly based on deficiency and excess. Among them, qi stagnation and blood stasis are the basic pathogenesis of the disease. Based on the three aspects of blood stasis, heart, and brain, TONGQIAO HUOXUE DECOCTION exactly corresponds to the pathogenesis of PSD, so TONGQIAO HUOXUE DECOCTION can be used in the treatment of this disease. A clinical trial conducted by Chu Caiyun [79] found that TONGQIAO HUOXUE DECOCTION can significantly improve the HAMD score of PSD patients, and its effect is better than that of fluoxetine hydrochloride (Prozac) group, which is consistent with the results of Liu Wei [80] and Zhang Yunxing [81]. Zhan Cuiqin et al., [82] found that in addition to significantly reducing BRMS and HAMD scores, TONGQIAO HUOXUE DECOCTION can also affect patients’ serum interleukin-4 (IL-4), interleukin-1 $\beta$  (IL-1 $\beta$ ) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) all had a significant effect. Kang et al., [83] found that increased levels of IL-6 and IL-18 after stroke are associated with depression. A systematic review carried out in 14 years [84] proved that anti-inflammatory treatment can reduce the symptoms of depression. These evidences suggest that the treatment of PSD by TONGQIAO HUOXUE DECOCTION may be related to anti-inflammatory response. Animal experiments [78] found that after high-dose TONGQIAO HUOXUE DECOCTION treatment, the Brain-Derived Neurotrophic Factor (BDNF) count in the hippocampal dentate gyrus of rats was higher than that in the model group (P<0.05). It is suggested that the effect of TONGQIAO HUOXUE DECOCTION on the expression of BDNF in the hippocampal dentate gyrus may be one of the factors that can improve the behavior of PSD rats.

### Others

In addition to the diseases mentioned above, TONGQIAO HUOXUE DECOCTION can also have a beneficial effect on other diseases. Such as stasis headache [85], sudden deafness [86], type 2 diabetes [87], diabetic optic neuropathy [88], oral lichen planus [89] and other diseases.

### Discussion

Although there are many studies confirming the therapeutic role of TONGQIAO HUOXUE DECOCTION in diseases, these studies have obvious limitations. 1 at present, the research of TONGQIAO

HUOXUE DECOCTION is mainly concentrated in the field of vascular diseases, and the number of studies on other diseases is relatively small. 2 The research of TONGQIAO HUOXUE DECOCTION is mainly based on clinical research, and the number of experimental studies on the treatment mechanism is limited. This makes the mechanism of TONGQIAO HUOXUE DECOCTION treatment not clearly understood, and ultimately directly affects the secondary development of TONGQIAO HUOXUE DECOCTION. 3 TONGQIAO HUOXUE DECOCTION related clinical studies are of poor quality. These studies have basically never used blinding (including single-blind and double-blind) and lack of multi-center joint and double-blind randomized controlled trials to verify. 4 TONGQIAO HUOXUE DECOCTION -related clinical research includes fewer indicators for evaluation, and some include more subjective evaluation indicators (such as efficiency indicators), which is not conducive to a more comprehensive and objective evaluation of its efficacy. 5 TONGQIAO HUOXUE DECOCTION related research is mainly published in Chinese. Up to now, CNKI database (<https://www.cnki.net/>), has published 872 articles related to TONGQIAO HUOXUE DECOCTION, but PubMed database (<https://pubmed.ncbi.nlm.nih.gov/>) there are only 4 items. This suggests that the TONGQIAO HUOXUE DECOCTION research may have language publication bias. 6 TONGQIAO HUOXUE DECOCTION -related studies rarely mention adverse events, and it is impossible to evaluate the safety of TONGQIAO HUOXUE DECOCTION in the treatment process. Therefore, the treatment of TONGQIAO HUOXUE DECOCTION on cerebrovascular diseases needs more rigorous clinical research to verify. In addition, more detailed research on effective mechanisms must be carried out in a timely and effective manner.

## Disclosure

No conflicts of interest in this work.

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