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REVIEW

# Traditional Chinese Medicine in the Comprehensive Management of Tourette Syndrome: Insights from Genetics and Pathophysiology: A Review

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**Abstract:** Tourette syndrome (TS) is a neurodevelopmental disorder characterized by recurrent motor and vocal tics, often accompanied by comorbid psychiatric symptoms. While pharmacological treatments are commonly used, they often provide incomplete symptom relief and may cause adverse effects. Traditional Chinese Medicine (TCM) has been increasingly applied in clinical practice and is considered a valuable complementary approach. This review summarizes current research on TS from the perspectives of genetics, pathophysiology, and TCM, with particular attention to how biological findings inform syndrome differentiation and treatment. Genetic studies have identified polymorphisms such as IL1RN and SLC1A3, which are associated with immune dysfunction and neurotransmitter imbalance, respectively. These findings may correspond to TCM syndromes such as "Liver Wind Stirring Internally", linked to inflammation, and "Liver Yin Deficiency with Yang Hyperactivity", associated with excitatory overactivity. Pathophysiological mechanisms, including cortico-striato-thalamo-cortical (CSTC) circuit abnormalities and dopaminergic dysregulation, have been recognized as core contributors to tic development. TCM interventions appear to target these mechanisms. Tianma Gouteng Decoction has been shown to regulate neurotransmitter function and reduce liver yang hyperactivity, while Ningdong Granule can inhibit neuroinflammatory responses by modulating microglial activity. These effects are consistent with modern findings on the neural and immune changes observed in TS. Moreover, clinical evidence supports that combining TCM with Western pharmacotherapy may improve overall treatment efficacy, reduce side effects, and enhance patient outcomes. By linking genetic and neural mechanisms with traditional syndrome patterns, this review offers a comprehensive framework for understanding and applying TCM in TS treatment. The integration of TCM principles with modern scientific knowledge may support more individualized and biologically informed approaches to care.

**Keywords:** Tourette syndrome, Traditional Chinese Medicine, genetic polymorphism, IL1RN, SLC1A3, CSTC circuit, integrated treatment

## Introduction

Tourette syndrome (TS) is a complex neurodevelopmental disorder characterized by multiple motor and vocal tics that typically begin in childhood.[1] Tics are defined as sudden, rapid, recurrent, nonrhythmic motor movements or vocalizations, which may be simple or complex in nature,[1–3] with a prevalence estimated at 0.3–0.9% among school-aged children and is notably higher in males than females.[4–6] TS often co-occurs with psychiatric comorbidities, particularly attention-deficit /hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD), complicating diagnosis and management.[7]

First-line pharmacological treatments for TS include typical and atypical antipsychotics such as haloperidol, pimozide, and risperidone.[8] While these agents can alleviate tic severity, their use is limited by variable efficacy and significant adverse effects, including sedation, weight gain, extrapyramidal symptoms, and emotional blunting.[9] Moreover, tics often recur following drug discontinuation, underscoring the need for long-term management strategies.[10] These therapeutic limitations highlight the necessity of exploring adjunctive or alternative interventions.

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Traditional Chinese Medicine (TCM) has gained increasing attention as a complementary therapeutic modality in TS management.[11] Its appeal lies in its individualized syndrome differentiation approach, holistic focus, and relatively favorable side-effect profile. While TS does not appear in classical Chinese medical texts as a discrete disease category, its core manifestations were historically understood within the nosological frameworks of "chronic convulsion", "wind stirring", and "muscle spasms".[12] These conditions were generally attributed to internal wind, phlegm, fire, qi stagnation, or organ deficiencies involving the liver, spleen, and kidney. For instance, the concept of "internal stirring of liver wind" is frequently invoked in TCM to explain convulsive movements and twitching.[13] Moreover, recent advances in genetics and neurobiology have begun to offer a mechanistic bridge between TCM theory and modern biomedical understanding. TS has a strong genetic component, with heritability estimates of approximately 50%.[14] Studies have identified associations between certain genetic polymorphisms, such as IL1RN and SLC1A3, and TS susceptibility.[15] The IL1RN polymorphism has been linked to increased inflammatory responses, which may correspond to the TCM concept of "external contraction of wind-heat" or "internal wind generated by heat toxins".[16] Similarly, the SLC1A3 variant, which affects glutamate transport, may relate to the concept of hyperactive liver yang or excitatory overactivity.[17] These findings suggest a potential biological basis for specific TCM syndromes and offer avenues for integrating biomedical diagnostics into TCM syndrome differentiation.

TS pathophysiology is characterized by functional abnormalities in the cortico-striato-thalamo-cortical (CSTC) circuit, dopaminergic hyperactivity, and impaired inhibitory control.[18] Emerging evidence has shown that several TCM herbal compounds and formulas may target these pathophysiological mechanisms. For instance, Tianma Gouteng Decoction has been shown to reduce hyperactive liver yang and modulate dopaminergic activity,[19] while Ningdong Granule can attenuate neuroinflammation by inhibiting microglial activation,[20] which supports the notion that TCM may exert therapeutic effects via modulation of neural and immune pathways relevant to tic generation.

This review aims to examine the therapeutic potential of TCM in conjunction with conventional treatments for TS, through the lens of genetics, pathophysiology, and clinical integration. Specifically, we will (1) describe the TCM understanding of TS based on syndrome differentiation, (2) explore the mechanisms of TCM formulas in modulating neurotransmitters, inflammatory signaling, and gene expression, (3) summarize clinical trial evidence for TCM monotherapy or integrative therapy, and (4) discuss future directions for combining individualized TCM approaches with molecular and neurological insights. By integrating modern scientific discoveries with traditional TCM principles, we aim to establish a comprehensive and biologically informed framework for TS management.

## Signs and Symptoms

Tics are characterized as "sudden, rapid, brief, repetitive motor tics or speech tics".[3] Consequently, motor and speech tics are the primary symptoms of TS, exhibiting considerable variability among individuals in terms of type, severity, frequency, and complexity. Tics are generally categorized into simple and complex forms that encompass a wide range of movements and vocalizations. Simple motor tics consist of brief, repetitive movements involving a single muscle group or body part, whereas complex motor tics entail coordinated movements involving multiple muscle groups. Simple speech tics are characterized by non-word vocalizations, whereas complex speech tics may include phrases or combinations of sounds. Approximately 28.1% of individuals with TS exhibit obscene or socially inappropriate gestures or vocalizations, referred to as fecal phenomena.[21] Research indicates that tic severity tends to be exacerbated under conditions of stress, fatigue, or excitement, while improvement is often observed during periods of mental or physical engagement or concentration.[22,23] Tics can manifest as involuntary or semi-voluntary actions, with the latter being a voluntary response to an impulsive or sensory stimulus; distinguishing between these two forms can be challenging even for seasoned clinicians.[24] Premonitory urges typically precede tics, although an observational study involving 21 adults with TS revealed that only 57–66% of individual tics consistently correlate with premonitory urges, depending on the measurement method.[21]

The onset of TS typically occurs between the ages of 4 and 8 years, with a peak in tic severity observed between the ages of 10 and 12 years, followed by a decline in the severity.[25] Many individuals experience complete remission, although tic recurrence may occur in adulthood.[26] Numerous studies have demonstrated that the severity of tics and associated psychiatric comorbidities during childhood significantly increase the risk of tic persistence into adulthood.[27] Consequently, a substantial number of children and adults may experience severe tics that necessitate emergency interventions. The term "phonetic tic" is preferred over "vocal tic", as involuntary sounds may originate from various anatomical structures, including the mouth, nose,

larynx, and pharynx, rather than solely from vocal cords. In certain cases, speech tics may be pronounced enough to cause hoarseness or even vocal cord damage.[28] In addition to producing simple nonsensical sounds, individuals with TS frequently articulate meaningful phrases or utterances, including swearing and obscenity, a phenomenon known as coprolalia.

For some patients with TS, tics can not only be bothersome, but also debilitating. For instance, blepharospasm, characterized by increased blinking, may intermittently obstruct vision, potentially rendering the individual functionally blind, which can interfere with activities such as driving.[29] A survey of 228 individuals with TS or chronic tic disorders revealed that 9% reported difficulties in passing a driving test.[30] Participants lacking a driver's license reported more severe tics than those who possessed one, with 60.7% of the former attributing their inability to obtain a license for the presence of tics.[30]

Coprophenomena are common manifestations of TS, encompassing socially inappropriate verbal expressions (coprolalia) or gestures (copropraxia) that contain offensive content such as vulgarity, obscenity, religious profanity, or racial slurs. These expressions are typically not motivated by direct anger or frustration, nor are they merely emphasis.[31] The presence of fecal phenomena may contribute to social stigma often experienced by individuals with TS. As the peak severity of TS coincides with the emergence of fecal phenomena, patients may become increasingly withdrawn and face social rejection.[32] More critically, behaviors such as shouting obscenities or engaging in inappropriate conduct in public or religious settings can lead to bullying and other aggressive or criminal behaviors.[33,34]

Self-injurious behavior (SIB) is defined as repeated, intentional, and persistent self-harm that is not indicative of a suicide attempt (ie, non-suicidal self-harm).[35] Although SIB and suicidal behavior may overlap, they differ in terms of frequency, intent, and lethality.[36] A review of 20 cohort studies estimated the prevalence of SIB in TS to be approximately 35%, with significant variability across studies ranging from 14% to 66%.[35,37] SIB in TS may arise directly from tics or pathological compulsions that lead to "self-directed" harm, such as self-cutting, self-punching, self-biting, or self-poisoning, through the ingestion of harmful substances.[38] Additionally, "extroverted" forms of SIB may involve striking walls, floors, or furniture with various body parts, characterized by an intent to inflict self-harm rather than damage inanimate objects.[38,39] This form of SIB should be differentiated from attacks on physical objects, although they may coexist. SIB in TS is often associated with various skin lesions, including ecchymosis, cuts, and scratches.[40]

TS frequently co-occurs with other mental and behavioral disorders, including obsessive-compulsive behavior or obsessive-compulsive disorder (OCD), attention-deficit hyperactivity disorder (ADHD), autism spectrum disorders, anxiety, depression, sleep disorders, and self-harm behaviors.[41] A cross-sectional study involving 1374 individuals indicated that isolated TS is relatively uncommon; up to 88% of TS patients are diagnosed with at least one additional psychiatric disorder during their lifetime and 58% are diagnosed with two or more comorbidities.[42] The most prevalent comorbidities include ADHD and OCD, with an estimated 72% of patients diagnosed with one of these conditions.[42] Although the onset of these comorbidities varies among individuals, ADHD is often the earliest to manifest, followed by OCD and mood disorders.[29] Furthermore, consistent with findings related to other psychiatric disorders, individuals with TS and comorbidities exhibit an increased risk of mortality from both natural and unnatural causes compared to those with TS alone, although the underlying factors contributing to this increased risk remain unclear.[43]

## Diagnosis

TS is diagnosed through clinical evaluation that includes a comprehensive assessment of an individual's medical history. According to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5), a diagnosis of TS requires that the onset of tics occur prior to the age of 18. Furthermore, the individual must exhibit at least two motor tics and one vocal tic, although the presence of tics for a minimum duration of one year is not a prerequisite. The DSM-5 categorizes tic disorders into transient tic disorders, persistent tic disorders, and TS, although there is a proposal to conceptualize these conditions as part of a spectrum.[44,45] Although a familial history of tics and TS can be informative, it is not essential for diagnosis.

Various rating scales are available to evaluate the symptoms of individuals with TS across all age groups,[46] with the Yale Global Tic Severity Scale (YGTSS) being the most widely utilized instrument. Due to the inherent variability and fluctuation of symptoms, guidelines[8] advocate for a multifaceted approach to measuring symptom severity, which includes direct observation in clinical settings, historical accounts from the individual and their family, and video-based assessments.

The diagnosis and assessment of TS can be particularly complex due to the clinical heterogeneity of the disorder, suppressibility of tics, and temporal variability of symptoms. Consequently, diagnosis may be delayed by a period ranging from 3 to 11 years following the initial onset of symptoms, with approximately 73% of patients experiencing an initial misdiagnosis. This misdiagnosis is often attributed to a general lack of awareness regarding TS among both the public and healthcare professionals.[47,48] Currently, no early diagnostic markers, such as imaging, blood tests, or cerebrospinal fluid (CSF) biomarkers, have been identified to facilitate diagnosis before the manifestation of symptoms. However, some studies indicate that certain individuals may be predisposed to developing tics, particularly those exhibiting behavioral issues, symptoms of autism spectrum disorder, obsessive-compulsive behaviors, and emotional difficulties, as suggested by a study conducted by a multicenter consortium.[46] Enhancing the awareness of TS and its associated risk factors may empower caregivers and healthcare providers to identify tics and initiate treatment at an earlier stage.

The accurate diagnosis of TS is often complicated[49,50] by the presence of comorbid behavioral disorders and the challenge of differentiating between tics and functional tic-like behaviors.[51] Functional tic-like behaviors are characterized by a sudden and late onset of symptoms, asymptomatic fluctuations, a higher prevalence in females compared than in males, and more complex movements. Early and precise diagnosis, along with timely intervention, is crucial as TS symptoms can significantly hinder social integration and cognitive development. Effective treatment can alleviate the symptoms and mitigate the challenges faced by individuals with TS and their caregivers.

## Genetics

Genetic investigations of TS have evolved in several phases. Initial research focused on multigenerational family lineages, which indicated a potential Mendelian inheritance pattern. However, subsequent segregation analyses have revealed a more intricate inheritance model.[52] Advances in technology have facilitated family, twin, and molecular genetic studies that have provided substantial evidence for the genetic underpinnings of TS, estimating heritability to be between 50% and 80%.[53] Recently, large-scale collaborative initiatives, such as the Tourette International Collaborative Genetics (TIC Genetics) study, have emerged to identify genetic risk factors for TS, encompassing both common and rare variants as well as potentially complex polygenic or monogenic inheritance patterns.[54] These studies used extensive patient cohorts and open-access databases. Furthermore, the application of Genome-Wide Association Studies (GWAS), whole exome sequencing (WES), and whole genome sequencing (WGS) has opened new avenues for identifying genes and pathways associated with TS.[55]

Family, twin, and molecular genetic studies provide robust support for the existence of a genetic component in TS that is characterized by high heritability.[53] The genetic architecture of TS is complex, involving both common and rare variants. Common variants may influence morbidity risk through the cumulative effect of minor contributions, whereas rare variants may exert more significant impacts.[52] Numerous candidate genes and chromosomal regions linked to TS risk have been identified, implicating biological pathways related to neurodevelopment, neurotransmission, and synaptic function.[53] For instance, certain genes may influence the metabolism and transmission of neurotransmitters such as dopamine and glutamate, which are associated with the manifestation of TS. Additionally, evidence suggests a genetic connection between TS and autism spectrum disorders, potentially mediated by neurodevelopmental pathways involving a series of transsynaptic complex-related genes.[56]

The etiology of TS is multifactorial, involving interactions among genetic, environmental, and immune factors. Genetic predisposition has been shown to exacerbate tic severity, comorbidities, and psychosocial and educational challenges in children with TS.[57] For example, individuals carrying the IL1RN (1) allele exhibit a 7.65-fold increased risk of developing TS compared with those carrying the IL1RN (2) allele, indicating that the IL1RN gene may serve as a valuable marker for susceptibility to TS.[58] Concurrently, environmental factors such as prenatal exposure to tobacco have also been linked to the onset and severity of TS.[59] Gene-environment interaction studies have identified specific gene loci that interact with prenatal and perinatal stressors to influence tic severity, although these findings require further validation.[60]

TS exhibits significant genetic heterogeneity, posing a challenge for genetic research. Variability in the genes and chromosomal regions associated with TS across different studies suggests the involvement of multiple genetic mechanisms in its etiology. For instance, distinct disease-causing genes or gene combinations may be present in different families or populations.[52] Structural variation studies have revealed that TS-related structural variations in various

families involve different genes, such as deletions or insertions in LDLRAD4, B2m, USH2A, and ZNF765, which affect diverse biological processes, including synaptic vesicle endocytosis, cell-front organization, and neurite growth signaling.[61] This genetic heterogeneity may contribute to a range of clinical phenotypes, complicating the identification of uniform inheritance patterns in genetic studies of TS.

The debate persists regarding whether TS is attributable to multiple genes or a single gene. Early investigations suggested that the inheritance pattern of TS in certain families resembled Mendelian inheritance, leading to the proposal of a single-gene inheritance model.[52] However, as research has progressed, accumulating evidence has indicated that TS may be a polygenic disorder, with the cumulative or interactive effects of multiple genes contributing to its manifestation. For instance, GWAS findings have identified multiple loci associated with TS risk, albeit with minimal effects attributed to individual loci, thereby supporting the notion of polygenic inheritance.[62] Additionally, some rare single-gene mutations, such as those in HDC, have been linked to TS phenotypes, although such instances are relatively uncommon. Consequently, it is posited that TS may arise from both polygenic and monogenic inheritance, with the precise mechanisms warranting further investigation.

Research on the genetics of TS has raised numerous ethical considerations. It is imperative to ensure informed consent from patients and participants, particularly children, necessitating the consent of their guardians and, where feasible, the patients themselves. For instance, during genetic testing and related research, participants should receive comprehensive explanations regarding the objectives, methodologies, potential risks, and benefits of the study. Moreover, the dissemination and application of research findings should be approached with caution to mitigate unnecessary psychological burdens or discrimination against patients. In terms of treatment, particularly with emerging interventions such as deep brain stimulation (DBS) in pediatric populations, it is essential to carefully weigh the risks and benefits to ensure that the treatment aligns with the best interests of the patients along with the establishment of appropriate ethical guidelines and protocols.

## Pathophysiology

Robust evidence derived from genetic studies and neuroimaging techniques provides substantial support for the classification of TS as a neurodevelopmental disorder.[63] Comparative neuroimaging research involving adults and children diagnosed with TS has identified notable differences in functional brain connectivity. Additionally, the developmental trajectories observed in individuals with TS suggest distinct patterns; specifically, functional brain connections in children with TS appear more advanced, while those in adults with TS seem less mature when compared to age-matched control groups.[64] These discrepancies may be attributable to variations in cellular and axonal pruning processes, which can be influenced by both genetic and environmental factors.[65] In summary, it is likely that a combination of genetic and environmental influences contributes to widespread dysfunction within neuronal networks, potentially leading to the manifestation of symptoms associated with TS.[65,66]

The primary focus of TS research is to elucidate the mechanisms underlying the tic generation. The observation that tics exhibit similarities to voluntary behaviors—being subject to inhibition upon request yet manifesting excessively and without an apparent purpose—carries significant pathophysiological implications. Specifically, this suggests that the neural pathways responsible for voluntary behavior are also implicated in tic production. This indicates that certain fundamental neural structures associated with motor inhibitory control may be incapable of suppressing the emergence of aberrant motor programs. In contrast, other neural structures that provide top-down inhibitory regulation of the execution of these unexpressed motor programs appear to operate within normal parameters.[67]

Research has revealed both structural and functional abnormalities at various levels within the corticostriatothalamocortical (CSTC) loops of individuals with TS. These circuits are essential for the development and execution of voluntary behaviors, indicating a potential correlation between the observed alterations in these structures and the initiation of tics.[67] Furthermore, two neuropathological studies conducted on a limited cohort of adults with TS who had previously undergone pharmacological treatment provided evidence of structural changes in the composition of inhibitory interneuronal populations, specifically GABAergic and cholinergic neurons. These alterations were particularly noted in the sensorimotor region of the striatum[68] and globus pallidus intersegment.[66] These findings support the hypothesis of a functional imbalance between inhibitory and excitatory processes within these neural structures.

At the network level, tics may arise from inhibitory dysfunction within the sensorimotor cortex-basal ganglia network,[57] which includes alterations in striatal inhibitory microcirculation[68,69] and difficulties with autoinhibitory mechanisms.[70] This

impairment in the ability to delay action is associated with the severity of tics.[71] Conversely, volitional inhibition, assessed through either active or reactive inhibition, remains relatively stable in individuals with TS[68] and is linked to their capacity to suppress tics.[72]

While informative, the disinhibition model fails to account for several fundamental characteristics of tic disorders, including fluctuations in personality and the presence of premonitory impulses. An alternative hypothesis posits that tics may be indicative of exaggerated and sustained behavioral patterns reinforced by an abnormal increase in dopamine release.[73] Evidence supporting this notion suggests that dopamine-related reward-guided learning, commonly referred to as reinforcement learning, is heightened in individuals with TS.[74] Furthermore, individuals with TS often rely on habitual behaviors when not under the influence of medication.[75] Consequently, the hypothesis that the increased aberrant tetanic release of dopamine facilitates the execution of learned behaviors through direct or indirect plastic changes within the cortico-basal ganglia pathway has garnered attention.[73] This perspective posits that tics, as habitual and learned behaviors, may elucidate the phenomenon of premonitory impulses. Specifically, the execution of tics may serve to terminate these impulses, thereby eliciting positive prediction errors and phasic dopamine release that further reinforce the learning of tics.[76] The prevailing model of premonitory impulses suggests that aberrant processing of interoceptive and exteroceptive stimuli may give rise to these impulses, which subsequently initiate behavioral responses and lead to the execution of tics via the cortico-basal ganglia sensorimotor network.[77]

The morbidity mechanism of TS is summarized as follows, as shown in Figure 1.

## TCM's Perception of TS

While TS does not have a direct equivalent in the classical texts of TCM, its clinical manifestations can be categorized under the concepts of "chronic convulsion" and "muscle disorders". TCM posits that the etiology and pathogenesis of TS are multifaceted, with significant associations with liver, spleen, and kidney.[12] The liver is responsible for the smooth circulation of qi and its regulation; when emotional disturbances occur, liver function may become impaired, leading to qi stagnation that can transform into fire, resulting in what is termed "liver wind", which may precipitate convulsions. The spleen serves as the foundation for acquired vitality and is the source of qi and blood, and deficiency in spleen function can lead to inadequate nourishment of tendons and vessels or the production of phlegm, which may disrupt mental clarity and contribute to convulsive episodes. The kidney, regarded as the source of congenital vitality, is responsible for storing essence and generating marrow. This can result in kidney essence deficiency, leading to inadequate nourishment of the brain and marrow, which may also manifest as twitching symptoms. Furthermore, children exposed to external pathogenic factors, such as wind-heat or damp-heat, may experience disturbances in the liver wind,

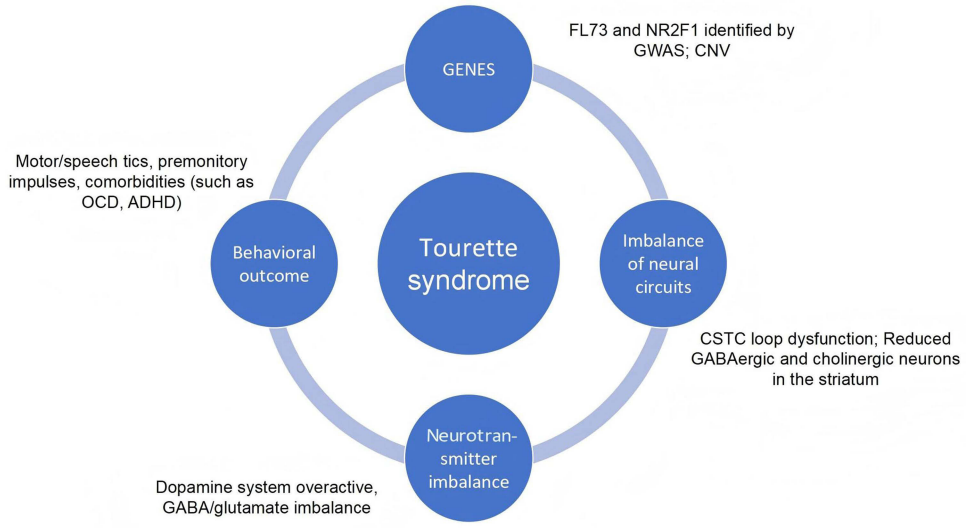


**Figure 1** Pathophysiological Mechanisms Underlying Tourette Syndrome.

contributing to the onset of TS. A study investigating gene polymorphisms in a cohort of 159 children with TS revealed a significantly higher frequency of the IL1RN (*) 1 allele in affected individuals than in healthy controls, indicating the potential role of immune factors in the pathogenesis of TS. This finding aligns with the TCM perspective that the interplay between internal and external factors is crucial in the development of the disorder.[58]

In recent years, TCM has made notable advancements in the elucidation of the pathological mechanisms associated with TS. TCM can modulate these mechanisms via various pathways. From the neurotransmitter perspective, TCM can influence the synthesis, release, and metabolism of neurotransmitters, thereby restoring their equilibrium. For instance, research has demonstrated that certain TCM formulations can modulate the expression of dopamine receptors, thereby enhancing dopaminergic neurotransmission.[78] Furthermore, in terms of the immune response, specific TCM interventions have been shown to regulate immune function and mitigate neuroinflammation. For example, Ningdong granules have been observed to inhibit the neuroinflammatory response in a rat model of tic disorders induced by 3,3'-iminodipropionitrile (IDPN), leading to a reduction in the release of inflammatory mediators.[20] Additionally, TCM may exert regulatory effects on gene expression and enhance neural plasticity, contributing to the amelioration of the pathological conditions associated with TS.

Research on genetic polymorphisms has indicated that certain genetic variations in patients with TS are associated with susceptibility to the disorder. TCM may exert therapeutic effects by modulating the expression of these pertinent genes. For instance, investigations into SLC1A3 have revealed that its sequence variations may correlate with the incidence of TS, suggesting that TCM could influence glutamate transport by altering the functionality of this gene, thereby alleviating symptoms.[79] Additionally, neuroimaging studies have demonstrated that individuals with TS exhibit abnormalities in both brain structure and function, with observable alterations in brain activity following TCM interventions. Functional magnetic resonance imaging (fMRI) studies have shown that TCM treatment can modulate neuronal activity in brain regions associated with TS and enhance neural functional connectivity. These findings provide valuable insights into the underlying pathological mechanisms through which TCM may facilitate the treatment.

## The Mechanism of TCM in the Treatment of TS

The therapeutic mechanisms of TCM in the management of TS are characterized by their engagement with multiple targets and pathways. From a neurotransmitter perspective, numerous studies have demonstrated that TCM can effectively address imbalances in neurotransmitters, such as dopamine, glutamate, and gamma-aminobutyric acid. Network pharmacology analyses of Qiangzhi decoction have revealed that its active components interact with various targets associated with the dopamine system, thereby influencing dopamine metabolism and signal transduction, which ultimately leads to the amelioration of tic symptoms.[78] Furthermore, from the standpoint of neuroinflammation, Ningdong granules have been shown to inhibit the activation of striatal microglia in a rat model of tics induced by 3,3'-iminodipropionitrile (IDPN). This intervention results in a reduction in inflammatory mediators, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1), thereby contributing to the control of tic manifestations.[20] Additionally, ChangPu YuJin Tang has been found to protect neuronal cells from structural damage by modulating the brain-derived neurotrophic factor (BDNF)/tyrosine kinase receptor B (TrkB) and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathways, leading to improvements in the symptoms observed in rats with TS.[80]

## TCM Treatment of TS Commonly Used Prescriptions and Drugs

Numerous TCM formulations are utilized in the management of TS, including Tianma Gouteng Decoction, Chaihu Shugan Powder, and Liuwei Dihuang Pill. Tianma Gouteng Decoction is recognized for its ability to calm the liver, alleviate wind, clear heat, promote blood circulation, and nourish the liver and kidneys. It is particularly effective for tic symptoms associated with hyperactivity of the liver yang and the internal movement of the liver wind. Chaihu Shugan Powder is known for its capacity to soothe the liver and regulate the flow of qi, demonstrating efficacy in addressing twitching resulting from emotional disturbances and liver qi stagnation. Liuwei Dihuang Pill primarily focuses on nourishing kidney-yin and is frequently used for TS characterized by liver-kidney yin deficiency.

In terms of individual herbal components, commonly utilized TCM herbs include Gastrodia elata, Uncaria rhynchophylla, Concha Haliotidis, Bupleurum chinense, Paeonia lactiflora, and Rehmannia glutinosa. Specifically, Rhizoma

Gastrodiae is effective in stopping wind and spasms while suppressing liver yang; Ramulus Uncariae Cum Uncis serves to clear heat, calm the liver, and arrest convulsions; Concha Haliotidis aids in calming the liver and suppressing yang, as well as enhancing vision; Radix Bupleuri is known to soothe the the liver and alleviate depression; Radix Paeoniae Alba nourishes the blood and softens the liver; and Radix Rehmanniae Preparata is utilized to nourish yin and tonify the kidneys.

Recent network pharmacology studies have indicated that certain components found in Xiaoyao Powder and Chaihu Shugan Powder, such as Bupleurum and Paeonia lactiflora, herbs commonly employed in the treatment of premenstrual syndrome, may exert their therapeutic effects through the regulation of multiple targets and signaling pathways. This finding offers valuable insights into the treatment of TS.[81]

The TCM syndrome differentiation and treatment pathway of TS are summarized as follows, as shown in Figure 2.

## Clinical Practice of TCM Combined Therapy for TS

Fan et al[82] conducted a randomized controlled trial (RCT) to evaluate the efficacy of Jianpi Shugan Huatan decoction in children diagnosed with TS and its impact on neurotransmitter secretion. The study involved 98 children with TS, who were randomly assigned to either a control group or an observation group, with 49 participants in each group. The control group received tiapride hydrochloride, while the observation group was administered Jianpi Shugan Huatan Decoction. After an 8-week treatment period, the researchers compared the clinical efficacy, disease severity, neurotransmitter secretion levels, recurrence rates, and adverse reactions between the two groups. The findings indicated that the combination of Jianpi Shugan Huatan decoction and tiapride hydrochloride tablets significantly reduced TS severity, enhanced neurotransmitter secretion levels, improved therapeutic outcomes, and demonstrated a favorable safety profile with a low likelihood of relapse.

Liu Shan et al[83] also designed an RCT to assess the clinical efficacy of Changma Xifeng Tablets in conjunction with Haloperidol Tablets in treating children with TS. This study included 96 children with TS who were divided into a control group and a treatment group, each comprising 48 participants. The control group received haloperidol tablets, while the treatment group was administered Changma Xifeng Tablets alongside haloperidol. The treatment duration was four weeks, during which clinical efficacy, cognitive development, therapeutic effects, electroencephalogram (EEG) results, YGTSS scores, and serum neurotransmitter levels were evaluated and compared. The results suggested that the combination of Changma Xifeng and haloperidol tablets effectively improved clinical symptoms, cognitive development, EEG results, and serum neurotransmitter levels (dopamine, norepinephrine, and serotonin) in children with TS.

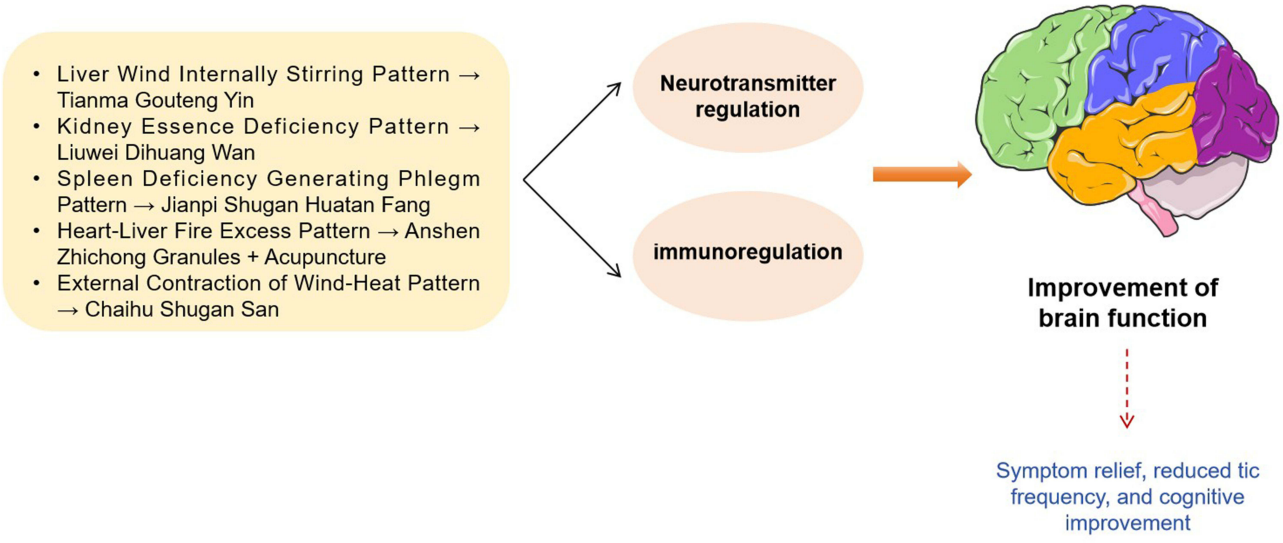


**Figure 2** Traditional Chinese Medicine Syndrome Differentiation and Corresponding Treatment Strategies for Tourette Syndrome.

Qiu et al[84] conducted an RCT to investigate the clinical efficacy of Xifeng granules combined with psychological interventions in treating children with TS. The study included 120 children with TS who were randomly assigned to a study group (n = 60) and a control group (n = 60). The control group received treatment with dopamine receptor blocker tiapride tablets, while the study group was treated with Xifeng granules in conjunction with psychological intervention. The researchers compared the clinical efficacy, TCM syndrome scores, YGTSS scores, recurrence rates, and adverse reactions between the two groups. The results indicated that the combination of Xifeng granules and psychological intervention yielded significant clinical improvements in children with TS, effectively alleviating symptoms and demonstrating a high safety profile.

Zhang Yao et al[85] designed an RCT to evaluate the clinical efficacy of acupuncture combined with Anshen Zhicheng Granule in treating pediatric TS characterized by hyperactivity of heart-liver fire. The study included 118 pediatric patients with TS who were randomly assigned to two groups: Group A (n = 59) received acupuncture combined with Anshen Zhicheng granules, whereas Group B (n = 59) was treated with Tiapride Hydrochloride Tablets. The researchers compared the clinical efficacy, YGTSS scores, American Spinal Injury Association scores, and changes in peripheral blood neurotransmitter levels before and after treatment. Adverse reactions were also assessed. The findings revealed that acupuncture combined with Anshen Zhicheng Granule effectively alleviated motor and vocal tics in children with TS of the hyperactivity of heart-fire and liver-fire types, improved neurotransmitter levels and neurological function, and exhibited superior efficacy and a lower incidence of adverse reactions compared to Tiapride Hydrochloride Tablets.

Beiru et al[86] conducted an RCT to assess the clinical efficacy of auricular point sticking combined with Yizhining Shenye in treating TS. The study included 90 children with TS who were randomly divided into two groups: the control group (n = 37) received Yizhiningshen liquid, while the treatment group (n = 53) received auricular point sticking in combination with Yizhiningshen liquid. The researchers evaluated the YGTSS and side effects scale before treatment, 12 weeks post-treatment, and 12 weeks after treatment. The results indicated that auricular point sticking combined with yizhiningshenye was both safe and effective in treating TS, with no significant toxic or side effects, and demonstrated superior outcomes compared to monotherapy with medication.

The mechanism of action of comprehensive TCM treatment of TS is summarized in Figure 3.

## Challenges on the Specificity of TCM in TS

Despite growing interest in the integration of TCM for the management of TS), concerns persist in mainstream biomedical discourse regarding the specificity, reproducibility, and scientific validation of TCM interventions, which

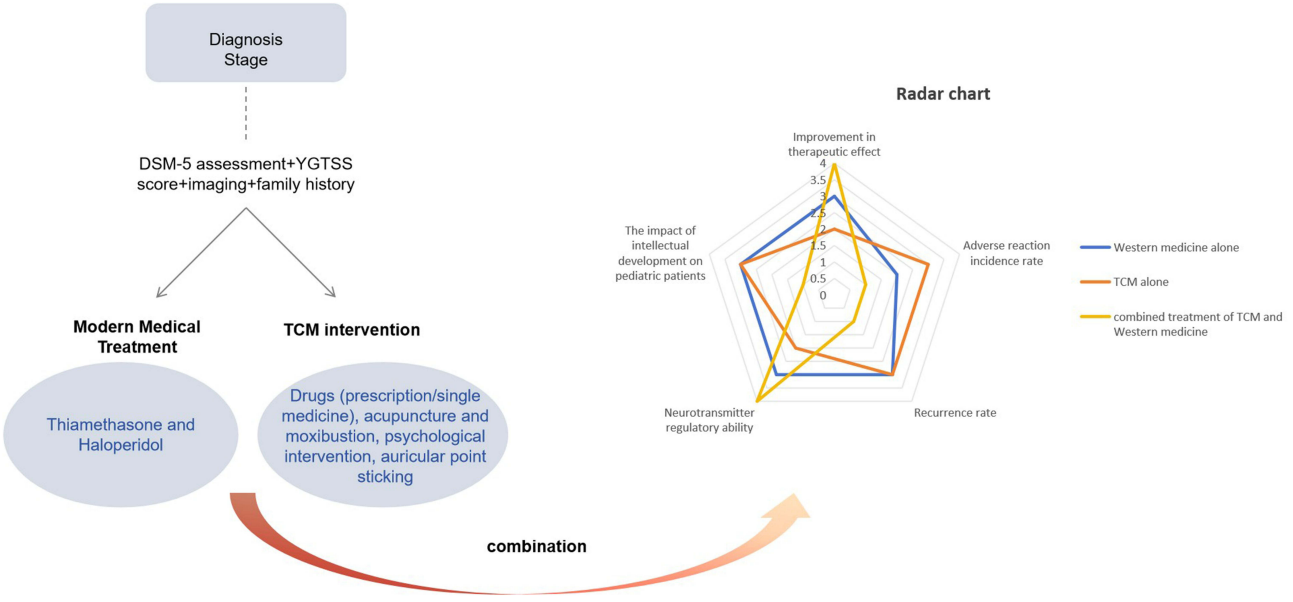


**Figure 3** Integrated Treatment Framework Combining Traditional Chinese and Western Medicine for Tourette Syndrome.


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largely center on methodological limitations, such as small sample sizes, inadequate placebo controls, lack of blinding, and difficulties in isolating pharmacologically active constituents within multi-herbal formulations.

First, many clinical trials evaluating TCM interventions for TS are single-center studies with limited sample sizes, which may restrict generalizability and inflate effect sizes due to random variation or selection bias. A 2020 meta-analysis of randomized controlled trials (RCTs) on TCM for TS highlighted generally favorable outcomes but also underscored that most included studies exhibited a high or unclear risk of bias due to suboptimal randomization procedures and limited blinding.[87] Placebo effects in neuropsychiatric conditions, particularly those with fluctuating symptoms such as TS, are well-documented and may account for part of the observed benefit in some trials that lack rigorous controls.

Second, the complexity of TCM formulas presents substantial challenges for mechanistic interpretation.[88] Unlike single-molecule Western drugs, TCM prescriptions often contain multiple herbal ingredients with synergistic or antagonistic interactions, which complicates the standardization of dose, bioavailability, and pharmacokinetics.[88] Efforts to deconstruct multi-component TCM formulas using systems biology and network pharmacology are still in their early stages and require further refinement to reliably identify active constituents and their molecular targets.[89]

Furthermore, from the standpoint of evidence-based medicine, the current body of literature evaluating TCM's efficacy for TS is disproportionately weighted toward Chinese-language publications, with underrepresentation in high-impact international journals.[90] This publication pattern may reflect regional preferences or positive publication bias. Therefore, calls for more rigorous, multicenter, placebo-controlled, double-blind RCTs have been echoed by international experts to validate preliminary findings and ensure reproducibility across diverse populations.

It is also important to acknowledge the ongoing epistemological debate regarding syndrome differentiation in TCM, which does not conform to nosological systems used in modern biomedicine.[91] While TCM syndrome classification offers a personalized treatment rationale, it may introduce subjectivity that limits replicability. As such, establishing robust diagnostic consensus criteria and integrating biomarker-informed stratification may help bridge this methodological gap.

Overall, while TCM offers a promising complementary approach for TS, the aforementioned concerns underscore the need for continued methodological rigor, pharmacological dissection of active components, and cross-disciplinary collaboration to validate and refine TCM-based interventions.

## Summary

The application of TCM in the treatment of TS has shown promising potential; however, it continues to encounter substantial scientific and clinical scrutiny due to the lack of standardized formulations, limited reproducibility of results due to herbal variability, and the scarcity of large-scale, multicenter randomized controlled trials. While TCM interventions are generally associated with fewer adverse effects compared to conventional pharmacotherapy, the long-term safety and potential toxicity of certain herbal components require further investigation. Moreover, the multi-component, multi-target nature of TCM complicates mechanistic elucidation within the reductionist framework of modern biomedicine.

This review highlights that bridging the gap between traditional TCM concepts and contemporary neurobiological understanding can be facilitated by integrating genetic and pathophysiological insights. For instance, polymorphisms in genes have shown preliminary alignment with TCM syndromes such as "wind-heat invasion" and "liver yang hyperactivity". Furthermore, abnormalities in the CSTC circuit, dopaminergic hyperactivity, and microglial activation, which are core pathophysiological features of TS, may conceptually correspond to TCM patterns such as "internal wind" or "phlegm-heat". Several TCM formulations have demonstrated modulatory effects on these biological processes, including the downregulation of IL1RN expression and the restoration of dopaminergic balance, suggesting a plausible basis for their therapeutic action through gene regulation and pathway modulation.

To enhance the clinical validity of TCM for TS, future studies could prioritize mechanistic investigations using tools such as molecular genetics, transcriptomics, and systems neuroscience, as they may provide critical insight into how individual herbs or multi-herbal formulas regulate neurotransmitter systems and gene expression networks implicated in TS. High-quality evidence could also require rigorously designed randomized controlled trials with multicenter collaboration, standardized herbal processing protocols, and harmonized diagnostic criteria. Notably, standardizing herbal cultivation and processing would reduce batch-to-batch variability, a necessary step toward TCM's recognition in

international clinical guidelines. Artificial intelligence and bioinformatics may further facilitate biomarker identification and pattern classification, contributing to precision-guided syndrome differentiation and personalized therapy.

From a clinical perspective, integrated TCM-Western medicine regimens have demonstrated superior outcomes compared to monotherapies. Meta-analyses and recent randomized controlled trials have shown that combining TCM with pharmacological treatments reduces tic severity and the incidence of adverse drug reactions, supporting their consideration as adjunctive first-line options, particularly in pediatric patients with poor tolerability to antipsychotics. Moreover, non-pharmacological TCM modalities, such as acupuncture and massage, may provide additional symptom relief and functional improvement when incorporated into broader rehabilitation strategies. In summary, aligning TCM theory with genetic and pathophysiological frameworks not only enhances its scientific interpretability but also offers a pathway for its integration into modern clinical practice. Future progress would depend on interdisciplinary collaboration, methodological rigor, and regulatory standardization to transform preliminary findings into biologically plausible, clinically meaningful, and globally acceptable interventions for TS.

## Disclosure

The authors report no conflicts of interest in this work.

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