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Review Article

Research Progress on the Use of the Traditional Chinese Formula Si-Jun-Zi Tang in the Prevention and Treatment of Schizophrenia

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ABSTRACT

Schizophrenia is a chronic and severe psychiatric disorder characterized by positive symptoms, negative symptoms, and cognitive deficits, imposing profound burdens on patients, families, and healthcare systems worldwide. Despite the central role of antipsychotic medications, they remain limited in efficacy against negative and cognitive symptoms, and are frequently associated with adverse effects and treatment resistance. Traditional Chinese Medicine (TCM) offers a complementary therapeutic avenue. This review aims to systematically examine the potential of Si-Jun-Zi Tang (SJZT), a canonical TCM formula for "strengthening the spleen and tonifying Qi," particularly in schizophrenia patients with spleen-deficiency patterns. Materials and Methods: We conducted a comprehensive synthesis of available literature focusing on the TCM theoretical foundations, modern pharmacological studies, and clinical evidence related to SJZT in the context of schizophrenia. Both historical TCM texts and contemporary research from electronic databases were analyzed to integrate traditional perspectives with current scientific insights. SJZT demonstrates multi-target pharmacological actions, including immunomodulation, neuroprotection, and gut microbiota regulation, which align with key pathophysiological mechanisms of schizophrenia, such as neuroinflammation and dysregulation of the gut-brain axis. Preliminary clinical observations suggest that SJZT may improve negative symptoms and enhance tolerance to antipsychotic drugs in spleen-deficiency patients. However, robust clinical evidence remains limited, and further high-quality studies are needed. SJZT represents a promising complementary approach for schizophrenia, especially in patients presenting spleen-deficiency patterns. Its multi-component, multi-target mechanisms offer a holistic strategy that addresses limitations of conventional antipsychotics. Future research should prioritize well-designed clinical trials and mechanistic studies to validate efficacy, optimize treatment protocols, and facilitate integration into modern psychiatric practice.

Keywords: Si-Jun-Zi Tang, Schizophrenia, Spleen-Deficiency with Phlegm Obstruction.

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INTRODUCTION

Clinical context and therapeutic challenges in schizophrenia

Schizophrenia is a highly disabling psychiatric disorder with a global prevalence of approximately 1%, typically emerging in late adolescence or early adulthood (Jauhar *et al*., 2022; Jongsma *et al*., 2019). Its clinical heterogeneity encompasses three major symptom clusters: positive symptoms (hallucinations, delusions, thought disorder), negative symptoms (blunted affect, anhedonia, avolition, social withdrawal), and cognitive deficits (impaired attention, working memory, executive function, and slowed information processing) (Ardizzi *et al*., 2016; Insel, 2010; Panov & Panova, 2023). The disease often follows a relapsing–remitting course that culminates in chronic disability, loss of social and occupational functioning, reduced life expectancy, and severe burdens on caregivers and healthcare systems (Cai *et al*., 2024; Simek *et al*., 2025).

Pharmacological management, although improved over decades, faces substantial limitations. First-generation antipsychotics (dopamine D_2 receptor antagonists) and second-generation agents (dopamine–serotonin modulators) demonstrate efficacy primarily in positive symptoms but exert little benefit on negative or cognitive dimensions (Angeli *et al*., 2025; Cheng *et al*., 2024). Moreover, first-generation drugs frequently induce extrapyramidal symptoms (e.g., tremor, rigidity), whereas second-generation agents predispose patients to metabolic syndrome (weight gain, dyslipidemia, glucose intolerance), cardiovascular risks, and sedation. These adverse effects

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significantly compromise treatment adherence and long-term quality of life. Treatment resistance, occurring in up to one-third of patients, underscores the urgent demand for adjunctive strategies that combine multi-target regulation with enhanced safety profiles (Desai *et al*., 2021; Goud *et al*., 2025).

Emerging research implicates neuroinflammation, immune dysregulation, oxidative stress, and gut microbiome alterations as integral to schizophrenia pathogenesis. These findings highlight the interplay between central and peripheral mechanisms and justify integrative therapeutic paradigms (Soltani *et al*., 2024). Within, schizophrenia-like disorders are classified as "dian" (predominantly negative symptoms), "kuang" (marked by positive symptoms), or dementia-like syndromes. The core pathogenesis is conceptualized as "phlegm turbidity obstructing the orifices," with spleen deficiency regarded as the root cause of phlegm accumulation. Accordingly, the principle of "strengthening the spleen, tonifying Qi, and resolving phlegm" represents a rational therapeutic strategy (Dubey & Kumar, 2025).

Si-Jun-Zi Tang (SJZT), a foundational spleen-fortifying and Qi-tonifying prescription, epitomizes this approach (Yuan *et al*., 2022). Modern studies have revealed its immunomodulatory, neuroprotective, gastrointestinal, and microbiota-regulating properties, providing biological plausibility for its role in schizophrenia management (Tseng & Li, 1996). This review integrates traditional and biomedical perspectives to evaluate SJZT's therapeutic potential, current evidence, and translational prospects.

Theoretical Basis of SJZT in TCM

SJZT, first recorded in the Tai Ping Hui Min He Ji Ju Fang during the Song dynasty, is the prototypical formula for treating "spleen Qi deficiency." It consists of four herbs—Panax ginseng (often substituted with *Codonopsis pilosula* for clinical safety), *Atractylodes macrocephala, Poria cocos*, and *Glycyrrhiza uralensis*-arranged according to the sovereign–minister–assistant–ambassador principle. Together, they restore spleen Qi, resolve dampness, harmonize functions, and secure the foundation of health (Ding *et al*., 2015; Sun *et al*., 2016).

Building on this formula, derivative prescriptions such as Liu-Jun-Zi Tang (adding *Pinellia ternata* and *Citrus reticulata*) and Xiang-Sha Liu-Jun-Zi Tang (further adding *Aucklandia lappa* and *Amomum villosum*) have been developed to address complex conditions involving phlegm, dampness, or Qi stagnation. This adaptability underscores SJZT's status as a core "basic spleen-tonifying formula" (Chiou *et al*., 2018; Jiang *et al*., 2023).

Pharmacological studies corroborate its multi-target profile: enhancing T-lymphocyte regulation, reducing pro-inflammatory cytokines (IL-6, TNF-α), inhibiting NF-κB activation, strengthening gastrointestinal mucosal integrity, and modulating energy metabolism (Chen *et al*., 2020). Additionally, SJZT exerts neuroprotective effects by alleviating oxidative stress and promoting Brain-Derived Neurotrophic Factor (BDNF) expression. Recent findings further reveal its capacity to modulate gut microbiota composition, increase beneficial genera (e.g., *Bifidobacterium, Lactobacillus*), and maintain intestinal barrier integrity, aligning with the microbiota–gut–brain axis framework (Li *et al*., 2024). These properties converge with pathophysiological pathways implicated in schizophrenia.

TCM Pathogenesis and Mechanistic Rationale for SJZT in Schizophrenia

From a TCM standpoint, schizophrenia arises from dysfunctions in the heart, spleen, liver, and kidney, leading to imbalances in Qi, blood, yin, and yang. "Spleen deficiency with phlegm obstruction" is regarded as the pivotal mechanism: impaired spleen function fails to transform food into Qi and blood, depriving the heart–mind of nourishment, manifesting as apathy and avolition. Simultaneously, dampness accumulates into phlegm, which clouds the orifices and disturbs mental clarity, giving rise to hallucinations, delusions, and disorganized thought (Shen *et al*., 2024; Yang *et al*., 2024).

Patients with spleen-deficiency schizophrenia often present with both psychiatric and somatic features: poor appetite, abdominal distension, loose stools, fatigue, pallor, scalloped tongue, and weak pulse-symptoms consistent with negative syndrome profiles. SJZT addresses this pathogenesis by replenishing spleen Qi, reducing phlegm formation, and harmonizing body–mind interactions (Shi *et al*., 2021).

Modern evidence supports this rationale: SJZT regulates immune-inflammatory responses, restores gut barrier integrity, mitigates oxidative stress, enhances synaptic plasticity, and modulates neurotransmitter systems (dopamine and glutamate) (Li *et al*., 2024). These converging mechanisms offer multi-target interventions for schizophrenia's complex pathology.

Current Evidence on SJZT in Schizophrenia

Clinical Observations

Existing clinical evidence remains preliminary, largely derived from small-scale observational studies and case reports. Findings suggest that adjunctive SJZT may alleviate gastrointestinal discomfort, improve vitality, enhance emotional stability, and modestly reduce negative symptoms such as affective flattening and social withdrawal. Some reports indicate improved treatment adherence when SJZT is combined with antipsychotics, potentially due to reduced gastrointestinal side effects and enhanced tolerability (Hoenders *et al*., 2014; Pu *et al*., 2023; Tseng & Li, 1996).

Nevertheless, significant limitations exist: the absence of multicenter RCTs, lack of standardized herbal preparations, heterogeneous diagnostic criteria, and outcome measures

restricted to symptom rating scales (e.g., PANSS). Few studies incorporate functional recovery, quality of life, or biological markers, leaving efficacy and safety unverified (Meng-Long *et al*., 2020; Wang *et al*., 2020).

Mechanistic Insights

Neurotransmitter regulation: Active constituents such as ginsenosides and polysaccharides modulate glutamatergic transmission (enhancing NMDA receptor activity, stabilizing synaptic plasticity) and may influence dopamine D_2 receptor dynamics, thereby targeting both negative and positive symptoms.

Gut–brain axis modulation: By reshaping microbiota composition, reinforcing intestinal barrier proteins (occludin, ZO-1), and influencing gut hormones (serotonin, cholecystokinin), SJZT indirectly regulates CNS function through immune and vagal pathways (Li *et al*., 2017).

Research Limitations

Challenges include: (1) insufficient sample sizes and lack of long-term follow-up, (2) poor standardization of herbal preparations, (3) absence of herb–drug interaction studies with antipsychotics, and (4) mechanistic studies limited to single targets, lacking integrative systems-level approaches.

Future Research Directions

Mechanistic and Translational Studies

Future research should integrate

Systems pharmacology and multi-omics (transcriptomics, proteomics, metabolomics, metagenomics) to construct compound–target–pathway networks.

Refined animal models mimicking spleen deficiency and schizophrenia (e.g., high-fat diet plus NMDA antagonist) to assess behavioral, neuropathological, and microbial outcomes. Computational methods such as molecular docking to validate compound–target interactions with D_2, NMDA receptors, and NF-κB.

Personalized and Biomarker-Driven Medicine

Combining TCM syndrome differentiation with objective biomarkers (e.g., gut microbial signatures, inflammatory markers, BDNF polymorphisms) may establish predictive models of treatment response. This integration can guide individualized therapy, optimize SJZT dosing, and enhance precision adjunctive strategies.

Interdisciplinary and Global Collaboration

Collaborations across psychiatry, neuroscience, pharmacology, microbiology, and TCM are critical. International consortia can harmonize protocols, validate efficacy across populations, and accelerate regulatory recognition. Partnerships with industry can facilitate the development of standardized SJZT formulations (e.g., granules, capsules) for clinical translation (Pu *et al*., 2023).

CONCLUSION

SJZT, rooted in the TCM theory of "spleen deficiency with phlegm obstruction," aligns with modern insights into schizophrenia's multisystem pathology. Its multi-target effects-including anti-inflammatory, immunomodulatory, gut–brain axis, and neuroprotective actions-offer a compelling rationale for adjunctive application. Preliminary evidence suggests benefits in alleviating somatic symptoms, improving negative symptoms, and enhancing tolerability of antipsychotics. However, robust clinical trials, standardized preparations, comprehensive mechanistic studies, and biomarker-driven frameworks are urgently needed. Advancing SJZT through integrative research pathways may bridge TCM and modern psychiatry, paving the way for holistic, personalized strategies in schizophrenia management.

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ABBREVIATIONS

TCM: Traditional Chinese Medicine; **SJZT:** Si-Jun-Zi Tang; **BDNF:** Brain-derived neurotrophic factor.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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