Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

YangXue QingNao

Evidence Summary

YXQN improves cerebral blood flow in people with chronic cerebral circulation insufficiency. A phase 2 clinical trial is ongoing in Alzheimer's disease patients.

Neuroprotective Benefit: YXQN improves cerebral blood flow and decreases blood viscosity in people with CCCI. Preclinical studies have shown anti-oxidative, anti-inflammatory, and anti-apoptotic effects. A phase 2 study in AD is ongoing.

Aging and related health concerns: YXQN appears to improve blood flow in people with cardiovascular diseases and reduce blood pressure in people with hypertension. However, rigorously designed large clinical trials with long follow-up are lacking.

Safety: Adverse events are typically mild, including nausea, vomiting, and gastrointestinal symptoms. Some people find the bitter taste to be intolerable.

Availability: available in China and through online vendors	**Dose**: Clinical studies have typically tested a dose of 4 grams taken 3 times daily, orally.	**Chemical formula:** N/A **MW**: N/A
Half-life: not documented	**BBB**: not documented	
Clinical trials: A 2020 meta-analysis included 31 RCTs with a total of 2,877 patients with chronic cerebral circulation insufficiency.	**Observational studies**: none available	

What is it?

Yangxue Qingnao (YXQN) is a type of Chinese traditional medicine that aims to "tonify blood and clear liver heat". It is believed to promote blood circulation, nourish the liver and blood, and decrease blood stasis (Guo et al., 2019). YXQN was approved by the Chinese health authorities in 1997 and has been used to treat headache, insomnia, vertigo, and dizziness due to blood deficiency and excessive 'liver yang' (Wu et al., 2013). It is also used for the treatment of chronic cerebral circulation insufficiency (CCCI), a condition in which there is chronic reduction in cerebral blood flow. YXQN granules are composed of 11 herbs: Radix angelicae sinensis (Dang Gui), 6.76%; Rhizoma chuanxiong (Chuan Xiong), 6.76%; Radix paeoniae alba (Bai Shao), 5.41%; Ramulus uncariae cum uncis (Gou Teng), 13.51%; Caulis spatholobi (Ji Xue Teng), 13.51%; Spica prunellae (Xia Ku Cao), 13.51%; Concha margaritifera usta (Zhen Zhu Mu), 13.51%; Radix rehmanniae preparata (Di Huang), 5.41%; Semen cassiae (Jue Ming Zi), 13.51%; Rhizoma corydalis yanhusuo (Yan Hu Suo), 6.76%; and Herba asari (Xi Xin), 1.35% (Pan et al., 2013). At least 6 chemicals derived from these herbs exhibit antioxidant activities, inhibit neutrophil adhesion to endothelial cells, and decrease tissue damage. YXQN has also been tested in people with hypertension and Parkinson's disease (Wang et al., 2013; Pan et al., 2013).

Neuroprotective Benefit: YXQN improves cerebral blood flow and decreases blood viscosity in people with CCCI. Preclinical studies have shown anti-oxidative, anti-inflammatory, and anti-apoptotic effects. A phase 2 study in AD is ongoing.

Types of evidence:

- 3 meta-analyses (2 in people with chronic cerebral circulation insufficiency, 1 in Parkinson's disease patients)
- 2 double-blind randomized controlled clinical trials (1 in patients with chronic cerebral circulation insufficiency and 1 in Parkinson's disease patients)
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

Chronic cerebral circulation insufficiency (CCCI) is a condition with a complex etiology in which there is persistent reduction in cerebral blood flow, and is considered to be associated with the occurrence or recurrence of ischemic stroke, vascular cognitive impairment, and development of vascular dementia (reviewed in Zhou et al., 2018 and Calabrese et al., 2016). Causes of CCCI include intracranial stenosis, hypertension, arteriosclerosis, hyperlipidemia, and diabetes. Reduction in cerebral blood flow can lead to neuronal damage and symptoms such as dizziness, headache, memory disorder, insomnia, and others. Changes in blood viscosity is thought to be one of the pathological mechanisms of CCCI. In a meta-analysis of 31 randomized controlled trials including a total of 2,877 patients with CCCI, YXQN treatment (ranging for 14 days to 3 months) resulted in- significantly higher efficacy in symptom improvement compared to control (RR=1.21; 95% CI, 1.17 to 1.26)(Jia et al., 2020). The combined mean difference in transcranial Doppler detecting carotid artery, vertebral artery, and basilar artery blood flows were 8.84 (95% CI, 5.83 to 11.85), 4.72 (95% CI, 3.71 to 5.73), and 3.89 (95% CI, 3.03 to 4.76), respectively, suggesting improved blood flow in the brain. The combined mean difference in plasma viscosity and fibrinogen were -0.35 (95% CI, -0.40 to -0.30) and -0.81 (95% CI, -1.12 to -0.50), respectively, suggesting reduction in blood viscosity. All studies included in this meta-analysis were conducted in China and all the patients were Chinese, so it is not known if these findings would also apply to people of other races and ethnicities. The authors also noted that the quality of studies included in the meta-analysis was not very high, so future rigorously designed trials are needed to validate these findings.

In an older meta-analysis of 15 randomized controlled trials including a total of 1,211 CCCI patients, YXQN treatment (4 grams, 3 times daily, orally) plus routine treatment was more effective in increasing blood flow velocity in the basilar artery (mean difference=3.34 based on 4 studies; p<0.00001), vertebral artery (mean difference=3.21 based on 3 studies; p=0.02), and internal carotid artery (mean difference=7.46 based on 2 studies, p=0.007), compared to nimodipine plus routine treatment (Guo et al., 2019). YXQN treatment plus routine treatment was also superior in improving symptoms such as headache, dizziness, and insomnia, compared to nimodipine plus routine treatment (p<0.00001), flunarizine plus routine treatment (p=0.01), troxerutin plus routine treatment (p<0.0001), and routine treatment alone (p=0.01). However, the authors commented that the clinical trials included in the meta-analysis had small sample sizes and were poor quality, so a definitive conclusion cannot be made on the efficacy or safety of YXQN.

In a double-blind randomized controlled trial (not included in the above meta-analyses) of 273 patients with CCCI, YXQN treatment (4 g, 3 times daily, orally; Tianjin Tianshili Pharmaceutical Co., Ltd.) for 8 weeks significantly improved symptoms (e.g., headache, heavy-headed feeling, dizziness, and sleep disorder) and the effects were similar to nimodipine treatment (10 mg, 3 times daily, orally)(Wu et al., 2013). This study was partly funded byTianjin Tianshili Pharmaceutical Co., Ltd.

Human research to suggest benefits to patients with dementia:

In a double-blind randomized controlled trial of 61 patients with Parkinson's disease, YXQN treatment (4 g, 3 times daily, orally) while maintaining anti-PD medications for 12 weeks improved evening activity, diurnal activity, and the Parkinson's disease sleep scale (PDSS)(Pan et al., 2013). The YXQN group also experienced better unified Parkinson's disease rating scale (UPDRS) at the end of the intervention compared to the placebo group, but there were no significant changes compared with baseline in either group. Thus, it is possible that the slight improvement in UPDRS with YXQN treatment may be due to changes in sleep rather than improvement in motor function.

In a meta-analysis of 10 studies examining the efficacies of various treatments for daytime sleepiness and sleep disorders in Parkinson's disease patients, the authors concluded that there is insufficient evidence to support or refute the efficacy of any interventions and further studies are warranted (Rodrigues et al., 2016). In this meta-analysis, 3 studies tested modafinil, 1 tested melatonin, 1 tested pergolide, 1 tested eszopiclone, 1 tested rivastigmine, 1 tested caffeine, 1 tested doxepin, and 1 tested YXQN.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

In a network pharmacology study, YXQN was shown to promote cerebral blood flow velocity by regulating platelet aggregation and the vasoconstriction/relaxation signal pathway, mechanisms and targets that are distinct from Western drugs used for Alzheimer's disease (donepezil, galantamine, rivastigmine, memantine, etc.) (Zhang et al., 2022). Gene ontology analysis showed that targets of YXQN were enriched in biological processes including inhibition of apoptosis, inflammatory response, aging, and positive regulation of nitric oxide biosynthesis process. Molecular targets included PI3K-Akt signaling, insulin resistance, and TNF signaling pathway. A tissue enrichment analysis showed that targets of YXQN were significantly enriched in the blood, liver, pancreas, and adipose tissue, but not in the brain. Thus, any neuroprotective benefit of YXQN may be achieved through the periphery and not directly through the brain. Based on a pathway analysis, YXQN may promote Aβ degradation in the liver by modulating glucose and lipid metabolism via the adiponectin-dependent pathway, RXR/PPAR-dependent lipid metabolism signal pathway, and the fatty acid synthase activity signal pathway. To verify these associations, the authors showed that YXQN promoted Aβ degradation in hepatic stellate cells, while memantine (NMDA receptor antagonist, treatment for Alzheimer's) showed no effects.

In a mouse model of Alzheimer's disease (APP/PS1 mice), YXQN treatment (0.69, 2.08, or 6.24 g/kg) for 2 months improved cognitive function (measured by the Morris water maze and Y-maze tests) and reduced amyloid plaques in the hippocampus and cortex by 47-72% (Wang et al., 2017). At the high dose of YXQN (6.24 g/kg), cognitive performance approached that of wild-type mice. YXQN treatment shifted APP processing from amyloidogenic to non-amyloidogenic pathway by enhancing sAPPα levels.

In a rat model of chronic cerebral hypoperfusion (by permanent occlusion of the bilateral common carotid arteries), YXQN treatment (2 or 4 g/kg/day, orally) for 4 weeks significantly improved learning and memory (measured by the Morris water maze) and reduced apoptosis in the hippocampus and cortex (Xiong et al., 2011). There were concomitant increases in total antioxidant capacity and choline acetyltransferase activity (important for acetylcholine production).

In rat model of CCI, YXQN treatment improved learning and memory measured by the Y-maze test and decreased a measure of vertigo+ (Gu et al., 2005).

In spontaneously hypertensive rats, YXQN treatment (0.5 g/kg/day, orally) for 4 weeks increased cerebral blood flow and decreased albumin leakage, brain water content, perivascular edema, and neuronal apoptosis in the hippocampus and cortex (Jiao et al., 2019). YXQN restored tight junction

proteins (protecting the blood-brain barrier), mitochondrial complex I, II, and V, upregulated caveolin-1, and inhibited Src/MLCK/MLC signaling, which is important for blood-brain barrier modulation.

In aged LDLR (+/-) golden Syrian hamsters, a model of hyperlipidemia, YXQN treatment improved cognitive function (measured by Y-maze task) while attenuating albumin leakage in the middle cerebral artery, decreasing neuronal damage in the hippocampus, and increasing cerebral blood flow (Gu et al., 2018). YXQN treatment also led to restoration of tight junction proteins (claudin-5, occluding, and ZO-1). YXQN treatment had no effects on plasma total cholesterol, triglycerides, LDL-C, and HDL-C. Thus, YXQN treatment exerts neuroprotective action through the protection of the blood-brain barrier and upregulation of tight junction proteins.

APOE4 interactions: Unknown.

Aging and related health concerns: YXQN appears to improve blood flow in people with cardiovascular diseases and reduce blood pressure in people with hypertension. However, rigorously designed large clinical trials with long follow-up are lacking.

Types of evidence:

- 2 meta-analyses, 1 in essential hypertension and 1 in cardiovascular diseases
- A few laboratory studies

In a meta-analysis of 30 clinical studies including a total of 2,784 patients with cardiovascular diseases, YXQN treatment significantly improved clinical efficacy, and increased blood flow velocity in the basilar artery, vertebral artery, anterior cerebral artery, middle cerebral artery, and posterior cerebral artery (Zhang et al., 2022). Though this meta-analysis was not clear on the precise definition of cardiovascular diseases and the inclusion criteria of clinical trials for meta-analysis.

YXQN is a widely used adjunctive treatment for essential hypertension in Chinese clinical practice (Wang et al., 2013). In a meta-analysis of 12 randomized controlled trials in essential hypertension, YXQN treatment (4 g, 3 times daily, orally) combined with antihypertensive drugs for 2-12 weeks decreased systolic blood pressure by 7.31 mmHg (95% CI, -11.75 to -2.87; p=0.001) and diastolic blood pressure by 5.21 mmHg (95% CI, -8.19 to -2.24; p=0.0006) compared to antihypertensive drugs alone (Wang et al., 2013). However, the methodological quality of the trials was evaluated as generally low and there was

likely a publication bias. Larger and longer clinical trials with rigorous double-blind, randomized, placebo-controlled designs are needed to validate these findings.

Safety: Adverse events are typically mild, including nausea, vomiting, and gastrointestinal symptoms. Some people find the bitter taste to be intolerable.

Types of evidence:

- 3 meta-analyses
- 2 randomized controlled clinical trials

In a meta-analysis of 31 randomized controlled trials including a total of 2,877 patients with CCCI, slight nausea and vomiting were reported with YXQN treatment in 2 of the studies, while 13 studies reported there were no significant adverse effects with YXQN; the remaining 16 studies did not include information on adverse events (Jia et al., 2020).

In an older meta-analysis of 15 randomized controlled trials including a total of 1,211 CCCI patients, 10 trials mentioned adverse events but only 1 trial described adverse events associated with YXQN treatment (4 grams, 3 times daily, orally) plus routine treatment, which included mild nausea, vomiting, and gastrointestinal reactions (Guo et al., 2019). However, these adverse events were tolerated after adding gastric mucosa-protective medications. Five trials indicated that there were no adverse events during the duration of the studies.

In a double-blind randomized controlled trial (not included in the above meta-analyses) of 273 patients with CCCI, YXQN treatment (4 g, 3 times daily, orally; Tianjin Tianshili Pharmaceutical Co., Ltd.) for 8 weeks resulted in a low incidence of adverse events (8.57%; 12 out of 140 subjects; nimodipine group had 6.02%; 8 out of 133 subjects) (Wu et al., 2013). Adverse events with YXQN treatment were mild to moderate in intensity, were transient, and resolved without the need to discontinue the study medication. The adverse events most commonly reported were those affecting the digestive system (n=4) and the nervous system (n=5). No clinically meaningful changes from baseline were observed in vital signs, physical examination findings, clinical chemistry, hematology, or urinalysis in either treatment groups.

In a double-blind randomized controlled trial of 61 patients with Parkinson's disease, YXQN treatment (4 g, 3 times daily, orally) while maintaining anti-PD medications for 12 weeks did not result in any serious

adverse events or treatment-related adverse events (Pan et al., 2013). However, 5 participants in the YXQN group withdrew from the study for drug-related reasons: 3 subjects could not tolerate the bitter taste and 2 subjects experienced nausea. In the placebo group, 4 participants dropped out: 2 subjects dropped out due to inefficacy, 1 dropped out due to inability to tolerate the bitter taste of placebo, and 1 dropped out due to conflict with other prescribed medications.

Drug interactions: Drug interactions have not been well studied or documented.

Sources and dosing:

YXQN is a type of Chinese traditional medicine approved by the Chinese health authorities to treat headache, insomnia, vertigo, and dizziness due to blood deficiency and excessive 'liver yang' (Wu et al., 2013). Clinical studies have typically tested a dose of 4 grams taken 3 times daily, orally.

Research underway:

There is a phase 2 efficacy and safety study testing Yangxue Qingnao treatment (5.0 or 7.5 grams, twice daily) in mild to moderate Alzheimer's patients (NCT04780399). This study is a double-blind randomized controlled study aiming to enroll 216 patients. Primary outcomes include cognitive (ADAS-Cog) and cognitive/functional scores (CDR-SB). Secondary outcomes include Mini-Mental State Examination, neuropsychiatric inventory, and activities of daily living scale (ADCS-ADL/23). Other outcome measures include blood biomarkers (Aβ42, Aβ40, total tau, ptau-181, NfL, TOM1, IL-1R1, IL-1β, IL-6, IL-8, TNF-α, FB, FH, sCR1, MCP-1, eotaxin-1, Ach, ChEI) and hippocampal volume measured with MRI. This clinical trial is scheduled to be completed in December 2024.

Search terms:

Pubmed, Google: YangXue QingNao, Yang-Xue-Qing-Nao, YXQN

Websites visited for YangXue QingNao:

- Clinicaltrials.gov
- NIH RePORTER (0)
- Examine.com (0)
- DrugAge (0)
- Geroprotectors (0)

- Drugs.com (0)
- WebMD.com (0)
- DrugBank.ca (0)
- Cafepharma (0)
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