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REVIEW

Evidence Based Research on Medication Patterns in the Traditional Chinese Medicine Treatment of Tic Disorders: A Complete Review

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Purpose: To investigate the medication principles of Traditional Chinese Medicine (TCM) in the treatment of tic disorders (TD) and to provide evidence-based references for clinical practice.

Patients and Methods: A comprehensive search was conducted for literature on the treatment of TD using TCM from CNKI, Wan Fang Data, VIP, and PubMed. Based on the inclusion and exclusion criteria, TCM prescriptions were extracted and entered into an Excel 2020 database. Statistical analyses, including frequency analysis, association rule mining, and hierarchical clustering, were performed using Excel 2020, SPSS Modeler 18.0, and SPSS Statistics 26.0 software.

Results: Totally 559 articles were included, comprising 1001 prescriptions, 369 herbs, and 13,678 frequencies. The properties of the herbs were primarily cold, warm, and mild, with the most common flavors being sweet, bitter, and pungent. The most frequent meridians were the liver, lung, and spleen. High-frequency herbs included Radix paeonia alba, Uncaria rhynchophylla, and Glycyrrhiza, etc. The primary efficacy included liver-soothing and wind-calming, tonifying spleen and Qi, and resuscitation-inducing aromatic, etc. The most frequent herb pairs were Uncaria rhynchophylla-Radix paeonia alba, Uncaria rhynchophylla-Glycyrrhiza, Radix paeonia alba-Glycyrrhiza, and Uncaria rhynchophylla-Glycyrrhiza-Radix paeonia alba, Radix paeonia alba-Gastrodia elata-Uncaria rhynchophylla. Forty herbs had a frequency of >100, which could be classified into 6 clusters: (1) hepatotropic and neuroregulatory herbs; (2) tonifying herbs; (3) hydragogue and dampness-regulating herbs, etc. Additionally, there were specific herb combinations such as Bupleurum chinense for liver-soothing, insect herbs for wind-expelling and meridian-unblocking, and Angelica sinensis and Ligusticum wallichii for removing blood stasis.

Conclusion: This study highlights the key medication principles and herb combinations used in the treatment of TD with TCM, providing valuable insights into current treatment practices. Further research, including standardized clinical assessments and investigation into the mechanisms of these herbs and their combinations, is needed to validate and optimize their potential therapeutic effects.

Keywords: Tic disorders, traditional Chinese medicine, data mining, regularity, herbs

Introduction

Tic disorders (TD) are neuropsychiatric conditions that typically manifest in childhood or adolescence, characterized by the presence of one or more motor tics and/or vocal tics.[1] The global prevalence of TD among children is approximately 0.77%, with a higher rate in males (1.06%) than in females (0.25%).[2] The prevalence rate among adults is approximately 0.05%. Based on clinical manifestations and the duration of the disease, TD are classified into transient tic disorder,

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chronic motor or vocal tic disorder, and tourette syndrome, among which transient tic disorder is the most common (2.99%).[3,4] The recent incidence rate of TD among Chinese children is 2.68%, involving nearly 10 million children.[5] The peak age of onset occurs between 4 and 8 years, with symptom severity typically peaking at ages 10–12 years. While symptoms gradually ameliorate with age, approximately 25% of patients experience persistent manifestations into adulthood.[6,7] A significant proportion of TD patients (85.7%) experience lifelong comorbid psychiatric disorders, including attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), anxiety, depression, and self-injurious behaviors. These comorbidities further complicate the clinical presentation, intensifying both the complexity and severity of the condition.[6,7]

The etiology of TD is multifactorial, with genetic, neurological, immunological, environmental, and psychological factors all potentially contributing to its development.[8,9] The prevailing pathophysiological hypothesis implicates dysfunction in the cortico-striatal-thalamo-cortical (CSTC) circuit and aberrant striatal dopamine receptor activity as central mechanisms in the disorder's pathogenesis.[10] In Western medical practice, there is currently no curative treatment for childhood TD. In addition to psychotherapy as the initial intervention,[11] first-line drugs mainly include dopamine D2 receptor antagonists (such as risperidone and aripiprazole), dopamine system stabilizers, selective monoamine antagonists, central α2 receptor agonists, antiepileptic drugs, etc.[12–15] However, these treatments often lead to extrapyramidal side effects, and the symptoms tend to recur after discontinuation, contributing to intractable Tourette syndrome.[16] Surgical interventions or non-invasive neuromodulation techniques-such as repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS)-are commonly associated with higher risks, substantial costs, and fluctuating therapeutic efficacy.[17]

In contrast, Traditional Chinese Medicine (TCM) approaches the treatment of TD by considering the child's physiological and pathological characteristics, offering a more individualized and targeted therapeutic approach. TCM's multimodal approach-integrating liver-soothing herbs (eg, Uncaria rhynchophylla), neuroprotective agents (eg, Radix Paeonia Alba), and spleen-tonifying formulations – achieves significant efficacy in treating TD, with a lower recurrence rate compared to conventional treatments.[18,19] TCM achieves therapeutic effects through modulation of neurotransmitter release via multiple targets, influencing both peripheral and central nervous system signaling. This modulation is thought to play an important role in addressing the underlying pathogenesis of TD and improving both tic symptoms and TCM-defined syndromes associated with the disorder.

Data mining has emerged as a promising strategy in TCM research for uncovering hidden treatment patterns and insights. By integrating manual classification with algorithm-based techniques, it facilitates the identification of meaningful treatment rules from extensive datasets, providing valuable evidence to support both clinical practice and medical research. Although literature on Tourette Disorder (TD) is growing, its precise etiology and pathophysiological mechanisms remain unclear. Current treatments primarily rely on Western pharmacological interventions; however, TCM offers an effective and safer alternative with fewer side effects, aligning more closely with pediatric characteristics.[20] This study employs data mining technology to investigate TCM treatment principles for TD, aiming to provide data-driven support for clinical management.

Literature Retrieval and Methods

Literature Retrieval

A systematic search was conducted to identify clinical studies on TCM interventions for TD across four major databases: the China National Knowledge Infrastructure (CNKI), Wan Fang Data Knowledge Service Platform, VIP Chinese Periodical Service Platform, and PubMed. The search covered all available records from each database's inception until December 31, 2024. To ensure a comprehensive retrieval, a Boolean logic search strategy was employed, incorporating both Medical Subject Headings (MeSH) terms and free-text keywords related to TD and TCM therapy. The disease-specific search terms included English keywords such as "Tourette Syndrome" "Tourette Disorder" "multiple motor and vocal tic disorder" "Gilles de la Tourette Syndrome" "Gilles de la Tourette Disorder" and "Tic Disorder" along with their Chinese equivalents: "抽动秽语综合征", "抽动障碍", "多发性抽动症", and "图雷特综合征". For TCM therapy, the search terms comprised English keywords as "Traditional Chinese Medicine" "Chinese Medicine" "herbal

medicine" "combination of acupuncture and medication" and "integration of Traditional Chinese and Western Medicine" as well as corresponding Chinese terms: "中医药", "中药", "针药结合", "针药并用", and "中西医结合".

The retrieved records were imported into EndNote X9 for deduplication, followed by manual screening based on predefined eligibility criteria. Studies meeting the inclusion criteria underwent full-text review, and relevant TCM prescriptions were systematically extracted. These prescriptions were then structured into a database using Excel 2020, facilitating subsequent analysis of herbal compositions, treatment efficacy, and therapeutic mechanisms. This approach ensured a rigorous and reproducible synthesis of evidence for TCM-based TD interventions.

Eligibility Criteria

The study employed stringent eligibility criteria to ensure the inclusion of high-quality, relevant literature. The inclusion criteria comprised: (1) clinical research studies or documented clinical experiences of renowned TCM practitioners; (2) studies involving participants meeting established diagnostic criteria for TD; (3) interventions primarily consisting of TCM oral decoctions, either as monotherapy or combined with other TCM/conventional therapies; (4) availability of complete and detailed prescription records; and (5) reported treatment efficacy. Conversely, exclusion criteria eliminated: (1) non-clinical literature (eg, reviews, meta-analyses, animal studies); (2) studies with incomplete prescriptions; (3) duplicate publications; and (4) literature with unavailable full texts.

Study Selection

Two independent researchers screened retrieved literature initial title/abstract review against eligibility criteria, followed by full-text evaluation of potentially eligible articles. Discrepancies were resolved via discussion. Key screening parameters included diagnostic/therapeutic standardization, prescription completeness, and efficacy reporting.

Data Extraction and Standardization

Following study selection, a systematic data extraction protocol was implemented to ensure comprehensive and standardized collection of relevant information. Two trained researchers independently extracted data from eligible studies using a predefined Excel 2020 template, capturing key elements including: (1) author information, (2) diagnostic criteria, (3) TCM syndrome differentiation, (4) therapeutic principles, (5) prescription names, and (6) complete herbal compositions. To maintain data integrity, duplicate prescriptions were identified and consolidated, with only unique formulations retained for analysis, and syndrome-specific prescriptions were analyzed collectively.

All extracted data underwent rigorous cross-verification by both researchers to ensure accuracy. For terminology standardization, authoritative references were employed: syndrome classifications were standardized according to the Terminology for Clinical Diagnosis and Treatment of Traditional Chinese Medicine (Part 2: Syndromes), treatment principles were aligned with Part 3 of the same reference, while herb names were normalized using the Pharmacopoeia of the People's Republic of China (2020 edition) supplemented by the Dictionary of Alternative Names for Chinese Herbs and the Great Dictionary of Chinese Herbs to resolve any nomenclature discrepancies. During analysis, prescriptions were first aggregated without syndrome distinction for core pattern mining, then categorized by six syndrome types.

Statistical Analysis

The extracted data underwent comprehensive statistical analysis to identify patterns within TCM prescriptions for TD. First, frequency analysis was conducted using the pivot table function in Excel 2020 to quantify the occurrence of individual herbs, as well as their properties (including taste and meridian tropism). Each herb was coded in a binary matrix (1 = present in prescription, 0 = absent) to facilitate quantitative comparison across formulations. Subsequently, association rule mining employed the Apriori algorithm to identify clinically significant herb combinations, with inclusion criteria set at minimum support (≥10%), minimum confidence (≥50%), and maximum antecedents (≤5) to ensure meaningful pattern recognition. This analysis specifically targeted high-frequency herbs (appearing in ≥100 prescriptions) to reveal core medication strategies. Finally, hierarchical clustering was performed through R-type hierarchical clustering (using inter-group linkage method and Pearson correlation coefficient) to explore potential functional groupings among high-frequency herbs, with cluster constrained to 5–10 groups for optimal discrimination.

The resulting dendrogram visualized herb relationships, revealing potential synergistic combinations in TCM approaches for TD.

Results

Literature Inclusion Results

A comprehensive literature search across four major databases yielded 2700 potentially relevant articles, comprising 1389 records from CNKI, 368 from Wan Fang, 886 from VIP, and 57 from PubMed. After applying inclusion/exclusion criteria, 2141 articles were excluded for: (1) non-conformance with study design requirements (eg, reviews or animal studies), (2) incomplete prescription data, or (3) inability to obtain full texts. This yielded 559 eligible studies meeting all criteria, including documented TCM prescriptions, clear diagnostic standards, and reported treatment outcomes, without Adverse Drug Reactions (ADR) reports. The selection process is detailed in Figure 1. All of the analyzed 559 studies were categorized into six syndrome types, totaling 773 occurrences: (1) Liver Hyperactivity with Wind Stirring (246, 31.82%), (2) Yin Deficiency with Wind Stirring (168, 21.73%), (3) Phlegm-Heat Harassing the Heart (125, 16.17%), (4) Liver Depression and Spleen Deficiency (97, 12.55%), (5) Spleen Deficiency with Phlegm Accumulation (78, 10.09%), and (6) Heart-Spleen Dual Deficiency (59, 7.63%).

Analysis of Herb Properties, Flavors, and Meridian Tropism

The analysis of 13,824 herb property records revealed a distinct distribution: cold properties predominated (5308 records, 38.38%), followed by mild (3717 records, 26.88%) and warm (3674 records, 25.57%) properties. Flavor analysis of 20,999 records demonstrated that sweet (6588 occurrences, 31.37%), bitter (5732, 27.30%), and pungent (5195, 24.74%) flavors as the most prevalent. Meridian tropism analysis of 30,344 records showed the liver meridian (7729, 25.47%) as the primary target, followed by lung (6495, 21.40%), spleen (5039, 16.60%), stomach (4261, 14.04%), and kidney (2877, 9.48%) meridians (Figure 2). These findings align with TCM theory regarding TD pathogenesis involving liver wind agitation and phlegm-heat accumulation syndromes.

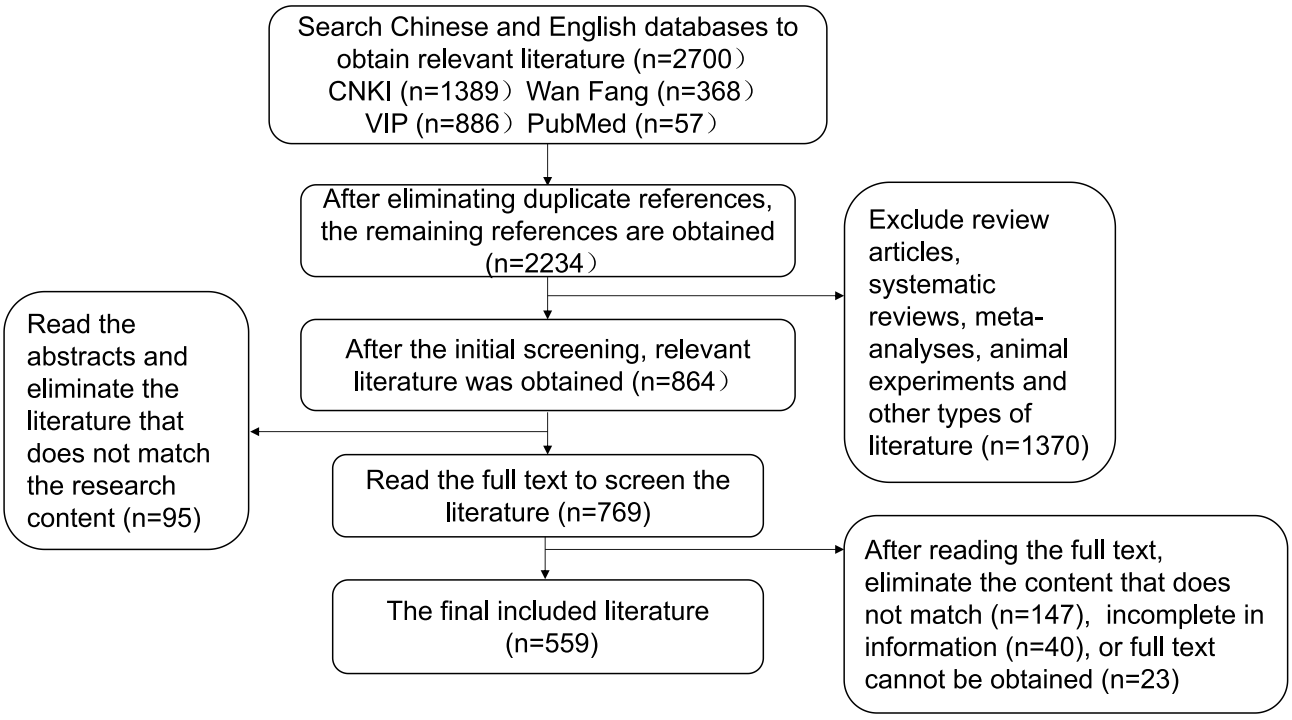

Figure 1 The literature inclusion process.

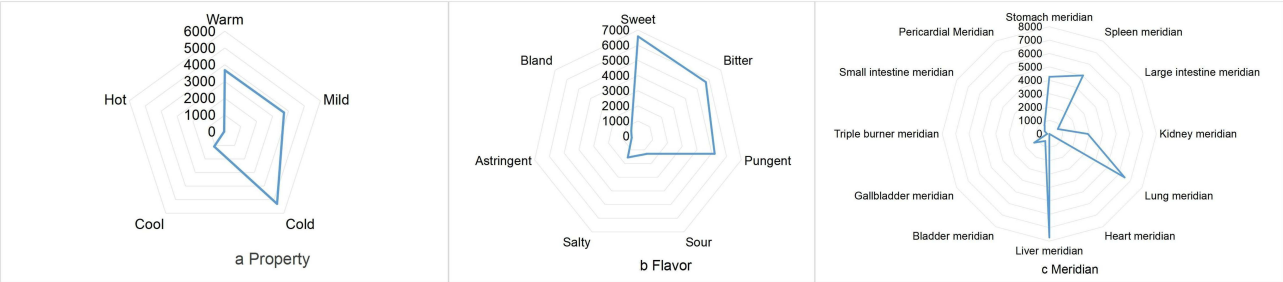

Figure 2 Radar chart of the property, flavor, and Meridian of herbs (**a**) Property; (**b**) Flavor; (**c**) Meridian.

High-Frequency Herb Utilization in TD Treatment

Our systematic analysis of 10,001 prescriptions identified 369 distinct herbal medicines with 13,678 applications. Among these, top 40 herbs demonstrated particularly high utilization frequencies over 100, including Radix paeonia alba, Uncaria rhynchophylla, Glycyrrhiza uralensis, Poria cocos, Silkworm, Scorpio maurus, Acorus tatarinowii, Pinellia ternata, Gastrodia elata, etc.

These high-frequency herbs were functionally classified into several therapeutic categories: (1) tonifying herbs (Radix paeonia alba, Glycyrrhiza uralensis, Atractylodes macrocephala, Angelica sinensis); (2) hepatotropic and neuroregulatory herbs (Uncaria rhynchophylla, Silkworm, Scorpio maurus, Gastrodia elata); (3) hydragogue and dampness-regulating herbs (primarily Poria cocos); (4) resuscitation-inducing aromatic herbs (primarily Acorus tatarinowii); (5) mucolytic and antitussive herbs (Pinellia ternata, Platycodon, Arisaema cum bile); (6) diaphoretic herbs (Chrysanthemum morifolium, Bupleurum chinense, Kudzu Root); (7) sedative herbs (Fossilized mammalian bone, Polygala tenuifolia, Jujube seed); (8) Qi-regulating herbs (Dried tangerine peel, Fructus aurantii); and (9) circulatory stimulants (Radix curcuma, Ligusticum wallichii).

This pharmacological profile reflects TCM's multidimensional approach to TD, simultaneously addressing primary neurological dysfunction through neuroregulatory mechanisms while managing secondary manifestations via metabolic regulation, fluid balance, and systemic homeostasis. The frequency distribution and categorical classifications of top 30 high-frequency herbs are presented in Table 1.

Table 1 Frequency, Botanical Part and Main Phytochemicals of Top 30 High-Frequency Herbs Use

Herb	Efficacy	Medicinal Part	Primary Components	Frequency	Percentage
Radix Paeonia Alba	Tonifying herbs	Dried root	Paeoniflorin	549	4.01
Uncaria Rhynchophylla	Liver-soothing and wind-calming herbs	Dry hooked stems and branches	Rhynchophylline	498	3.64
Glycyrrhiza	Tonifying herbs	Roots and rhizomes	Glycyrrhizic acid, Liquiritin	374	2.73
Poria cocos	Hydragogue and dampness-regulating herbs	Dried sclerotium	Pachyman, Pachymic acid	370	2.71
Silkworm	Liver-soothing and wind-calming herbs	Dried body	Ammonium oxalate	360	2.63
Scorpion	Liver-soothing and wind-calming herbs	Dried body	Buthotoxin	327	2.39
Acorus Tatarinowii	Resuscitation-inducing aromatic herbs	Dried rhizome	β-Asarone, α-Asarone	322	2.35
Pinellia Ternata	Mucolytic and antitussive herbs	Dried tuber	Pinelline, Pinellin	321	2.35
Gastrodia elata	Liver-soothing and wind-calming herbs	Dried tuber	Gastrodin	314	2.30

(*Continued*)

Table 1 (Continued).

Herb	Efficacy	Medicinal Part	Primary Components	Frequency	Percentage
Cicada Slough	Exterior-releasing herbs	Exuviae	Chitin, Amino acids	294	2.15
Oyster Shell	Liver-soothing and wind-calming herbs	Shell	Calcium carbonate	281	2.05
Fossilized mammalian bone	Sedative herbs	Fossilized Bone	Calcium carbonate	276	2.02
Dried Tangerine Peel	Qi-regulating herbs	Dried Pericarp	Nobiletin, Hesperidin	240	1.75
Chrysanthemum	Exterior-releasing herbs	Dried capitulum	Volatile oils, Flavonoids	239	1.75
Bupleurum chinense	Exterior-releasing herbs	Dried root	Saikosaponins	238	1.74
Atractylodes Macrocephala	Tonifying herbs	Dried rhizomez	Atractylenolide	201	1.47
Polygala Tenuifolia	Sedative herbs	Dried root	Tenuifolin, Polygalaxanthone	193	1.41
Radix Curcuma	Blood-activating and stasis-resolving herbs	Dried tuberous root	Curcumin, Volatile oils	190	1.39
Kudzu Root	Exterior-releasing herbs	Dried root	Puerarin, Pueraria lobata total flavonoids	182	1.33
Fried Glycyrrhiza	Tonifying herbs	Honey-fried roots and rhizomes	Glycyrrhizic acid (Changes in content after processing)	173	1.26
Rehmannia Glutinosa	Heat-clearing herbs	Fresh or dried tuberous roots	Catalpol, Rehmannioside	167	1.22
Scutellaria Baicalensis	Heat-clearing herbs	Dried root	Baicalin, Baicalein, Wogonoside	165	1.21
Angelica Sinensis	Tonifying herbs	Root	Ferulic acid, Ligustilide	155	1.13
Ligusticum Wallichii	Blood-activating and stasis-resolving herbs	Dried rhizome	Tetramethylpyrazine, Ligustilide	146	1.07
Magnolia Bud	Exterior-releasing herbs	Dried inflorescence	Eucalyptol	131	0.96
Fructus Gardeniae	Heat-clearing herbs	Dried ripe fruit	Geniposide, Crocin	130	0.95
Lycopodium	Wind-dampness-dispelling herbs	Dried whole plant	Lycopodine	129	0.94
Concha Haliotidis	Liver-soothing and wind-calming herbs	Abalone shell	Calcium carbonate	127	0.93
Siler	Exterior-releasing herbs	Root	Cimifugin, Saposhnikovan	123	0.90
Scolopendra	Liver-soothing and wind-calming herbs	Dried body	Scolopendrin, Histamine	115	0.84

Association Rules Analysis of High-Frequency Herb Combinations

The association patterns among high-frequency herbs were analyzed using the Apriori algorithm with predefined parameters (minimum support = 10%, minimum confidence = 50%, maximum antecedent = 5). This generated 252 significant association rules, revealing core combinatorial patterns in clinical prescriptions (Figure 3).

The most frequent pairwise herb combinations were: (1) Uncaria rhynchophylla - Radix paeonia alba (support = 54.85%, confidence = 56.47%), (2) Uncaria rhynchophylla - Glycyrrhiza uralensis (support = 49.75%, confidence = 62.24%), (3) Radix paeonia alba - Glycyrrhiza uralensis (support = 37.36%, confidence = 62.57%), (4) Uncaria rhynchophylla - Poria cocos (support = 36.96%, confidence = 51.62%), (5) Radix paeonia alba - Poria cocos (support = 36.96%, confidence = 54.60%), and (6) Uncaria rhynchophylla - Silkworm (support = 35.96%, confidence = 55.28%) (Table 2). For three-herb combinations,

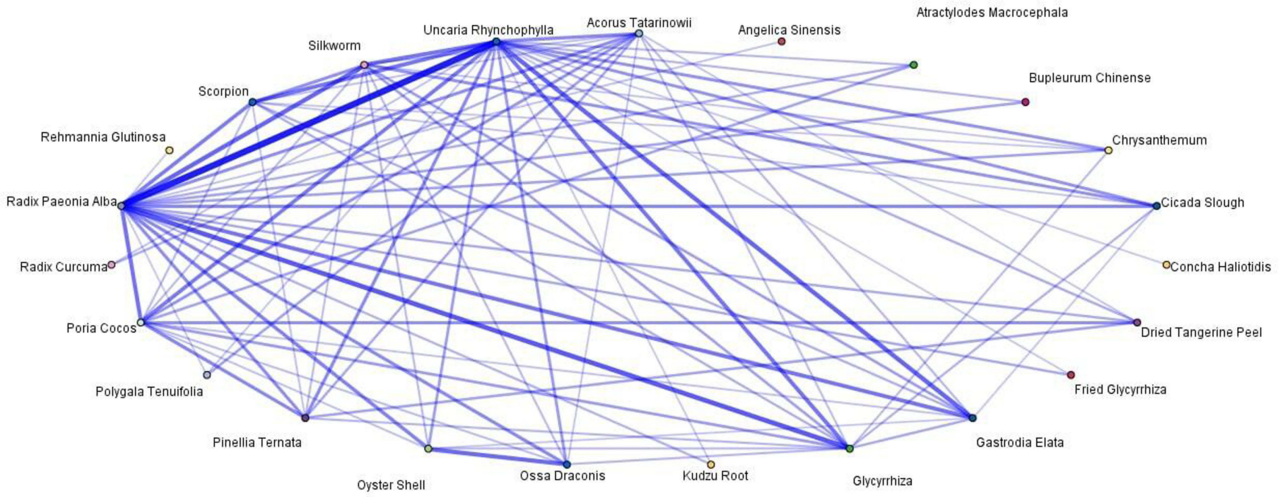

Figure 3 High-frequency herbs association rules network.

the most prevalent rules included: (1) Uncaria rhynchophylla - Glycyrrhiza uralensis - Radix paeonia alba (support = 23.38%, confidence = 59.83%), (2) Radix paeonia alba - Gastrodia elata - Uncaria rhynchophylla (support = 21.78%, confidence = 68.81%), (3) Uncaria rhynchophylla - Silkworm - Radix paeonia alba (support = 21.68%, confidence = 61.29%), (4) Uncaria rhynchophylla - Fossilized mammalian bone - oyster shell (support = 21.18%, confidence = 52.36%), and (5) Radix paeonia alba - Fossilized mammalian bone - oyster shell (support = 21.18%, confidence = 60.85%).

These combinatorial patterns demonstrate consistent clinical preferences for neuroactive herb combinations that synergistically target multiple TD pathological mechanisms, particularly integrating liver-soothing, wind-calming, and spleen-strengthening agents (Table 3).

Systematic Cluster Analysis of High-Frequency Herbs

A hierarchical cluster analysis (R-type) was performed on herbs with usage frequency ≥100 times using SPSS 26.0 software. The analysis employed Pearson's correlation coefficient as the similarity measure, with case-based clustering

Table 2 Association Rules of Two Herbs

Top 15 Associations Between 2 Types of Herbs Based on Support Degree					
Herb	**Preceding Item**	**Support Degree**	**Confidence Degree**	**Lift**	**Frequency**
Uncaria Rhynchophylla	Radix Paeonia Alba	54.85	56.47	1.14	549
Radix Paeonia Alba	Uncaria Rhynchophylla	49.75	62.24	1.14	498
Uncaria Rhynchophylla	Glycyrrhiza	37.36	53.21	1.08	374
Radix Paeonia Alba	Glycyrrhiza	37.36	62.57	1.14	374
Uncaria Rhynchophylla	Poria cocos	36.96	51.62	1.04	370
Radix Paeonia Alba	Poria cocos	36.96	54.60	1.00	370
Uncaria Rhynchophylla	Silkworm	35.96	55.28	1.11	360
Radix Paeonia Alba	Silkworm	35.96	60.28	1.10	360
Uncaria Rhynchophylla	Scorpion	32.67	60.55	1.22	327
Radix Paeonia Alba	Scorpion	32.67	57.80	1.05	327
Uncaria Rhynchophylla	Acorus Tatarinowii	32.17	53.73	1.08	322
Radix Paeonia Alba	Acorus Tatarinowii	32.17	51.24	0.93	322
Poria cocos	Pinellia Ternata	32.07	54.21	1.47	321
Uncaria Rhynchophylla	Pinellia Ternata	32.07	52.96	1.07	321
Radix Paeonia Alba	Pinellia Ternata	32.07	51.71	0.94	321

Table 3 Association Rules of Three Herbs

Top 15 Associations Between 3 Types of Herbs Based on Support Degree					
Herb	**Preceding Item**	**Support Degree**	**Confidence Degree**	**Lift**	**Frequency**
Uncaria Rhynchophylla	Glycyrrhiza + Radix Paeonia Alba	23.38	59.83	1.20	234
Radix Paeonia Alba	Gastrodia elata + Uncaria Rhynchophylla	21.78	68.81	1.26	218
Uncaria Rhynchophylla	Silkworm + Radix Paeonia Alba	21.68	61.29	1.23	217
Uncaria Rhynchophylla	Fossilized mammalian bone + Oyster Shell	21.18	52.36	1.052	212
Radix Paeonia Alba	Fossilized mammalian bone + Oyster Shell	21.18	60.845	1.11	212
Uncaria Rhynchophylla	Poria cocos + Radix Paeonia Alba	20.18	59.41	1.19	202
Uncaria Rhynchophylla	Gastrodia elata + Radix Paeonia Alba	19.88	75.38	1.52	199
Scorpion	Silkworm + Uncaria Rhynchophylla	19.88	50.75	1.55	199
Radix Paeonia Alba	Silkworm + Uncaria Rhynchophylla	19.88	66.83	1.22	199
Radix Paeonia Alba	Glycyrrhiza + Uncaria Rhynchophylla	19.88	70.35	1.28	199
Silkworm	Scorpion + Uncaria Rhynchophylla	19.78	51.01	1.42	198
Radix Paeonia Alba	Scorpion + Uncaria Rhynchophylla	19.78	63.13	1.15	198
Pinellia Ternata	Poria cocos + Uncaria Rhynchophylla	19.09	52.36	1.63	191
Radix Paeonia Alba	Poria cocos + Uncaria Rhynchophylla	19.08	62.83	1.15	191
Silkworm	Scorpion + Radix Paeonia Alba	18.88	52.38	1.46	189

methodology to identify natural herb groupings. Given its exploratory nature, cluster solutions were constrained to 5–10 groups to optimize interpretability while maintaining clinical relevance. The dendrogram (Figure 4) revealed distinct pharmacological clusters based on prescription patterns, with herbs grouping according to therapeutic properties and traditional functional classifications. This approach identified coherent herb clusters reflecting both TCM theory and contemporary TD treatment practices, providing empirical validation for established herbal categories while potentially revealing novel therapeutic combinations worthy of further investigation.

Discussion

Properties, Flavors, and Meridian Tropism of Herbs

Analysis of 13,824 herb property records revealed distinct therapeutic patterns. Cold properties predominated (38.38%), followed by mild (26.88%) and warm properties (25.57%). This distribution reflects core TCM therapeutic principles as: cold-natured herbs clear heat and resolve phlegm, targeting the liver Qi stagnation and phlegm-heat disturbance central to TD pathogenesis.[21,22] The inclusion of mild-natured herbs demonstrates a therapeutic consideration for pediatric patients, allowing for gentle regulation while minimizing potential adverse effects.[23] Warm-natured herbs are incorporated to support spleen Qi and digestive function, which is crucial for chronic condition management.[24]

Analysis of 20,999 flavor records identified sweet (31.37%), bitter (27.30%), and pungent (24.74%) as the predominant therapeutic flavors. Sweet-flavored herbs are primarily used to tonify the spleen and stomach, addressing common digestive deficiencies in TD patients, which is crucial for patients exhibiting nutritional deficiencies.[21,23] Bitter-flavored herbs serve dual therapeutic roles in both resolving phlegm accumulation and clearing heat manifestations.[22] Pungent-flavored herbs promote Qi circulation and provide calming effects, addressing both physical and neurological symptoms.[24]

Meridian tropism analysis revealed a focused distribution pattern, with the liver (25.47%), lung (21.40%), spleen (16.60%), stomach (14.04%), and kidney (9.84%) meridians receiving primary attention. This distribution aligns with current understanding of TD pathophysiology in TCM theory, where liver system regulation forms the treatment cornerstone.[22,24] The inclusion of lung meridian herbs reflects the importance of respiratory and immune functions in symptom management.[23] Spleen and Stomach meridian herbs provide digestive support addressing both core pathology and comorbidities,[23] while kidney-nourishing herbs provide foundational support for neurological development and function.[24]

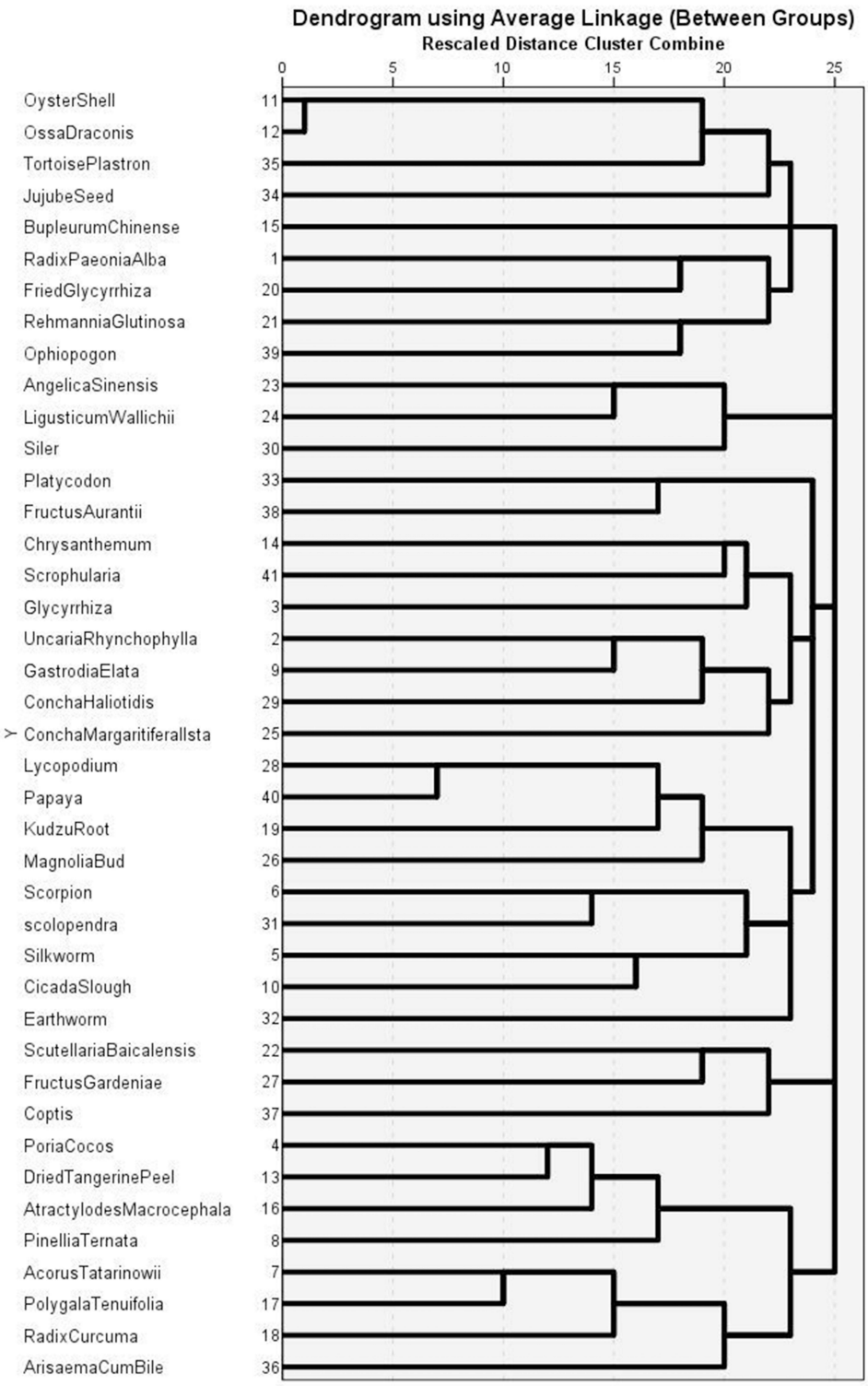

Figure 4 Dendrogram of herbs clustering analysis.

The clinical applicability of these herbs can be shaped by their dosage forms and administration routes. Most high-frequency herbs identified in this study are administered as oral decoctions, allowing for systemic absorption and multi-target modulation.[25] Processing methods such as stir-frying or steaming are applied to reduce toxicity or enhance bioavailability. Topical applications, including medicated plasters or herbal baths, are used to deliver localized

therapeutic effects. Studies suggest that oral formulations primarily act by modulating neurotransmitter systems, anti-inflammatory signaling pathways, and antioxidant defenses, whereas topical forms may exert effects through transdermal absorption.[26] The diverse dosage forms not only broaden the therapeutic scope but also enable treatment individualization according to individual patient needs.

High-Frequency Herbs in TD Treatment

The pharmacological analysis revealed distinct categories therapeutically effective herbs for TD, with liver-soothing and wind-calming herbs constituting the core approach. Among the 30 most frequently prescribed herbs (usage >100 times), Radix paeonia alba, Uncaria rhynchophylla, and Glycyrrhiza were most prevalent. These were followed by tonifying herbs, diuretic dampness-excreting herbs, and resuscitation-inducing aromatic herbs, with additional contributions from phlegm-resolving, exterior-releasing, sedative, Qi-regulating, and blood-activating herbs.

Radix paeonia alba demonstrated multifaceted therapeutic effects, including blood nourishment, liver modulation, and pain relief.[27] Its active component, total glucosides of paeony (TGP), exhibits neuroprotective properties through modulation of monoamine neurotransmitter levels in cerebral tissue, potentially inhibiting tic occurrence via neurotransmitter regulation.[28]

The liver-soothing and wind-calming herb category, particularly Uncaria rhynchophylla, Silkworm, Gastrodia elata, and Scorpio, showed significant dopaminergic and serotonergic modulation.[29–31] Isorhynchophylline, an active alkaloid from Uncaria rhynchophylla, exhibited dual mechanisms: (1) nigrostriatal dopamine system modulation via 5-HT2A receptor blockade and (2) neuroprotection through enhanced autophagy and reduced oxidative stress-induced apoptosis.[32–34] Gastrodin exhibited striatal 5-HT concentration normalization and glutamatergic modulation via NMDA receptor pathway inhibition.[30,35]

Formulations derived from Scorpio demonstrated multimodal mechanisms, including monoamine neurotransmitter modulation and anti-inflammatory effects via TNF-α and IL-1β suppression.[36,37] Both Silkworm and Scorpio extracts showed superior anticonvulsant activity compared to conventional sedatives, with additional benefits from essential trace element supplementation (zinc, iron, calcium, magnesium).[38–41] Complementary neuropharmacological effects were observed with Fossilized mammalian bone (calcium-mediated muscle excitability reduction) and Polygala tenuifolia (multipotent central nervous system modulation including sedation and neuroprotection).[42]

Beyond pharmacological classification, the therapeutic potential of high-frequency herbs is further substantiated by their principal bioactive phytochemicals. For instance, Radix paeonia alba is rich in paeoniflorin, a monoterpene glycoside with anti-inflammatory and neuromodulatory activities,[28] Uncaria rhynchophylla contains rhynchophylline, an indole alkaloid with neuroprotective and anticonvulsant effects;[29] Gastrodia elata contains gastrodin, which exerts sedative, anticonvulsant, and antioxidant actions;[32] and Pinellia ternata provides alkaloids and lectins associated with antiemetic and neuroregulatory properties.[43] Identification of these representative compounds not only reinforces clinical efficacy but also establishes a mechanistic bridge linking TCM therapeutic indications with contemporary biomedical evidence.

To further strengthen the link between TCM theory and modern neuroscience, we summarized the neuroactive mechanisms of the most frequently (top 15) used herbs from the perspectives of their principal bioactive constituents, molecular targets, and pharmacological actions (Table 4). This analysis established a translational framework that connects traditional therapeutic indications with contemporary neurobiological evidence. The integration revealed potential mechanisms-such as neurotransmitter modulation, neuroprotection, anti-inflammatory activity, and synaptic plasticity enhancement-through which these herbs may exert therapeutic effects in TD.

Herb Combination Mechanisms and Association Rules

The pharmacological analysis revealed significant therapeutic synergies between key herb pairs in TD treatment. The Uncaria rhynchophylla-Radix paeonia alba combination demonstrated multimodal neuroregulatory effects, primarily influencing chemical synaptic transmission, monoamine transport, and circulatory system processes.[28] This pairing modulates dopaminergic and serotonergic neurotransmission through synergistic interaction of total glucosides of paeony (TGP) and Uncaria alkaloids, effectively regulating DA and 5-HT levels in striatal pathways.[27,28,31]

Table 4 Modern Pharmacological Mechanisms of Top 15 High-Frequency Herbs for TD Treatment

Herb	Major Active Compounds	Primary Molecular Targets	Neuropharmacological Mechanisms
Uncaria rhynchophylla	Isorhynchophylline, rhynchophylline	5-HT_2A receptor, DA receptors, NMDA receptor	Modulates dopaminergic/serotonergic transmission; inhibits NMDA-mediated excitotoxicity; suppresses TNF-α/IL-1β–driven neuroinflammation.
Radix paeonia alba	Paeoniflorin, albiflorin (TGP)	Monoamine transporters, NF-κB	Balances DA/5-HT/NE; inhibits NF-κB signaling; neuroprotection against oxidative/inflammatory injury.
Glycyrrhiza uralensis	Glycyrrhizic acid, liquiritigenin	NF-κB, BDNF/TrkB	Broad anti-inflammatory effects; elevates hippocampal BDNF; supports monoamine homeostasis; synergizes with *Paeonia*.
Poria cocos	Pachymic acid, polysaccharides	NF-κB, p38 MAPK	Down-regulates neuroinflammation; modulates neuro-immune response; supports spleen function relevant to phlegm-damp patterns.
Silkworm	Proteins, amino acids, trace elements	PI3K/Akt, cholinergic/ endocannabinoid systems	PI3K/Akt-mediated neuroprotection; anticonvulsant/ antispasmodic actions; adjusts cholinergic/endocannabinoid signaling.
Scorpio	Peptide toxins, amino acids	VGSCs; inflammatory mediators	Modulates monoamines; anticonvulsant/sedative; suppresses TNF-α/IL-1β; trace-element support.
Acorus tatarinowii	β-asarone, α-asarone	DA/5-HT systems	Enhances cognition; regulates DA/5-HT transmission; attenuates neuroinflammation.
Pinellia ternata	Alkaloids, polysaccharides	Cholinergic & inflammatory pathways	Anti-inflammatory/antiemetic; mitigates phlegm-related neuro-somatic symptoms; supports gut–brain modulation.
Gastrodia elata	Gastrodin, vanillyl alcohol	NMDA; PI3K/Akt/GSK-3β; SERT/DAT	Inhibits glutamatergic excitotoxicity; activates survival signaling; normalizes 5-HT/DA turnover; anti-inflammatory.
Cicada slough	Chitin, amino acids, peptides	Inflammatory cytokines; ion-channel stabilization (indirect)	Anti-inflammatory/immunoregulatory effects; helps stabilize neuronal excitability in pediatric TD contexts.
Oyster shell	Calcium carbonate, trace minerals	Neuromuscular excitability; GABAergic tone (indirect)	Sedative/anxiolytic properties; reduces neuromuscular hyperexcitability; supports calcium-mediated inhibitory balance.
Fossilized mammalian bone	Calcium salts, trace minerals	Neuromuscular excitability	Sedative/antispasmodic; complements Concha ostreae in reducing motor hyperexcitability in TD.
Dried tangerine peel	Nobiletin, hesperidin	NF-κB; cholinergic pathways	Anti-inflammatory/antioxidant; modulates cholinergic signaling; supports gut–brain axis and symptom control.
Chrysanthemum morifolium	Luteolin, apigenin, chlorogenic acids	NF-κB/iNOS/COX-2	Antioxidant and anti-inflammatory actions; potential neurosedative support; adjunct for wind-heat components.
Bupleurum chinense	Saikosaponins (eg, SSa/SSd)	NF-κB/MAPK; HPA axis	Reduces neuroinflammation; modulates stress/HPA responses; supports monoamine balance; often paired with *Paeonia*.

Abbreviations: TD, Tic disorders; DA, dopamine; NE, norepinephrine; 5-HT, 5-hydroxytryptamine (serotonin); TGP, total glucosides of Paeonia; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; BDNF, brain-derived neurotrophic factor; TrkB, tropomyosin receptor kinase B; NMDA receptor, N-methyl-D-aspartate receptor; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; GSK-3β, glycogen synthase kinase-3 beta; MAPK, mitogen-activated protein kinase; p38 MAPK, p38 mitogen-activated protein kinase; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1 beta; SERT, serotonin transporter; DAT, dopamine transporter; VGSCs, voltage-gated sodium channels; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; and HPA axis, hypothalamic–pituitary–adrenal axis.

The Uncaria rhynchophylla-Gastrodia elata combination exhibited neuroprotective properties through two primary mechanisms: (1) activation of PI3K/Akt/GSK-3β signaling pathway phosphorylation, promoting neuronal survival,[44] and (2) simultaneous reduction of striatal dopamine and pro-inflammatory cytokines (TNF-α, IL-1β), attenuating neuroinflammation-induced apoptosis.[45] Gastrodia elata further modulates dopaminergic activity through dual regulation of D2 receptor density and dopamine transporter (DAT) expression, while concurrently influencing serotonergic transmission via 5-HT transporter (SERT) modulation.[46]

The Radix paeonia alba-Glycyrrhiza pairing demonstrated complementary anti-inflammatory and neuromodulatory effects. This combination significantly suppressed pro-inflammatory mediators (IL-1β, TNF-α, PGE2) while elevating cortical neurotransmitter levels.[47,48] Clinical observations noted particular efficacy in alleviating peripheral muscle spasms and enhancing immune function, potentially reducing TD symptom exacerbation.[49] Glycyrrhiza's broad-spectrum pharmacological profile, including anti-inflammatory and immunomodulatory properties, synergized with Radix paeonia alba's neuroprotective effects.[50]

Poria cocos-containing combinations addressed both neurological and systemic manifestations. The Poria cocos-Radix paeonia alba pairing normalized prefrontal cortex DA/5-HT metabolism while suppressing inflammatory signaling (P38, NF-κB pathways).[51,52] This combination proved particularly effective for TD patients with spleen deficiency and dampness-phlegm syndromes, requiring simultaneous spleen fortification and phlegm resolution.[53]

Mechanistic studies of Silkworm revealed: (1) PI3K/Akt-mediated protection against oxidative neuronal damage,[54] and (2) modulation of endocannabinoid and cholinergic synaptic pathways.[55] When combined with Uncaria rhynchophylla, this pairing demonstrated targeted immunomodulation through TNF-α, IL-6, and IL-12 regulation, affecting multiple cellular processes including RNA transcription and apoptotic signaling.[29] Uncaria rhynchophylla's geissoschizine methyl ether contributed additional serotonergic modulation through differential 5-HT receptor activity.[56]

Cluster Analysis of Herbal Formulations for TD Treatment

Cluster analysis identified six distinct therapeutic patterns in TCM approaches to TD, each demonstrating unique mechanisms of action supported by contemporary pharmacological research. The Shaoyang regulation cluster (Groups C1/C3) primarily utilized modified Bupleurum chinense Formulations to regulate the Shaoyang meridian system, with Rehmannia Glutinosa demonstrating significant neuroprotective effects through activation of the ERK1/2-Nrf2-HO-1 antioxidant pathway (enhancing cellular defense against oxidative stress), suppression of COX-2/iNOS/NO inflammatory signaling (reducing neuroinflammation), and upregulation of BDNF/TrkB neurotrophic factors (promoting neuronal survival and plasticity).[57,58] Glycyrrhiza in these formulations contributed additional anti-inflammatory effects through modulation of NF-κB signaling while simultaneously elevating hippocampal levels of BDNF and its receptor TrkB, suggesting synergistic neuroprotective benefits.[59] The wind-calming cluster (Group C2), based on Gastrodia elata Uncaria Rhynchophylla Formulations, incorporated Kudzu root for its cerebrovascular effects, with demonstrated efficacy in normalizing monoamine neurotransmitter imbalances (particularly reducing hypothalamic norepinephrine and striatal dopamine levels) and improving cerebral hemodynamics through β-adrenergic blockade, while its isoflavone components provided endothelial protection.[60,61]

For cases presenting with spleen deficiency manifestations, the spleen-fortification cluster (Group C4) employed Liujunzi Tang and Erchen Tang to address underlying dampness-phlegm pathology through comprehensive regulation of digestive and metabolic functions, while the phlegm-heat clearing cluster (Group C5) utilized Coptis Wendan Decoction to resolve heat-toxins and phlegm-accumulation, with Acorus tatarinowii contributing specific neuromodulatory effects through regulation of dopaminergic and serotonergic pathways.[62] The blood-stasis resolution cluster (Group C6) demonstrated particular efficacy in cases with vascular components, where Angelica sinensis-Ligusticum wallichii combinations reduced expression of inflammatory mediators (NF-κB, iNOS, COX-2) in midbrain and striatal regions while normalizing striatal dopamine levels and improving motor function outcomes.[63]

To enhance clinical applicability, the identified high-frequency herb pairs and functional clusters were systematically correlated with typical TCM syndrome patterns observed in TD, such as Liver wind stirring, phlegm disturbance, and liver-spleen disharmony. Establishing these correlations bridges data-mining outcomes with established diagnostic frameworks, facilitating precise syndrome differentiation and targeted prescription formulation. For example, clusters dominated by liver-soothing and wind-calming herbs (eg, Uncaria rhynchophylla-Radix paeonia alba) align closely with the "Liver wind stirring" pattern, while phlegm-resolving and dampness-regulating clusters (eg, Poria cocos-Pinellia ternata) correspond to the "phlegm-heat" pattern. This mapping reinforces the theoretical underpinnings of the findings and supports their integration into individualized, syndrome-based treatment strategies for TD.

This systematic clustering approach not only validates traditional treatment principles but also provides a neurobiological framework for personalized TD management. It enables the selection of specific herbal combinations

based on individual symptom profiles and underlying pathophysiological mechanisms, bridging TCM theory with modern neuropharmacological understanding.

Limitations and Future Directions

This study has several limitations. About 16.64% (93/559) of included studies are clinical controlled trials and semi-randomized controlled trials, constituting moderate-quality evidence. The remaining 83.4% (466/559) were expert experience reports, representing low or very low-quality evidence to Grading of Recommendations Assessment, Development and Evaluation (GRADE). Among the 93 clinical studies, most adopted the Yale Global Tic Severity Scale (YGTSS) as the primary endpoint, defining treatment response as 30–35% reduction in YGTSS total score with reported statistical significance. Supplementary assessment tools-including the Achenbach Child Behavior Checklist (CBCL), Screen for Child Anxiety-Related Emotional Disorders (SCARED), and TCM syndrome scales-enabled multi-dimensional efficacy evaluation of TCM for TD. Several studies also analyzed biomarkers including ANAb, cytokines (IL-6, IL-12), neurotransmitters (5-HT, DA, GABA, NE), and BDNF to explore potential treatment mechanisms. While the 466 expert reports suggested potential efficacy mainly based on TCM theory and clinical observations, they generally lacked standardized scales or biomarker assessments. These findings require validation through more rigorous clinical trials. Overall, studies met GRADE criteria for moderate-to-high quality evidence remain insufficient, with common methodological weaknesses including inadequate randomization procedures, lack of blinding, and insufficient sample size calculations.[64]

Despite the consistency in herb patterns, the predominance of low-evidence expert reports necessitates cautious interpretation. Although stratified analysis mitigates potential selection bias, it does not eliminate it. While our comprehensive approach incorporated 559 publications, the expert experience reports lacked control groups, which may introduce bias and limits the strength of our conclusions.[65] In addition, the herb combinations identified in this data-mining analysis represent statistical associations rather than proven therapeutic mechanisms. The aggregated data-sourced from studies with differing diagnostic criteria, treatment protocols, and reporting methods-may obscure clinical heterogeneity.

To strengthen the evidence for TCM in TD treatment, future research should prioritize multicenter randomized controlled trials that incorporate proper sample size calculations, computer-generated randomization, double-blinded assessment, standardized outcome measures using validated rating scales, and rigorous adverse event monitoring.[66] Such studies should adhere to international quality standards including modified Jadad scale criteria, Cochrane Risk of Bias Tool, and CONSORT statement guidelines,[67] with particular attention to longitudinal assessments of both short-term symptom control and long-term developmental outcomes in pediatric populations.[68] Future work should also emphasize the integration of mechanistic studies with clinical trials to validate the connections between identified herb clusters and therapeutic outcomes.

Conclusions

This study systematically analyzed 1001 TCM prescriptions for TD, identifying 369 medicinal herbs including 30 high-frequency core herbs. These herbs predominantly exhibited cold/mild/warm properties, sweet/bitter/pungent flavors, and tropism for the liver, lung, and spleen meridians. Therapeutic strategies focused on liver-soothing, wind-calming, and tonifying herbs, with association rules revealing 92 herb pairs (eg, Uncaria rhynchophylla-Radix paeonia alba) and cluster analysis identifying 6 key combinations. TCM treatment emphasized syndrome differentiation, employing strategies like liver-spleen regulation, phlegm resolution, and heat clearance. The core approach–calming liver wind, resolving dampness-phlegm, and strengthening the spleen–was consistent with clinical management strategies for symptom control and showed potential relevance to children's long-term quality of life. Both TCM monotherapy and integrative therapies demonstrated therapeutic potential in the analyzed literature, suggesting a contributory role in TD management that warrants further validation.

This study also highlights the potential role of diagnostic tools and biological markers in enhancing the precision of TD diagnosis and treatment evaluation. Although not the primary focus of this study, existing evidence suggests that integrating clinical rating scales, such as YGTSS and TCM syndrome scales with biological indicators could improve

syndrome differentiation accuracy and therapeutic outcome prediction. Future research should adopt standardized diagnostic frameworks that combine TCM syndrome assessment with validated biomedical markers, enabling multi-dimensional data analysis to more comprehensively characterize the complex pathophysiology of TD.

However, several methodological limitations affect the clinical applicability of these findings: the retrospective design prevents causal inference; heterogeneity in syndrome classification and treatment protocols may introduce bias; and prescription frequency alone does not confirm therapeutic efficacy. While the predominance of cold/mild-natured herbs and liver/lung meridian tropism aligns with TCM theory, these results should be interpreted as hypothesis-generating rather than definitive clinical guidance. To advance TCM as a complementary and alternative medicine (CAM) approach for TD, further research should prioritize areas such as randomized controlled trials comparing TCM with standard treatments, and pharmacokinetic studies to elucidate bioactive compound interactions, thereby strengthening the evidence base.

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Disclosure

The author(s) report no conflicts of interest in this work.

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