Available Online: 21 May 2025 DOI: 10.54254/3049-5458/2025.23271

Effects of Xuefu Zhuyu Decoction on cognitive function in patients with depression

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Abstract. Depression is a common, serious, and recurrent mental disorder that is closely associated with decreased quality of life, increased medical morbidity, and higher mortality rates. Currently, over 300 million people worldwide are affected by depression. According to reports from the World Health Organization (WHO), psychological disorders account for 12% of the global disease burden, and 46% of all illnesses are directly related to depression. WHO experts have warned that, if this trend continues, by 2030 the number of patients with depression will exceed the total number of patients with all cardiovascular diseases, making depression the leading cause of disability worldwide. It has thus become a major global public health concern. Xuefu Zhuyu Decoction, originally recorded in *Correction of Errors in Medical Classics* by Qing dynasty physician Wang Qingren, is known for its functions of promoting blood circulation, removing blood stasis, regulating qi, and relieving pain. It is now widely used in clinical practice for various conditions characterized by qi stagnation and blood stasis, with notable efficacy. This paper systematically elaborates on the therapeutic effects and mechanisms of Xuefu Zhuyu Decoction in treating depression accompanied by cognitive dysfunction.

Keywords: Xuefu Zhuyu Decoction, depression, cognitive impairment

1. Introduction

Depression, as a highly prevalent psychiatric disorder, represents a widespread global health issue. Its profound impact on both physical and psychological functions not only severely undermines individual quality of life but also poses a pressing challenge for public health systems worldwide [1]. Numerous studies have reported that patients with depression frequently exhibit cognitive impairments, including deficits in executive functioning, working memory, and information processing [2-3]. Research suggests that there is a continuous relationship between depression, cognitive impairment, and dementia, with cognitive dysfunction possibly serving both as a symptom of depression and a potential precursor to the development of dementia [4].

Xuefu Zhuyu Decoction, from Correction of Errors in Medical Classics by Wang Qingren, is recognized as an outstanding formula among those designed to promote blood circulation and eliminate stasis. An increasing body of research indicates that "blood stasis" plays a crucial role in the pathogenesis of neuropsychiatric disorders [5]. The comprehensive blood-activating and stasis-resolving properties of Xuefu Zhuyu Decoction align closely with the fundamental pathomechanism of depression accompanied by cognitive impairment characterized by blood stasis obstructing the channels. By promoting blood circulation and clearing obstructions in the cerebral vessels, as well as harmonizing the blood and restoring the clarity of spirit, this formula not only improves mood disorders in patients with depression but also enhances their sleep quality and cognitive function.

2. Traditional Chinese Medicine background of Xuefu Zhuyu Decoction

Xuefu Zhuyu Decoction stands as a representative formula in the theory of blood stasis in Traditional Chinese Medicine (TCM). It was developed based on Wang Qingren's profound insights into the pathogenic role of blood stasis. Centered on promoting blood circulation and resolving stasis, while also facilitating qi movement and alleviating pain, the formula reflects the core principles of TCM's theories of qi and blood as well as holistic body regulation. Although it is a classical blood-activating formula,

its modern clinical applications span multiple fields including internal medicine, gynecology, and psychiatry. This widespread application demonstrates the TCM principle of "treating different diseases with the same method."

3. Research mechanisms underlying depression with cognitive impairment

3.1. Traditional Chinese Medicine understanding of depression and cognitive impairment

Traditional Chinese Medicine (TCM) has a long-standing history in the study of cognitive impairment, accumulating rich theoretical insights and clinical experience concerning disease nomenclature, location, etiology, pathogenesis, and treatment approaches. Cognitive impairments are traditionally referred to as "Jian Wang" (amnesia), "Shan Wang" (easy forgetting), or "Xi Wang" (joyful forgetting), with memory decline being the primary clinical manifestation [12].

According to TCM, cognitive impairments are primarily located in the brain and are mainly caused by the dysfunction of the five viscera, resulting in the dysregulation of qi, blood, and bodily fluids. These imbalances lead to kidney essence deficiency, insufficient nourishment of the brain, accumulation of phlegm and blood stasis, and obstruction of the sensory orifices, manifesting as forgetfulness. The eminent physician Zhang Zhongjing stated in *Treatise on Febrile Diseases*: "Those prone to forgetfulness must have blood retention," emphasizing that chronic blood stasis is not only the core pathological factor but also the initial trigger of cognitive dysfunction in depression associated with blood stasis.

In TCM theory, "Blood houses the mind"; blood is considered the material foundation for mental activities. The heart governs blood circulation and houses the mind, while the liver stores blood and shelters the soul. Blood deficiency or stasis leads to insufficient nourishment of the mind, resulting in mental disturbances. Prolonged emotional distress, such as worry, anger, and frustration, causes liver qi stagnation and impaired qi circulation. Since qi is the commander of blood, qi stagnation results in blood stagnation. Over time, this blood stasis obstructs cerebral vessels, leading to insufficient nourishment of the brain—the residence of the primordial spirit—and ultimately cognitive decline, emotional disturbance, memory impairment, and slowed thinking. Furthermore, the combined effects of disrupted qi-blood dynamics and phlegm-stasis accumulation exacerbate the obstruction of the sensory orifices, intensifying cognitive dysfunction. Progressive failure to nourish the cerebral collaterals ultimately results in a pathological evolution from emotional distress to blood stasis and brain marrow depletion. This vicious cycle—qi stagnation, blood stasis, and spirit disturbance—highlights the interconnection between qi disorders and blood pathologies in depression-associated cognitive impairment. *Clinical Guide to Medical Records* also notes, "When blood stasis is internal, consciousness becomes confused, and only by dispelling stasis can clarity be restored," emphasizing the central role of activating blood circulation in restoring mental functions. Therefore, therapeutic approaches must simultaneously address qi regulation and blood stasis resolution for patients with depression characterized by blood stasis obstructing the channels. Classical TCM formulas, offering multi-pathway, multi-target, and multi-layered interventions, have accumulated abundant clinical evidence over centuries. Xuefu Zhuyu Decoction, as a prominent blood-activating prescription, aligns well with the common pathomechanism of depression accompanied by cognitive dysfunction caused by blood stasis.

3.2. Modern medical understanding of depression-cognitive impairment comorbidity

3.2.1. Neuroinflammation and immune dysregulation

Recent studies suggest that chronic neuroinflammatory responses and maladaptive immune mechanisms within the Central Nervous System (CNS) form the pathological basis for the comorbidity of depression and cognitive impairment. Hayley [5] pointed out that antidepressants targeting inflammatory pathways can delay cognitive decline in specific populations, implying that immune-neuro regulatory mechanisms could serve as key targets for interventions. Clinical evidence demonstrates that plasma levels of IL-6, IL-1β, and Corticotropin-Releasing Hormone (CRH) are significantly elevated in patients with Major Depressive Disorder (MDD). Moreover, CRH levels positively correlate with social cognitive dysfunction and negatively with Hamilton Anxiety Rating Scale (HAMA) scores [6]. Tumor Necrosis Factor-Alpha (TNF-α), while maintaining Blood-Brain Barrier (BBB) integrity and neural homeostasis under physiological conditions, abnormally upregulates Amyloid Precursor Protein (APP) expression and β-/γ-secretase activity, promoting Amyloid-β (Aβ) deposition. In turn, Aβ plaques further stimulate microglial TNF-α release, forming a vicious "inflammation-amyloid" cycle [7-9]. Clinical studies have shown that TNF-α antagonists simultaneously improve depressive symptoms and cognitive function [10], reinforcing the pivotal role of immune-mediated neuroinflammation in depression and cognitive decline.

3.2.2. Abnormalities in neurotrophic molecules

Brain-Derived Neurotrophic Factor (BDNF) is a critical regulator of CNS development, playing a central role in the comorbidity of depression and cognitive impairment. BDNF modulates neuronal proliferation, differentiation, synaptic plasticity, and the construction of neural networks involved in emotional regulation and cognitive function. Clinical studies reveal that lower peripheral BDNF levels are significantly associated with accelerated hippocampal atrophy and cognitive impairments in semantic

memory and emotion recognition [11]. Animal experiments further demonstrate that BDNF knockout or suppression leads to hippocampal neuronal abnormalities and cognitive deficits. Additionally, patients with higher baseline BDNF levels exhibit more significant improvements in verbal fluency and working memory during antidepressant therapy, suggesting that BDNF could serve as a potential biomarker for cognitive recovery [12]. These findings underscore the dual regulatory role of BDNF signaling in depression-related cognitive impairments, offering important insights for targeted interventions.

3.2.3. Systematic degradation of brain network nodes

Brain network imaging techniques have confirmed that hippocampal atrophy, prefrontal cortex gray matter reduction, and cerebellar region shrinkage collectively contribute to dysregulation of cognitive control networks in depression [13]. Hippocampal atrophy positively correlates with depression duration and negatively with subjective memory performance. Prefrontal cortical thinning, particularly in the Dorsolateral Prefrontal Cortex (DLPFC) and Anterior Cingulate Cortex (ACC), is associated with impaired executive functions [14]. Functional MRI studies show that during working memory tasks, depressed patients exhibit hyperactivation in the DLPFC and ACC compared to healthy controls, with excessive ACC activation correlating positively with executive dysfunction, suggesting functional decompensation of the prefrontal-limbic circuitry [15]. Diffusion Tensor Imaging (DTI) further reveals decreased Fractional Anisotropy (FA) values in the right inferior longitudinal fasciculus, indicating compromised fiber integrity between the ACC and parietal regions, which may underpin cognitive-depressive comorbidity [16]. These structural and functional abnormalities collectively contribute to impaired emotion regulation and cognitive control networks, offering important evidence for targeted intervention strategies.

3.2.4. Neurotransmitter dysregulation

Neurotransmitter systems—including Serotonin (5-HT), Norepinephrine (NE), Dopamine (DA), Acetylcholine (Ach), and Gamma-Aminobutyric Acid (GABA)—play crucial roles in regulating mental activities, mood, and cognitive functions. Numerous studies have shown that dysfunctions in the 5-HT/NE systems directly contribute to the pathophysiology of depression [17-18]. Consequently, Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) have become mainstream clinical treatments for depression [19]. Clinical studies of low-intensity pulsed ultrasound interventions reveal significant improvements in cognitive functions (evidenced by elevated Mini-mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) scores) following treatment, alongside concurrent increases in 5-HT, NE, and DA levels [20], suggesting that restoring neurotransmitter balance plays a synergistic role in relieving depressive symptoms and enhancing cognitive function. These results highlight the complexity and central role of neurotransmitter networks in emotional and cognitive regulation.

3.2.5. Vascular factors

Chronic cerebral ischemia induced by hypertension and atherosclerosis predominantly affects brain regions critical for emotional regulation and cognition, such as the prefrontal cortex and hippocampus, leading to neuronal injury and impaired synaptic plasticity [21-22]. Endothelial dysfunction and increased BBB permeability facilitate the infiltration of neuroinflammatory cytokines (e.g., Interluekin-6 (IL-6), Tumor Necrosis Factor-α (TNF-α)) and oxidative stress products into brain parenchyma, inhibiting neurotransmitters like 5-HT and BDNF, exacerbating depressive behaviors and cognitive decline [23-24]. Moreover, impaired cerebral blood flow regulation reduces the clearance efficiency of metabolic waste such as Aβ by the glymphatic system, accelerating neurodegenerative processes [25]. Vascular pathology, neuroinflammation, and oxidative stress together form a vicious cycle that disrupts neurovascular unit integrity, allowing peripheral inflammatory factors to perpetuate central nervous system damage. These pathological interactions reveal the role of the vascular-neural-immune network in the comorbidity of vascular cognitive impairment and depression.

4. Effects of Xuefu Zhuyu Decoction on depression-cognitive impairment comorbidity

Xuefu Zhuyu Decoction, a classical prescription for promoting blood circulation and removing blood stasis in Traditional Chinese Medicine (TCM), is based on the theoretical framework of "qi stagnation and blood stasis – impaired nourishment of cerebral collaterals – dysfunction of mental activities." Through the synergistic effects of soothing the liver and regulating qi (as represented by Si Ni San) and activating blood circulation and unblocking collaterals (as represented by Tao Hong Si Wu Tang), this formula specifically targets the pathological mechanisms underlying the comorbidity of depression and cognitive impairment. In TCM theory, "blood stasis obstructing the cerebral collaterals results in dysfunction of mental activities," suggesting that blood stasis in the brain leads to high-order cognitive decline, corresponding closely with modern medical concepts such as cerebral microcirculation disorders, neuroinflammation, and oxidative stress. Modern pharmacological studies have revealed that active compounds in Tao Ren (peach kernel) and Hong Hua (safflower)—such as pyrethrin, quercetin, baicalin, and 6-hydroxykaempferol—regulate multiple targets including AKT1. They act on the PI3K-Akt signaling pathway to inhibit excessive

phosphorylation of tau proteins and modulate the MAPK pathway to reduce Amyloid-Beta (Aβ) production and its associated neurotoxicity, ultimately ameliorating the pathological progression of Alzheimer's Disease (AD) [26]. Additionally, Chai Hu (Bupleurum) and Zhi Ke (Fructus Aurantii) improve mood by modulating the 5-HT system [27], while Tao Ren and Chuan Xiong (Ligusticum) directly target neurovascular protection and synaptic plasticity. These findings underscore the multi-target therapeutic effects of Xuefu Zhuyu Decoction. Notably, even in the absence of overt depressive symptoms, Xuefu Zhuyu Decoction can still enhance executive function through "removing blood stasis and unblocking collaterals," embodying the synergy between TCM's principle of "clearing stasis to restore mental clarity" and modern medicine's "vascular-neural multi-target intervention" approach. It is particularly suitable for cognitive impairment patients presenting with a purplish tongue and choppy pulse—hallmarks of blood stasis in TCM diagnosis.

Contemporary studies further confirm that its multi-target mechanisms encompass neurotransmitter regulation, enhancement of synaptic plasticity, and activation of anti-inflammatory pathways: Upregulating monoamine neurotransmitters (NE, 5-HT, DA) and 5-HT1A receptor expression in the hippocampus to restore monoaminergic system function [28-29]; Activating the NMDAR/CaMKII/GAP-43 signaling pathway to promote synaptic proteins such as PSD-95 and synaptophysin, thereby repairing synaptic plasticity [30]; Inhibiting neuroinflammation and neuronal apoptosis via the PI3K-Akt, MAPK, and TNF signaling pathways [31]. Clinical studies have demonstrated that combined application of Xuefu Zhuyu Decoction significantly improves depressive symptoms (Hamilton Depression Scale (HAMD), Safety Data Sheet (SDS) scores) and cognitive functions (MMSE, CNS scores), with efficacy superior to SSRI monotherapy and a favorable safety profile [32-33]. Furthermore, co-administration with butylphthalide (Noninvasive Blood Pressure, NBP) synergistically ameliorates post-ischemic memory impairment [34], highlighting the formula's advantage in modulating the neurovascular-immune network holistically.

Moving forward, integrating metabolomics and neuroimaging technologies will be crucial to identify "blood stasis" biomarkers (e.g., inflammatory cytokines such as Interluekin-6 (IL-6), hemorheological parameters), elucidate dynamic interactions between formula components, molecular targets, and signaling pathways, and conduct large-scale, multicenter randomized controlled trials. Such efforts will facilitate the precise application of Xuefu Zhuyu Decoction and the evidence-based advancement of integrated Chinese-Western medical approaches, providing innovative strategies rooted in both traditional wisdom and modern scientific validation for psychiatric and neurological disorders.

5. Conclusion and future perspectives

Cognitive impairment and depression interact through complex mechanisms, forming a bidirectional and mutually reinforcing relationship that can lead to a vicious cycle. Depression may both trigger cognitive decline and present as one of its manifestations. Therefore, early intervention and treatment of depression have become crucial strategies for preventing and mitigating cognitive impairment or dementia. Current pharmacological treatments offer limited efficacy and often suffer from issues such as drug resistance and adverse effects. In contrast, TCM therapies offer unique advantages through holistic regulation, multi-target intervention, and better safety profiles. However, further progress requires overcoming barriers in mechanistic research, enhancing the level of clinical evidence, and promoting innovative, personalized treatment strategies through interdisciplinary integration. In the future, with deeper integration of basic research and clinical practice, TCM is expected to play an increasingly important role in the field of psychiatric and neurological diseases, providing novel therapeutic avenues that blend traditional knowledge with modern scientific rigor.

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