

# Yangxue qingnao granule in the treatment of cerebral circulation insufficiency and cognitive impairment

## Abstract

Yangxue Qingnao Granule (YXQN), an herbal medicine formula that is composed of eleven herbal extracts based on “Traditional Principles for Constructing Herbal Medicinal Formulae” of Traditional Chinese Medicine, has been extensively used in clinical practice for treatment of various headaches, such as migraine, tension headache, hypertension-related headache, dizziness and insomnia due to chronic cerebral circulation insufficiency. It is also used in patients with vascular cognitive impairment (VCI) or vascular dementia (VD) in order to improve their cognition. Recently, its effect in Alzheimer’s disease (AD) has also been reported. This review is to provide scientists comprehensive knowledge in YXQN’s effect in the treatment of cerebral circulation insufficiency and cognitive impairment evidenced by animal and clinical studies, and hopefully to stimulate more research on its application.

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## Introduction

Cerebral circulation insufficiency is one of the most common risk factors of dementia. Dementia is a syndrome that has manifestation of deterioration in memory, thinking, behavior and the ability to perform everyday activities, which are collectively called cognitive impairment. Worldwide, 35.6million people were reported to have dementia in 2012, and there were 7.7million new cases reported every year. Therefore dementia is deemed one of the most expensive medical condition with no effective treatment options.<sup>1</sup>

Yangxue Qingnao Granule (YXQN), also known as Cerebralcare Granule, is an herbal medicine formula that consists of eleven herbal extracts developed upon the “Traditional Principles for Constructing Herbal Medicinal Formulae” of Traditional Chinese Medicine. The formula is composed of the following herbs: *Angelica sinensis* (Oliv.) Diels (Dang Gui), *Ligusticum chuanxiong* Hort. (Chuan Xiong), *Paeonia lactiflora* Pall (Bai Shao), *Uncaria sinensis* (Oliv.) Havil. (Gou Teng), *Spatholobus suberectus* Dunn (Ji Xue Teng), *Prunella vulgaris* L. (Xia Ku Cao), *Hyriopsis cumingii* (Zhen Zhu Mu), *Rehmannia glutinosa* Libosch (Di Huang), *Cassia tora* L. (Jue Ming Zi), *Corydalis yanhusuo* W.T.Wang (Yan Hu Suo), *Asarum sieboldii* Miquel (Xi Xin). It has been extensively used in clinical practice for treatment of various disorders resulted from chronic cerebral circulation insufficiency.<sup>2-13</sup> It also has been used in treatment of various headaches, dizziness and insomnia,<sup>9</sup> and in patients with vascular cognitive impairment (VCI) or vascular dementia (VD)<sup>14-15</sup> in order to improve their cognitive impairment. Recently, its effect on Alzheimer’s disease (AD)<sup>16</sup> has also been reported. This review provides the summary of YXQN’s mechanism and application in managing patients with chronic cerebral circulation insufficiency and cognitive impairment.

## Cerebral circulation insufficiency and cognitive impairment

### Cerebral blood supply and cognitive impairment

Vascular dementia, the second most common type of dementia, characterized by brain damage resulted from reduced or blocked

blood flow in blood vessels leading to the brain, accounts for 20-30% of dementia.<sup>1,17,18</sup> A growing number of experts prefer the term vascular cognitive impairment (VCI) over vascular dementia (VD) because the former suggests that vascular thinking changes could have various levels of severity, ranging from mild to severe.<sup>18</sup> Vascular dementia (VD) and Alzheimer’s disease (AD) were once believed to have separate pathological mechanisms, however a growing number of recent studies suggested that both diseases shared the common risk factors and pathological changes, indicating vascular factors may contribute to not only VD but also neurodegenerative cognitive impairment including AD.<sup>19-20</sup>

One of the vascular risk factors in dementia is cerebral hypoperfusion. Subjects diagnosed subcortical ischemic vascular dementia (SIVD) and AD showed marked cerebral blood flow (CBF) reduction in the frontal and parietal cortices.<sup>21</sup> And decrease of CBF was seen, compared to normal control, in those patients with mild cognitive impairment (MCI) who later converted to AD after 2years of clinical follow-up, suggesting CBF might be of predictive value in the detection of AD.<sup>22</sup> Although the underlying mechanism of how hypoperfusion influences the pathogenesis of AD remains unclear, a growing number of evidence implicated that oxidative stress might be pivotal in linking hypo perfusion and pathological alteration in AD.<sup>23</sup> Multiple studies have confirmed that oxidative stress correlated with the severity of cerebral hypoperfusion, especially in vulnerable brain regions such as cerebral cortex and hippocampus.<sup>24-26</sup> In addition, a few experimental studies have demonstrated the effect of anti-oxidants in treatment of cognitive deficits and brain damage in animal models of cerebral hypoperfusion,<sup>27-29</sup> which support the causal relationship between oxidative stress and cognitive deficits.

### Dysfunction of cholinergic system and cognitive impairment

Acetylcholine (Ach) is known as a neurotransmitter involved in learning, memory, judgment, and concentration process. Ample evidences have revealed that reduction of cholinergic transmission is related to the pathology of AD and VCI. The cholinergic theory was first initiated based on the finding of the loss of cholinergic nerves in brain tissue of AD patients.<sup>30</sup> Animal study in stroke-prone spontaneously-

hypertensive rats reported a significantly reduced level of cholinergic markers including acetylcholine in the hippocampus, neocortex, and cerebrospinal fluid that appears to correlate with impaired learning and memory.<sup>31</sup> Afterward, more experimental studies indicated that blocked central cholinergic activity may reproduce memory deficits in human and the deficits were reversed by treating with cholinergic agonist.<sup>32</sup> Autopsy in patients with VCI has also shown significantly reduced choline acetyl-transferase activity in the brain.<sup>31</sup> Based on the cholinergic depletion theory, clinical trials have been conducted on three cholinesterase inhibitor (ChEIs), donepezil, rivastigmine and galantamine to explore their effect on AD. It was reported that all three medications remarkably slowed the progress of cognitive impairment while no significant difference among three drugs has been observed.<sup>33,34</sup> Thus the three aforementioned ChEIs have been approved to be used as symptomatic treatment for mild to moderate AD and VCI. While upon research, ChEIs demonstrated statistically significant efficacy in improving subjects' symptoms with the benefit described as "modest" at best,<sup>23</sup> meta-analysis on randomized clinical trials involving these three ChEIs in the treatment of vascular dementia showed significantly increased risks of adverse events associated with the ChEIs.<sup>35,36</sup> Several trials have exhibited increased morbidity associated with donepezil and galantamine, respectively, which suggested poor safety profiles of ChEIs. In addition, it was reported that some of the subjects did not respond to ChEIs.<sup>37</sup>

## Studies on YXQN

### YXQN and ischemia-reperfusion (I/R) injury

It has long been noted that the reperfusion following ischemia could exacerbate the cellular and tissue injury initiated by ischemia and the phenomenon was termed ischemia-reperfusion injury. It is generally believed that leukocytes play a pivotal role in the development of reperfusion injury. Shortly after disruption of blood flow, neutrophils were accumulated in the reperfusion sites along with red blood cells and platelets which may occlude capillaries and lead to persistent ischemia.<sup>38,39</sup> The potential mechanism of leukocytes infiltration mainly consists of three major steps: firstly leukocytes (primarily neutrophils) roll on the endothelium (facilitated by endothelial P-selectin upregulation resulted from the increase in free radicals generated during ischemia and reperfusion); secondly leukocytes adhere to the endothelium (facilitated by leukocyte  $\beta 2$  integrins CD11a/CD18 and CD11b/CD18 with endothelial intercellular adhesion molecule 1 (ICAM-1); thirdly leukocytes transigrate into parenchyma (facilitated by platelet-endothelial cell adhesion molecule-1 (PECAM-1)).<sup>40</sup> Neutrophils release various chemical mediators including reactive oxygen species (ROS), leukotrienes, and prostaglandins, etc., causing increase of vascular permeability, breakdown of blood brain barrier (BBB) and subsequent albumin leakage and vasogenic edema. Study also suggested that patients subjected to ischemia/reperfusion injury who manifested BBB disturbance had poorer clinical outcome than patients who had unaffected BBB<sup>41</sup> and the secondary edema remarkably resulted in death in patients within first few days of stroke.<sup>42</sup>

YXQN successfully reduced leukocyte adhesion on cerebral venular wall, DHR (indicator of oxidative stress) formed in the venule and albumin leakage from the venule after reperfusion in Mongolian gerbil.<sup>43</sup> The study found that ischemia led to dramatic morphologic alteration as well as significant reduction of neuron cells in the CA1 region of the hippocampus, while YXQN alleviated such effect by reducing the adhesion of leukocytes on cerebral wall, therefore alleviates I/R-elicited cerebral injury, which is associated

with inhibition of leukocytes adhesion and oxidative stress in micro vessels, and interference of hippocampal CA1 neuron apoptosis pathways. The antioxidant effect might be related to the six herbs in the formula of YXQN that possess antioxidant property.

Huang P et al.,<sup>44</sup> have specifically investigated the therapeutic effect of YXQN in the treatment of BBB disruption associated with ischemia/reperfusion injury in rats. Temporary occlusion of middle cerebral artery has been adopted to reproduce condition of cerebral ischemia in rat model. It was observed that I/R significantly reduced CBF while YXQN attenuated the decrease to a marked extent. Moreover YXQN evidently ameliorated the alteration in cerebral microvasculature after I/R and restored the decrease in the number of open capillaries elicited by I/R. Claudin-5, occludin, JAM-1 and ZO-1 were the important proteins that involve in tight junction, the type of pathway being impaired during BBB disruption.<sup>45-48</sup> Study indicated that degradation of claudin-5, occludin, JAM-1 and ZO-1 were significantly restored after the treatment with YXQN. YXQN may significantly reduce the caveolae, a key mediator involving in transcytosis of albumin in capillary endothelial cells which was increased after I/R. The study suggested that YXQN presents the protective effect on BBB integrity through both inter-endothelial and trans-endothelial pathways.<sup>44</sup>

### YXQN and chronic cerebrovascular insufficiency

Chronic cerebrovascular insufficiency (CCI) is defined as insufficient blood flow to the brain with abnormalities of the cerebral function and decline of overall well-being, a syndrome that clinically manifests as vertigo, head heaviness, and limb numbness, with fluctuation of severity from time to time, but void of any signs of focal neurological system.

The effect of YXQN on cerebral blood flow was studied in rat models with occlusion of the carotid artery.<sup>49</sup> Dynamic cerebral blood flow was monitored using biological microscope in rats before and after the treatment of YXQN. The study showed that YXQN treatment can significantly restore the cerebral blood flow. Xiong et al.<sup>50</sup> investigated the effects of YXQN on memory loss and cholinergic dysfunction by comparing it with Rivastigmine, a ChEI, in hope of understanding its pharmaceutical mechanism. In the study, cerebral hypoperfusion was induced by introducing permanent occlusion on bilateral common carotid arteries (2-vessel occlusion, 2-VO) in rats in all groups except sham operation group. After 4-week YXQN treatment, Morris water maze test was given to all groups. It was observed that rats in 2-VO model group exhibited significant elongation of escape latency and shortening of time spent in quadrant 1 indicating impaired spatial learning ability. The groups treated with both YXQN and rivastigmine showed significant improvement in learning and memory. No significant difference was observed between groups of YXQN and rivastigmine. Neuron apoptosis in hippocampus and frontal cortex lobes was increased after occlusion of carotid arteries, and YXQN treatment demonstrated reversible effect while rivastigmine group did not (no difference from control group). Moreover total anti-oxidative capability (T-AOC) decreased in all groups, indicating increased oxidative stress in affected tissue, while YXQN treatment exhibited reduced oxidative stress. Additionally AchE and ChAT activities were both impaired in both hippocampus and frontal lobe cortex in all groups. It was reported YXQN ameliorate the reduction in ChAT while rivastigmine significantly reverse the loss of AchE activity. This study suggested that YXQN may has neuroprotective effect during hypoperfusion and the mechanism of memory improvement might be associated with the improvement of

ChAT activity and preservation of neuron cells. Similar results were generated in another study too.<sup>51</sup> By using. Hence the mechanism of YXQN's effect on cholinergic transmission need further studies to elucidate. Gu et al.,<sup>2</sup> employed the similar 2-VO model the similar 2-VO rat models, YXQN's effect in improvement of spatial learning and memory, amelioration of apoptosis of hippocampal neurons and oxidative stress in hippocampal tissue were confirmed. An increase in AchE in hippocampus in YXQN treatment group was also observed and successfully reproduced impaired spatial learning ability in models (manifested as prolonged vertigo incubation period in assessment of Y maze test). The result showed YXQN treatment significantly attenuated the deficit. In a ischemia/reperfusion model in rats, Tao T et al.,<sup>52</sup> observed increased expressions of nuclear factor- $\kappa$ Bp65 (NF- $\kappa$ Bp65), interleukin-6 (IL-6) and decrease of neurofilament protein-200 (NF-200, a neurofilament protein supports the structure in axons; its increase reflects the regeneration of axons) in cortex. The expression of all factors was markedly attenuated in the group treated with YXQN granule. This indicated that YXQN granule has inhibitive effect on neuro-inflammation following I/R injury as well as neuroprotective effect in promoting axon regeneration.

A large body of literature reported that treating CCI subjects with YXQN granule or YXQN granule plus a co-administering chemical drug (drugs of vasodilatation effect such as calcium channel blocker nimodipine or flunarizine, etc.) for 2 to 12 weeks led to marked improvement in vertigo scale score (1), relief of headache and/or dizziness (2-7), improvement in cognitive assessment scores (2), increase in blood flow in internal carotid artery, vertebral artery and basilar artery (3-5) and decrease in hemorheological index (plasma viscosity, hematocrit, red blood cell aggregation index, fibrinogen etc.) (2-4), total cholesterol and triglyceride (2-3), and marked improvement in sleep disorder associated with CCI (7-9), as compared to placebo group or chemical drug monotherapy group. In general the co-administration of YXQN and calcium channel blocker was able to yield better benefit as compared to calcium channel blocker alone. The therapeutic effect could be potentially attributed to the improvement of cerebral blood circulation. It was revealed by some studies that increase of blood viscosity and fibrinogen were closely correlated with the decrease in cerebral blood flow. The elevation of blood viscosity also increases the resistance to flow, subsequently deteriorating the cerebral blood flow and increasing the risk of ischemic cardiovascular event (10-11). Thus it is reasonable to believe that YXQN does have benefit in improving cerebral blood flow and is of preventative value for potential ischemic damage due to hypoperfusion. Clinical study also indicated that YXQN can significantly increase the concentration of NO and Calcitonin Gene-Related Peptide (CGRP) and decrease that of endothelin (ET), therefore improves endothelial function (12).

### YXQN and vascular cognitive impairment

The therapeutic effect of YXQN in vascular cognitive impairment are limited. Liu N et al.,<sup>14</sup> have investigated the efficacy of YXQN in treatment of subjects with mild vascular cognition impairment. Cognitive deficits were assessed by mini-mental state examination (MMSE) and memory quotient (MQ) before and after treatment. After 16 weeks treatment with YXQN, subjects demonstrated significant improvement in memory, recall and calculation abilities.

Fu Q<sup>15</sup> conducted a clinical research in 421 subjects with vascular cognitive impairment. Cognitive deficits were assessed by MMSE and Montreal Cognitive Assessment (MoCA) whereas functional status was assessed by Activities of Daily Living (ADL) before and after treatment. After 3-month treatment with YXQN, MMSE scores

showed significant increase in scores of memory, attention and recall, and MoCA showed markedly increased total score, scores of naming, delayed recall, and attention. Total score of ADL was also decreased. This study also indicated that YXQN may benefit patients with vascular cognitive impairment.

### YXQN and Alzheimer's disease

Alzheimer's disease is currently the most devastating progressive neurodegenerative disorder that causes cognitive impairment and contributes to 60-70% of dementia.<sup>16-17</sup> Although massive effort has been devoted to the investigation of its etiology, the underlying mechanism still remains unraveled. Alzheimer's disease is characterized by two major neuropathologic alterations – formation of amyloid plaque and neurofibrillary tangles.

A series of recent studies have been conducted to investigate the effect and mechanism of YXQN in treatment of Alzheimer's disease in APP<sup>swe</sup>/PSEN1<sup>dE9</sup> transgenic mice.<sup>15</sup> One study treated transgenic mice with YXQN continuously for 2 months, and conducted Y maze test when mice reached age of 6 months. The group treated with YXQN exhibited better accuracy and memory than the two groups treated with saline and Donepezil (cholinesterase inhibitor), respectively.<sup>15</sup> At age of 6 months, it was observed that transgenic mice developed obvious A $\beta$  plaques in frontal cortex and hippocampus. Treatment with YXQN markedly reduced the total amount and area of A $\beta$  plaques as compared to group treated with saline. It is known that the abnormal proteolytic processing of amyloid precursor protein (APP) leading to an increased A $\beta$ 42/A $\beta$ 40 ratio is a central step in the pathogenesis of Alzheimer's disease (AD) and ADAM10 is an alpha-secretase which can cleave APP into soluble peptide sAPP $\alpha$ , a substance that inhibits the production of A $\beta$ .<sup>53</sup> The study showed a low level of expression of ADAM10 in group treated with saline. Group treated with YXQN and group treated with Donepezil all exhibited increase in expression of ADAM10, with YXQN group showed significant difference as compared to Donepezil group. This study suggested that YXQN presented an effect in improvement of learning memory, inhibition of pathological accumulation of A $\beta$  protein, and the effect might be related to its stimulation in increase of alpha-secretase. Considering the Primary Cerebral Blood Flow Deficiency showed close relation with Alzheimer's disease.<sup>54</sup> and YXQN's effect in improving cerebral blood flow and cognitive impairment as evidenced by aforementioned studies, it's extrapolated that YXQN may benefit the patients with AD as well.

### Future Investigation

Current studies indicate the value of YXQN in cerebral circulation insufficiency, vascular cognitive impairment and dementia; well designed basic and clinical studies may be needed to confirm its mechanism and role in the prevention and improvement of several neurological diseases, such as Alzheimer's disease, Dementia and/or other causes of brain injury (traumatic brain injury, TBI) and blood flow insufficiency.

### Conclusion

Decreased/blocked cerebral blood supply is one of the most common risk factors for cognitive impairment and dementia, including both vascular and neurodegenerative dementia such as Alzheimer's disease. Studies have indicated that YXQN may improve cerebral microcirculation, enhance endothelial function, and protect the integrity of BBB. Its clinical applications provide promising results that suggest YXQN's positive effect in negating cognitive

impairment in patients with cerebral circulation insufficiency and dementia, although further clinical studies may be needed.

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## Conflicts of interest

Author declares there are no conflicts of interest.

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