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Traditional Chinese medicine research on rare diseases: Publication trends and future perspectives

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SUMMARY: Traditional Chinese medicine (TCM) has increasingly attracted the attention of researchers as a potential complementary or supportive approach for selected rare diseases, but the characteristics and evidentiary strength of this literature remain unclear. This Correspondence summarizes publication patterns identified for the 121 conditions in the First Chinese Rare Disease List using Chinese and English sources searched from database inception through June 30, 2021. Fifty-five rare diseases were identified in 3,030 TCM-related publications, though the ten most frequently studied conditions accounted for more than 80% of the literature. Generalized myasthenia gravis, idiopathic pulmonary fibrosis, and multiple sclerosis together accounted for nearly half of all publications. Clinical studies and case reports or experience summaries predominated, whereas experimental studies represented only 9.03%. Oral herbal formulas were the most frequently reported intervention, and more than 95% of publications originated from mainland China. These patterns indicate growing interest but a fragmented, geographically concentrated, and methodologically limited evidence base; publication volume should not be interpreted as evidence of efficacy or safety. Future research should prioritize mechanistic studies, standardized and innovative clinical designs, rigorous safety and quality-control procedures, real-world evidence, patient-centered outcomes, and international collaboration to clarify the potential roles and limitations of TCM in rare disease management.

Keywords: traditional Chinese medicine, rare diseases, publication trends, clinical evidence, research methodology

1. Introduction

Rare diseases, though individually rare, collectively affect millions worldwide. In China, the official Rare Disease List has expanded from 121 conditions in 2018 to 207 in 2023, reflecting growing recognition in policy (*1-3*). For most of these diseases, however, effective treatments remain scarce and prohibitively expensive. Rare diseases are clinically heterogeneous and often associated with substantial unmet needs, although standard care varies widely across diseases (*4-6*).

In this context, traditional Chinese medicine (TCM)-related approaches have attracted attention in research on selected rare diseases, mainly as potential complementary or supportive strategies. Rooted in a holistic framework, TCM emphasizes syndrome differentiation. This diagnostic process identifies patterns of physiological imbalance and guides the use of multi-component herbal formulas tailored to each patient (*7,8*). Rather than targeting a single molecular pathway, TCM aims to restore overall physiological equilibrium. This individualized framework may partly explain why TCM-related approaches have attracted interest in research on selected rare diseases characterized by insidious onset, progressive courses, and multisystem involvement (*9*).

Conditions such as systemic sclerosis (SSc), generalized myasthenia gravis (GMG), and multiple sclerosis (MS) exemplify this complexity. All are chronic, autoimmune-mediated disorders with heterogeneous presentations and no definitive cure. Previous reports by our group suggested potential clinical relevance and patient acceptance of TCM-related approaches in SSc; however, these observations should not be interpreted as definitive evidence of efficacy (*10,11*). TCM-related

interventions have been reported in GMG and MS, often alongside conventional treatments, but the strength and quality of this evidence remain uncertain (*12-18*).

Despite these promising signals, the literature on TCM for rare diseases remains poorly characterized. Which diseases have attracted sustained interest in research? What types of studies and therapeutic interventions dominate? This article seeks to examine these critical questions, offering a concise overview of observations regarding TCM research on rare diseases, based on the literature, and highlighting directions for future investigation.

2. Key observations from publications

Data source and scope: We based our observations on TCM-related publications involving the First Chinese Rare Disease List (CRDL) of 121 conditions (*19*). Publications were searched in Chinese and English sources, including CNKI, Baidu Academic, DUXIU, PubMed, Bing Academic, and Microsoft Bing, from database inception to June 30, 2021. TCM-related research was broadly defined as publications involving Chinese herbal medicine, compound prescriptions, acupuncture, moxibustion, tuina, rehabilitation-related TCM approaches, integrated Chinese and Western medicine, syndrome differentiation, or related interventions. The analysis examined publication patterns and disease distribution; it was not designed as a systematic review or an assessment of efficacy, safety, or evidence quality. The detailed search strategy is provided in Supplementary File (*https://www.irdrjournal.com/action/getSupplementalData.php?ID=313*).

Concentration on a subset of diseases: Among the 55 rare diseases with TCM publications, just ten accounted for over 80% of all papers. Three conditions stand out: GMG, idiopathic pulmonary fibrosis (IPF), and MS, which together accounted for nearly half of the literature. GMG alone accounted for more than one-fifth of all publications (Table 1).

Emphasis on chronic rare disease management: What unites these highly researched diseases? Nearly all share a common profile: they are chronic, multisystem disorders with adult onset, are poorly understood, and have multifactorial origins. GMG and IPF exemplify this pattern. Both involve complex immune dysregulation rather than a single genetic defect, and both require long-term, multi-system management. This clinical complexity may explain why these diseases have attracted attention in research on TCM-related studies.

The concentration of publications on GMG, IPF, MS, and SSc may reflect clinical familiarity, disease prevalence, research trends, availability of TCM interventions, chronic disease course, and publication bias. Therefore, this distribution should be interpreted as attention in research rather than evidence that TCM is more effective in treating these diseases.

Predominance of clinical studies: Clinical studies (37.25%) and case reports or experience summaries (31.25%) accounted for the largest share of 3,030 TCM publications on rare diseases. These were followed by literature reviews and theoretical studies, while experimental studies were the least frequent, accounting for only 9.03% of the total. This distribution demonstrates that TCM research on rare diseases remains primarily oriented toward clinical observation and empirical experience rather than mechanistic investigation (Figure 1). The evidence level appears limited. Most publications were clinical studies, case reports, or experience summaries, whereas experimental studies accounted for only 9.03%. We did not perform a formal risk-of-bias assessment, and the broad category of "clinical studies" may include heterogeneous designs. Therefore, these publications should be viewed as preliminary signals for future research rather than evidence sufficient to establish efficacy or safety.

Diversity of therapeutic approaches: Oral herbal formulas predominated overall (59%), but their application varied by disease. GMG, a neuromuscular disorder, was mainly treated with medication, likely

Table 1. Rare diseases with the highest numbers of TCM-related publications

ID*	Top 10 rare diseases in TCM-related publications**	Number (*n*)	Proportion (%)
032	Generalized myasthenia gravis	665	21.95%
055	Idiopathic pulmonary fibrosis	498	16.44%
076	Multiple sclerosis	314	10.36%
102	Retinitis pigmentosa	192	6.34%
004	Amyotrophic lateral sclerosis	182	6.01%
037	Hepatolenticular degeneration	164	5.41%
077	Multiple system atrophy	157	5.18%
112	Systemic sclerosis	153	5.05%
081	Neuromyelitis optica	116	3.83%
088	Paroxysmal nocturnal hemoglobinuria	86	2.84%

*Disease ID in the First Chinese Rare Disease List (CRDL) of 121 conditions. **Publications were searched in Chinese and English sources, including CNKI, Baidu Academic, DUXIU, PubMed, Bing Academic, and Microsoft Bing, from database inception to June 30, 2021. *Note:* The number of publications and each proportion on top 10 rare diseases were counted. The results of the analysis are shown in the table. The table shows publication counts and proportions of TCM-related publications identified for 121 CRDL-listed rare diseases. Publication volume should not be interpreted as evidence strength, disease burden, or clinical importance.

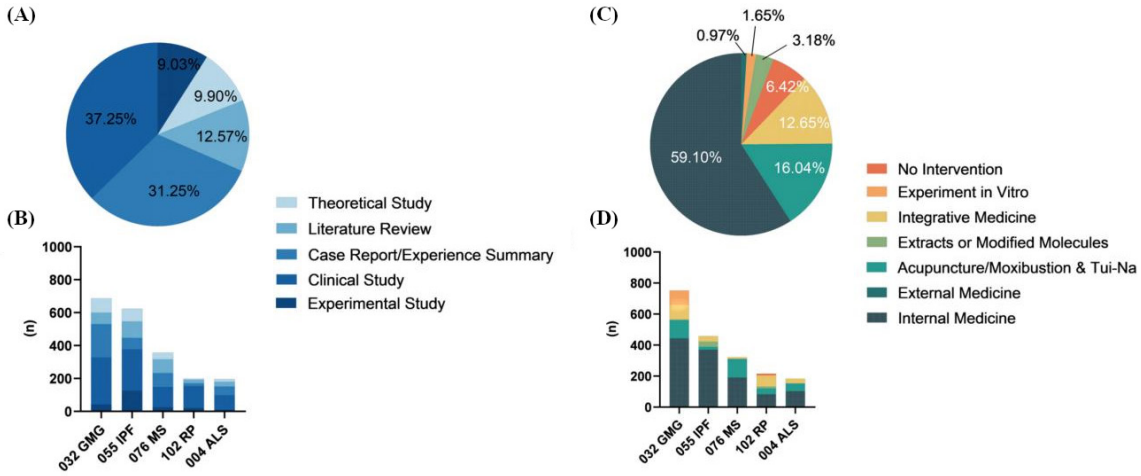

Figure 1. Distribution of study types among TCM-related publications on rare diseases. (A) Types of studies in publications on all diseases; **(B)** Types of studies in publications on the top 5 rare diseases; **(C)** Types of interventions in publications on all diseases; **(D)** Types of interventions in publications on the top 5 rare diseases. *Note*: Publications were categorized by study and intervention types. Publications on all diseases were compiled as different percentages in pie charts and stacked bar charts for the top 5 rare diseases. These categories describe publication types and intervention categories only; they do not indicate evidence quality, efficacy, safety, or clinical recommendation strength. *Abbreviations*: GMG, generalized myasthenia gravis; IPF, idiopathic pulmonary fibrosis; MS, multiple sclerosis; RP, retinitis pigmentosa; ALS, amyotrophic lateral sclerosis.

targeting systemic immune regulation. In contrast, IPF was treated with herbal extracts or modified molecules, perhaps reflecting a focus on a more targeted pulmonary intervention. Acupuncture and integrative therapies were also often used, underscoring the multimodal nature of TCM (Figure 1).

3. Implications and future directions

The patterns observed in the publications highlight several implications for the role of TCM in rare disease management.

3.1. The concentration of research on chronic rare diseases is not incidental

Concentrated research on chronic rare diseases points to a fundamental alignment between the holistic, syndrome-based approach of TCM and the clinical realities of diseases for which conventional targeted therapies are often limited. Conditions such as GMG, IPF, and SSc exemplify this pattern. Care for these diseases is mainly symptomatic and supportive care, an area where TCM-related approaches have been explored. The predominance of such conditions in the TCM publications therefore sends an important message. Future research may clarify whether TCM-related approaches have potential roles in treating the complex, multisystem manifestations of selected rare diseases.

This is not to suggest that TCM has no role in hereditary rare diseases. In conditions such as hemophilia, where monogenic defects are well-defined, TCM has been used adjunctively to manage bleeding complications and associated musculoskeletal symptoms. However, the literature on such applications remains sparse, averaging fewer than three publications annually since 1958. This contrast reinforces the conclusion that TCM's primary contribution lies in complex, non-Mendelian conditions.

3.2. Attention in research has steadily increased over time

After a single publication in 1958, the field remained dormant for decades. A turning point came in around 2011, when annual publications began to increase steadily, coinciding with growing international awareness following the first Rare Disease Day in 2008. By 2019, annual output had peaked at 240 publications.

However, this increasing trend has revealed significant gaps that must be addressed. Experimental research is still scarce, accounting for less than 10% of publications. Mechanistic studies need to be conducted to move beyond empirical observation. Clinical evidence is predominated by case reports and uncontrolled studies, highlighting the need for well-designed trials that incorporate TCM syndrome differentiation. Given the inherently small patient populations in rare diseases, conventional large-scale randomized trials are often unfeasible. Therefore, clinical trial designs require not only standardization, including rigorous controls and consistent outcome measures, but also methodological innovation. Moreover, the wealth of clinical experience calls for systematic synthesis, an area where data mining techniques could prove valuable in distilling the expertise of renowned TCM practitioners.

Beyond traditional clinical trials, real-world data offer a complementary pathway. Large-scale patient registries,

electronic health records, and prospective observational studies can discern the effectiveness of TCM in routine practice, where treatments are individualized and long-term outcomes matter most. Such evidence, while not replacing randomized trials, could inform clinical decisions and generate hypotheses for further investigation.

In summary, TCM rare disease research is predominantly case-based, with few experimental studies. The future integration of N-of-1 randomized controlled trials (RCTs), Bayesian trials, and comprehensive patient registries will be crucial to transforming individualized pattern differentiation into high-quality evidence. This shift from mere observation to rigorous validation will enable the field to overcome the limitations of small samples and to clarify the potential role and limitations of TCM-related approaches in rare disease research.

3.3. The international dimension warrants attention

Currently, over 95% of TCM publications on rare diseases originate from mainland China, with fewer than 3% published in international journals. This geographic concentration, compounded by regulatory differences and challenges in herbal quality control, limits global attention.

3.4. To bridge these gaps, we propose several priorities for future research:

Mechanistic studies need to be conducted to elucidate the molecular pathways modulated by TCM formulas, moving beyond empirical observation towards scientific validation. For GMG and SSc, this might involve immune profiling and biomarker discovery; for IPF, it may focus on fibrotic pathways.

Standardized clinical trial designs are essential to enhancing scientific validity. This includes rigorous controls, consistent outcome measures, and incorporation of TCM syndrome differentiation. Pragmatic trials that reflect real-world clinical practice could bridge the gap between explanatory efficacy studies and clinical applicability. TCM may be discussed as a potential complementary or supportive approach for further study but not as an established alternative to evidence-based therapy.

Safety monitoring and quality control should be a central component of future studies. Patients with rare diseases often receive prolonged and complex standard therapies, and TCM interventions may involve multi-component herbal formulas or combined modalities. Future research should therefore include adverse event monitoring, quality control of herbal products, dose and formulation reporting, and evaluation of potential herb–drug interactions with standard therapies.

Real-world evidence should be systematically collected and compiled. Patient registries, electronic health records, and prospective observational studies can complement clinical trials by capturing long-term outcomes and treatment patterns in routine practice.

A TCM-specific evidence framework is needed to transcend conventional RCT limitations. An integrated evidence framework may help organize heterogeneous evidence from case reports, observational studies, mechanistic research, and trials, but it should complement rather than replace rigorous clinical evaluation. For rare diseases with limited numbers of patients, approaches such as rare disease registries, N-of-1 trials, Bayesian designs, and real-world evidentiary studies may provide additional evidence-generating strategies.

International collaboration is needed to harmonize research methodologies, facilitate regulatory recognition, and expand the global acceptance of TCM in rare disease management. Joint initiatives, including multinational patient registries and collaborative clinical trials, could accelerate progress.

Patient-centered research should be prioritized. Understanding patient preferences, treatment adherence, and quality of life outcomes will be essential to demonstrating the value of TCM beyond symptom control. The high rate of TCM acceptance among patients with SSc in our study suggests that patient perspectives may be a powerful driver of integration.

3.5. Limitations

Several limitations should be acknowledged. First, this Correspondence is based on published literature and may be affected by publication bias, language bias, and database coverage limitations. Second, the analysis was based on the first CRDL of 121 diseases and publications available up to June 30, 2021, so it does not represent the expanded list of 207 diseases or subsequent literature. Third, we did not assess the risk of bias, evidence quality, or the efficacy, safety, or clinical appropriateness of individual TCM interventions. Finally, concentrated publications on selected diseases may reflect research trends, clinical familiarity, disease prevalence, or availability of interventions rather than stronger clinical evidence.

In conclusion, TCM-related publications suggest growing interest in research on selected rare diseases, but the current evidence base remains fragmented and preliminary. Future studies should use rigorous designs, standardized interventions, safety monitoring, and clinically meaningful outcomes.

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