Review

DOI: 10.5582/irdr.2025.01028

Traditional Chinese medicine for intractable and rare diseases: Research progress and future strategies

Yuanzheng Liu[1], Yanming Ren[1,*], Peipei Song[2,*]

[1] Department of Traditional Chinese Medicine, Medical College, Qinghai University, Xining, China;
[2] Center for Clinical Sciences, Japan Institute for Health Security, Tokyo, Japan.

SUMMARY: Rare diseases have become a global public health challenge due to their low prevalence, difficult diagnosis, and limited treatment options. Intractable diseases are more common but often involve complex mechanisms, treatment with limited efficacy, and high medical costs, placing a heavy burden on patients and healthcare systems. In recent years, traditional Chinese medicine (TCM) has demonstrated unique advantages in the treatment of intractable and rare diseases and has gradually become an important complementary treatment. The current work is a systematic review of the progress of clinical and experimental research on TCM in typical rare diseases such as amyotrophic lateral sclerosis (ALS), systemic lupus erythematosus (SLE), mitochondrial encephalomyopathy, aplastic anemia (AA), and Wilson's disease (WD). It focuses on the multi-target therapeutic mechanisms of key Chinese herbal compound formulas, including immune regulation, antioxidative stress, and neuroprotection. The core TCM theories of "syndrome differentiation", "different treatments for the same disease" and the "same treatment for different diseases" are also discussed in the context of personalized medicine. In recent years, China has continuously promoted the development of TCM through a series of national plans and supportive policies, such as the 14th Five-Year Plan for TCM development, funding for key special projects, expedited approval pathways, and expanded coverage by medical insurance. These efforts have provided strong support for the clinical translation of TCM and technological innovation in the field of intractable and rare diseases. Notwithstanding the encouraging advances, the field of Chinese medicine continues to grapple with numerous challenges. In the future, the enhancement of mechanistic studies and quality multicenter clinical trials needs to be promoted while further enhancing policy support and international collaboration to substantiate the scientific basis and clinical value of TCM in the prevention and treatment of intractable and rare diseases.

Keywords: traditional Chinese medicine (TCM), intractable diseases, rare diseases, herbal compound formulas, multitarget mechanisms

1. Introduction

Rare diseases are an emerging public health priority, which are umbrella terms for diseases with very low prevalence. To date, between 6,000 and 8,000 distinct rare diseases have been identified, approximately 80% of which are of genetic origin and 50-75% of which manifest in childhood (*1,2*). There is no universal definition of rare diseases and their prevalence varies in different regions of the world. The European Union Orphan Drug Regulation defines a rare disease as a condition affecting < 50 per 100,000 of the European population (*3*), the American Orphan Drug Act defines a rare disease as a condition affecting < 200,000 people in the U.S. (*4*), and the most recent definition of a rare disease in China, published in 2021, defines it as a condition with an incidence of less than 1 in 10,000 live births, a prevalence of less than 1 in 10,000 individuals, or fewer than 140,000 people affected nationwide (*5*). In China, rare diseases affect approximately 20 million people, with over 200,000 new cases reported annually (*6,7*). In 2010, the Shandong Rare Disease Prevention and Control Association was established, becoming the first provincial-level academic organization for rare diseases in China. With the increasing national attention to rare diseases, the project for "China Rare Disease Prevention Research and Demonstration" (No. 2013BAI07B00) under the National Science and Technology Support Program of the 12th Five-Year Plan (*8*) and the project for a "Clinical Cohort Study of Rare Diseases" (No. 2016YFC0901500) under the 13th Five-Year Plan (*9*) have been launched. These

initiatives aim to promote the diagnosis and treatment of rare diseases and the development of orphan drugs. On October 24, 2018, the China Alliance for Rare Diseases was established in Beijing and built the China Rare Diseases Comprehensive Cloud Service Platform, which has registered about 780,000 cases of rare diseases as of November 2023, covering 31 provinces, municipalities, autonomous regions, and 502 hospitals across the country (*10*).

In addition to rare diseases, many conditions with a relatively high prevalence but complex diagnosis and poor treatment outcomes are collectively referred to in traditional Chinese medicine (TCM) as "intractable and rare diseases". These conditions pose similar challenges in clinical practice and are managed through pattern differentiation. China is the birthplace of TCM, and its extensive clinical use has established TCM's significant role in the field of herbal medicine. In recent years, the market share of Chinese herbal medicine has reached as high as 32.4% of the pharmaceutical market in China (*11*). In contrast, the number of traditional medicines produced account for about 2.2% of total pharmaceuticals production in Japan (*12*). The Chinese Government places great importance on the development of TCM and has introduced a series of supportive policies. The "14th Five-Year Plan for the Development of TCM" (*13*) and the "Implementation Plan for Major Projects in the Revitalization and Development of TCM" (*14*) have provided strong support for the industry's growth. Notably, the 14th Five-Year Plan emphasizes enhancing specialty disciplines in TCM and enhancing the capacity to diagnose and treat major and complex diseases. Moreover, Chinese medicine has long gained experience in diagnosing and treating rare and complex diseases, forming a systematic and mode of "Pattern Identification and Treatment". It offers unique advantages in managing multi-system damage and chronic progressive conditions. Recent research has increasingly highlighted its potential value in rare disease treatment, and especially through mechanisms such as immune regulation, modulation of antioxidative stress, and neuroprotection.

The aims of this review are to systematize the progress of research on Chinese medicine in the treatment of several typical intractable and rare diseases and to explore the prospects and challenges of its use to treat rare diseases by combining modern medical mechanisms and traditional theories.

2. Research on TCM in rare diseases and analysis of compound TCM Formulations

TCM has been increasingly explored in the treatment of various rare diseases. The following section highlights representative case studies, focusing on the clinical use of and animal experiments on selected TCM formulas and their components as well as the underlying pharmacological mechanisms from a modern perspective (Table 1).

2.1. Amyotrophic lateral sclerosis (ALS)

ALS is a rare and fatal neurodegenerative disease that primarily affects the upper and lower motor neurons in the motor cortex, brainstem, and spinal cord. It leads to progressive, painless muscle weakness, and patients typically die from respiratory failure within 3 to 5 years (*15*). At present, commonly used western medicines such as riluzole and edaravone have limited efficacy in slowing disease progression. Riluzole requires long-term administration and imposes a significant financial burden, while edaravone is an intravenous preparation that is inconvenient to use and that demonstrates suboptimal therapeutic efficacy.

In contrast, TCM has unique advantages in the treatment of ALS. It can effectively alleviate clinical symptoms, delay disease progression, enhance quality of life, and is associated with fewer obvious adverse effects (*16*). Huoling Shengji Decoction, developed based on TCM syndrome differentiation, has demonstrated promising therapeutic potential in both clinical and experimental studies. A randomized controlled trial (RCT) confirmed that Huoling Shengji Decoction has a positive therapeutic effect on patients with ALS (*17*). In animal experiments, this formula has also been shown to prolong the survival time of SOD1-G93A transgenic mice, protect motor neurons, and suppress neuroinflammation (*18*). The therapeutic effects of Huoling Shengji Decoction are believed to arise from the synergistic interaction of its herbal constituents, which collectively modulate oxidative stress, immune responses, and neuronal apoptosis. *Astragalus membranaceus* significantly enhances the scavenging capacity of nitric oxide free radicals, reduces NO-induced cytotoxicity, and improves the recovery rate of leukocyte levels (*19*). Astragalus polysaccharides, a key extract of *Astragalus membranaceus*, also possess strong antioxidant properties (*20*). *Epimedium brevicornum* has neuroprotective effects by modulating the expression of apoptosis-related factors and neurotrophic factors (*21*). Notably, the cannabis plant is also believed to have therapeutic potential. Medicinal uses of cannabis were documented as early as in Qianjin Yaofang and Bencao Gangmu. Modern studies have further shown that Δ^9-tetrahydrocannabinol, the active component of cannabis, has neuroprotective effects. In 2004, Raman *et al*. reported that Delta(9)-tetrahydrocannabinol could delay the onset of motor dysfunction and prolong survival in an ALS mouse model (*22*). Additionally, the endogenous cannabinoid system has been shown to have neuroprotective effects in SOD1-G93A transgenic mice through the activation of CB1 and CB2 receptors (*23*).

2.2. Systemic lupus erythematosus (SLE)

Table 1. Case studies and analysis of compound Chinese herbal formulas

System category	Disease	Study type	TCM compound	Main herbal medicine or key ingredients	Effects	*Ref.*
Nervous system	Amyotrophic lateral sclerosis	RCT	Huoling Shengji Decoction	*Astragalus membranaceus, Epimedium brevicornum*	Neuroprotection, regulation of apoptosis and trophic factors	(*17-21*)
		Animal study	Cannabis	Delta (9)-tetrahydrocannabinol	Neuroprotection, alleviation of excitotoxicity	(*22*)
Immune-related	Systemic lupus erythematosus	RCT	Shenqi Dihuang Decoction	*Astragalus membranaceus, Rehmannia glutinosa*	Immunomodulation, anti-inflammatory effects	(*28-30*)
		Animal study	Arsenic trioxide	Arsenic trioxide	Immunosuppression, anti-inflammatory effects	(*33*)
		Clinical study	Kunxian Capsule	Tripterygium wilfordii polyglycoside	Anti-inflammatory and immunosuppressive effects	(*34-35*)
Metabolic-related	Mitochondrial encephalomyopathy	Retrospective study	Xinnaoxin Capsule	Salidroside, *Lycium barbarum* polysaccharides	Antioxidation; improvement of mitochondrial function	(*39-41*)
Hematologic system	Aplastic anemia	RCT	Huangqi Injection	*Astragalus membranaceus*	Hematopoietic support, immune enhancement	(*49*),(*51*)
		Animal study	Danggui Buxue Decoction	Angelica polysaccharide	Replenishment of blood, immune regulation	(*50-52*)
		Clinical multi-center study	Pai-Neng-Da Capsule	*Astragalus membranaceus,* panaxadiol saponins	Hematopoietic support, modulation of immune function	(*53-55*)
Digestive system	Wilson's disease	RCT	Gandou Decoction	Curcumin, *Rhubarb* root, Berberine, Coptisine	Antioxidative effects, copper detoxification	(*62-66*)
		Animal study	Gandouling	Berberine, Coptisine, Aloe-emodin, Catechin	Anti-inflammatory and antioxidative effects	(*65-71*)

SLE is a diffuse connective tissue disease characterized by autoimmune inflammation. Its clinical manifestations are diverse and complex, primarily marked by the presence of multiple autoantibodies in serum and the involvement of multiple organs and systems (*24*). SLE significantly reduces patients' quality of life and imposes a substantial public health and economic burden (*25*). The mortality rate and risk of irreversible organ damage are considerably higher than those of the general population. Patients frequently require long-term medication; however, the use of conventional drugs is limited by adverse effects such as infections, metabolic disturbances, osteoporosis, and retinopathy (*26*).

TCM has a long history in the treatment of SLE and is considered one of the advantageous approaches in the field of rheumatology. A systematic review and meta-analysis of 14 RCTs with a total of 1,002 participants evaluated the efficacy and safety of combining Shenqi Dihuang Decoction with conventional Western medicine in the treatment of lupus nephritis (*27*). Results indicated that compared to Western medicine alone, the combination therapy significantly improved clinical efficacy, vascular endothelial growth factor levels, complement C3 levels, the erythrocyte sedimentation rate, and SLE Disease Activity Index scores. *Astragalus membranaceus* has demonstrated immunomodulatory and anti-inflammatory effects. One study found that astragalus improved pregnancy outcomes and alleviated renal pathological damage in a murine model of SLE by suppressing Th17 cell differentiation and reducing the expression of IL-17A and RORγt (*28*). Extracts of *Rehmannia glutinosa* have been shown to reduce the expression of inflammatory cytokines such as IL-2, IFN-γ, IL-6, and IL-10, thereby mitigating immune-mediated tissue damage associated with SLE (*29*). A clinical trial involving 52 patients with SLE showed that benefits in the treatment group, which received standard therapy combined with *Rehmannia glutinosa* and *Astragalus membranaceus*, included a reduction in the glucocorticoid dosage, lowering of 24-hour urinary protein levels, and alleviation of adverse effects such as insomnia, hot flashes, spontaneous sweating, and obesity (*30*). The cytokine IFN-γ plays a key role in the pathogenesis of SLE (*31,32*). Arsenic trioxide (As_2O_3), a TCM, has immunomodulatory effects in both MRL/lpr mice and human SLE patients by downregulating IFN-γ gene expression *via* epigenetic mechanisms (*33*). In addition, Kunxian Capsule , a novel TCM formula listed as a "Key Scientific and Technological Achievement" during China's 9th Five-Year Plan, has been used clinically to treat lupus nephritis for over ten years, and it may alleviate renal damage and T-cell infiltration in lupus nephritis by blocking the JAK1-STAT1 signaling pathway (*34*). Tripterygium wilfordii polyglycoside, a major component of Kunxian Capsule, has therapeutic effects on SLE by inhibiting the IL-17 signaling pathway and suppressing Th17 cell differentiation, thereby modulating immune responses and reducing disease activity (*35*).

2.3. Mitochondrial encephalomyopathy

Mitochondrial encephalomyopathy is a multisystem disorder caused by mitochondrial dysfunction due to mutations in mitochondrial DNA or nuclear DNA (*36*). Clinically, it is classified into four major subtypes: mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes, myoclonic epilepsy with ragged red fibers, Kearns-Sayre syndrome, and mitochondrial neurogastrointestinal encephalomyopathy (*37*). The main clinical manifestations include hearing loss, ptosis, optic atrophy, and exercise intolerance (*38*). Currently, treatment strategies focus on supportive care, including improvement of energy metabolism, antioxidant therapy, free radical scavenging, and mitochondrial support. However, the overall efficacy of these treatments remains limited.

In recent years, several studies of TCM have suggested potential benefits in the treatment of mitochondrial encephalomyopathy. Xinnaoxin Capsule, as a foundational formula, combined with conventional "cocktail" therapy, has shown clinical potential in alleviating neurological symptoms and exercise tolerance, significantly enhancing treatment efficacy and long-term prognosis (*39*). These effects may be attributed to the neuroprotective properties of its key herbal components, such as salidroside and *Lycium barbarum* polysaccharides. Experimental studies have demonstrated that salidroside can have neuroprotective effects by downregulating complement component C3 expression (*40*). *Lycium barbarum* polysaccharides have shown neuroprotective effects in Parkinson's disease models, possibly by improving mitochondrial function (*41*). Nevertheless, systematic studies on TCM treatment for mitochondrial encephalomyopathy remain limited, with current evidence largely derived from case reports or small-scale clinical observations (*42,43*).

2.4. Aplastic anemia (AA)

AA is a bone marrow failure syndrome caused by multiple etiologies and is characterized primarily by hematopoietic stem cell damage, fatty degeneration of the bone marrow, and peripheral pancytopenia (*44*). In Western countries, treatment mainly relies on immunosuppressive agents and hematopoietic stem cell transplantation, while androgens are used only as adjunctive therapy and are rarely used (*45,46*). In China, however, a combined therapeutic strategy involving immunosuppressive agents, androgens, and kidney-tonifying TCM is often used in clinical practice (*47,48*).

In recent years, multiple domestic clinical trials have reported on the efficacy of a Huangqi Injection (prepared from the single herb *Astragalus membranaceus*)

combined with androgens in the treatment of AA. A meta-analysis showed that the combination therapy group had superior improvement in hematopoietic function and peripheral blood cell counts compared to the androgen monotherapy group, with an overall response rate approximately 50% higher than that of the control group (*49*). In addition to injectable formulations, oral compound Chinese herbal prescriptions are also widely used in the treatment of AA. For instance, Danggui Buxue Decoction (consisting of *Angelica sinensis* and *Astragalus membranaceus*) is frequently used in clinical practice. Animal studies have shown that Modified Danggui Buxue Tang can ameliorate immune-mediated AA models by modulating T cell differentiation and inhibiting the Jak/Stat signaling pathway (*50*). As the core component of both formulas, *Astragalus* is considered to be an immunoenhancing biological response modifier that promotes hematopoiesis by increasing the CD4/CD8 ratio and reducing negative regulatory factors such as IL-2 and TNF-α (*51*). The active constituent extracted from *Angelica sinensis* - Angelica polysaccharide - has also displayed significant hematopoietic effects in experimental studies, possibly by regulating the Treg/Th17 cell balance and inhibiting mitochondrial apoptosis in bone marrow cells (*52*).

Moreover, a multicenter clinical study demonstrated that the efficacy of Pai-Neng-Da Capsule combined with cyclosporine and androgen was 88.1%, which was significantly higher than that in the control group (77.8%) (*53*). The primary constituent of Pai-Neng-Da-Capsule is panaxadiol saponins, which have been demonstrated to possess both the capacity to replenish blood and to regulate immunity (*54,55*).

2.5. Wilson's disease (WD)

WD is an autosomal recessive genetic disorder caused by mutations in the ATP7B gene, leading to dysfunctional copper metabolism and subsequent accumulation of Cu^{2+} in the liver, brain, cornea, and other organs. This accumulation results in liver damage, neurological symptoms, and multi-organ dysfunction (*56*). The liver is the earliest organ affected, and hepatic fibrosis can occur in the early stages of the disease. Therefore, early intervention is crucial to prevent the progression to cirrhosis and hepatic failure (*57*). Currently, copper-chelating agents and liver transplantation are the main therapeutic approaches (*58*). However, Western medications such as D-penicillamine, trientine, zinc preparations, and dimercaptopropanol, though capable of achieving a negative copper balance, are often associated with serious adverse effects including nephrotoxicity, dermatologic reactions, bone marrow suppression, and AA, which affect long-term treatment adherence (*59*).

TCM has been widely used to treat WD (*60*), with Gandou Decoction and Gandouling being the most studied. These medicines show promise as adjuvant therapies. A RCT indicated that Gandou Decoction combined with conventional copper-chelating therapy significantly improved dysfunctional balance in patients and their TCM syndrome scores, and the combination markedly increased 24-hour urinary copper excretion (*61*). In copper-loaded rat models, aqueous extracts of Gandou Decoction were shown to reduce serum ALT levels and alleviate histological liver damage by modulating oxidative stress and the Wnt/β -catenin signaling pathway (*60*). One of its active components is curcumin, which can partially restore the expression of mutated ATP7B protein and promote functional copper excretion (*60*). *Rheum palmatum* root and its active compounds possess antioxidant, antifibrotic, and anti-inflammatory properties (*62-64*). The active components of *Coptis chinensis*, berberine and coptisine, exhibit antifibrotic effects (*65,66*).

In the study of antifibrotic mechanisms, Gandouling has demonstrated action through multiple signaling pathways. It has significant anti-WD effects *via* anti-inflammatory and antioxidant activities (*67,68*). It also blocks the Wnt-1/β -catenin signaling pathway by binding to Wnt-1, thereby inhibiting hepatic stellate cell (HSC) activation and alleviating hepatic fibrosis in WD (*69*). Its effective constituents of berberine (*65*), coptisine (*66*), aloe-emodin (*70*), and catechin (*71*) have all shown antifibrotic effects.

3. Theoretical basis and concepts of TCM in treating ALS

In recent years, TCM has been increasingly emphasized by the academic community as a complementary alternative therapy for intractable and rare diseases. TCM is supported by clinical and experimental evidence. Here, ALS is used as an example to describe the theoretical basis and concepts of TCM in treating intractable and rare diseases from 3 various aspects (Figure 1).

ALS is a progressive neurodegenerative disorder characterized by the degeneration of motor neurons. Currently, there is no curative treatment available. The clinical presentation at disease onset is often heterogeneous and may mimic other neurological conditions, frequently resulting in delayed diagnosis (*15*). To date, modern medicine has achieved only limited progress in ALS treatment. The U.S. Food and Drug Administration has approved four pharmacologic agents for ALS: Riluzole, Edaravone, Tofersen (Qalsody), and AMX0035 (Relyvrio) (*72-74*). However, Relyvrio was voluntarily withdrawn from the market in April 2024 following its failure to meet endpoints in a phase III clinical trial (*75*). Overall, these treatments have demonstrated only modest benefits, primarily in slowing disease progression for a few months in select patient populations.

3.1. Treatment based on syndrome differentiation

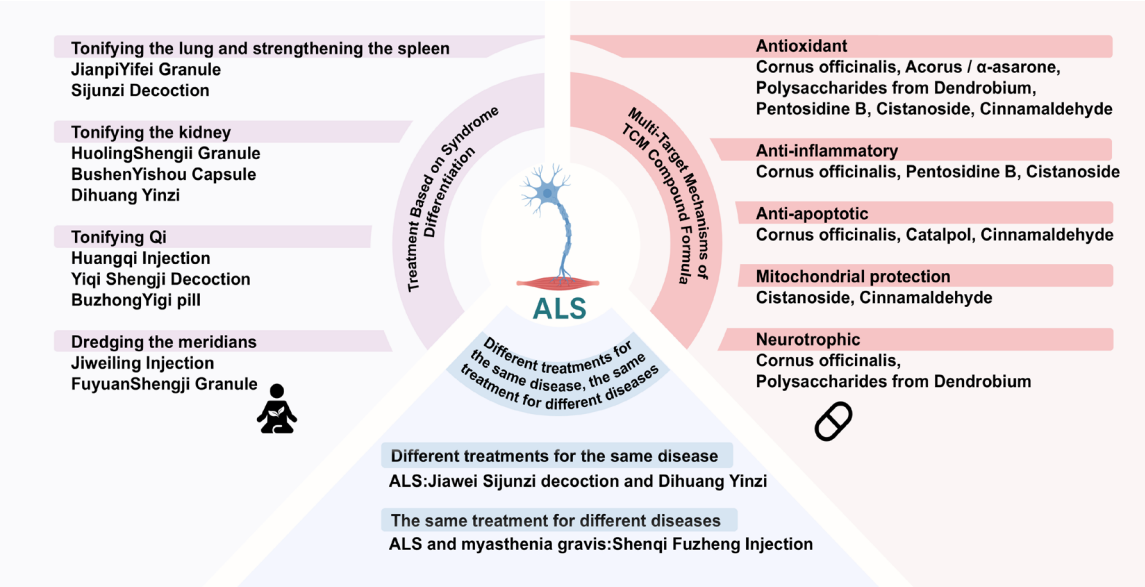

Figure 1. Theoretical basis and principles of TCM for ALS. TCM, traditional Chinese medicine; ALS, amyotrophic lateral sclerosis.

The London staging system offers a simple and practical method for assessing disease progression by categorizing ALS into five stages based on functional clinical milestones: Stage 1 is defined by the initial involvement of a single functional region, manifesting as weakness, muscle atrophy, spasticity, dysarthria, or dysphagia, functional regions are classified as bulbar, upper limb, lower limb, or diaphragmatic; Stage 2a denotes the formal diagnosis of ALS, while Stage 2b indicates the involvement of a second functional region; Stage 3 corresponds to the involvement of a third functional region; Stage 4a is characterized by the need for gastrostomy and Stage 4b by the initiation of non-invasive ventilation; and Stage 5 reflects the requirement for tracheal intubation, tracheostomy, or is defined by death (*76*). Interestingly, the disease trajectory reflected in the London staging system aligns with the TCM understanding of disease transmission and organ involvement, providing a potential framework for integrating TCM perspectives into the clinical management of ALS.

The primary syndrome differentiation-based therapeutic strategies for ALS in TCM include tonifying the kidney, strengthening the spleen and lung, tonifying "Qi," and dredging meridians. Kidney deficiency symptoms commonly observed in ALS often manifest in the lower limbs, such as lumbago, knee pain, and muscle atrophy. In a small clinical trial, use of Huoling Shengji Granule for 12 weeks resulted in comparable functional outcomes to riluzole but significantly improved TCM syndrome scores (*17*). Patients using Dihuang Yinzi also displayed significant improvement in bulbar paralysis and muscle fibrillations of the lower limbs (*77*). In ALS patients, progressive weakness of the diaphragm and other respiratory muscles leads to a decline in pulmonary ventilation function, thereby impairing gas exchange and resulting in hypoxemia and hypercapnia (*78*). Jianpi Yifei granules alleviated symptoms such as fasciculations, dysarthria, dysphagia, weak voice, and weak cough, particularly enhancing motor function in the upper limbs - an area where Riluzole fails to provide effective improvement (*79*). A clinical study indicated that patients treated with a combination of Riluzole and Jiawei Sijunzi Decoction displayed delayed disease progression, and especially in the sub-item evaluations of dyspnea and fatigue; the treatment group demonstrated superior outcomes compared to the Riluzole-only control group (*80*). Numerous studies have demonstrated a correlation between "Qi" and immune function (*81-83*). In ALS, abnormalities in the immune system are also thought to be associated with disease progression (*84,85*). A clinical experiment showed that Yiqi Shengji Decoction combined with acupuncture could alleviate symptoms of ALS in SOD1-G93A mice and slow disease progression (*86*). Buzhong Yiqi Tang is a traditional formula for tonifying "Qi." The formula was found to enhance locomotor activity, prolong survival, and have neuroprotective effects through anti-neuroinflammatory and antioxidant effects in an animal model of ALS (*87*). TCM theories contend that meridians are low hydraulic resistance channels that facilitate the transmission of various chemical substances and physical energies (*88,89*). Guided by the theories of extraordinary meridians and collateral disorders, a series of clinical studies led by Jinliang Chen's team demonstrated that Jiweiling injection has significant therapeutic effects. In a study involving 710 patients, the treatment group received a Jiweiling injection alone or in combination with oral Jiweiling capsules (*90*). The overall efficacy against neurodegenerative diseases such as ALS was as

high as 86.34%, which was significantly higher than that in the riluzole group. Jiweiling markedly alleviated the major clinical symptoms and signs of ALS.

3.2. Multi-target mechanisms of TCM compound formula

ALS is characterized by complex pathological mechanisms involving oxidative stress, glutamate excitotoxicity, mitochondrial dysfunction, autophagy impairment, and neuroinflammation (*91,92*). Conventional Western pharmacotherapy predominantly targets individual pathways, frequently resulting in suboptimal efficacy. Conversely, traditional Chinese herbal formulas, which are characterized by their composition of numerous bioactive components, have the capacity to induce multi-target and multi-pathway regulatory effects.

Dihuang Yinzi, a classic herbal formula consisting of 12 medicinal ingredients, is commonly prescribed in clinical practice to manage ALS. This formula exemplifies the multi-target therapeutic strategy of TCM. Cornus officinalis extract significantly reduces indicators of oxidative stress and attenuates neuronal cell damage: in a rat stress model, administration of cornus officinalis reduced the levels of reactive oxygen species (ROS), malondialdehyde, and pro-inflammatory cortisol, while up-regulating the expression of SOD, CAT, and BDNF in brain tissue and regulating the Bax/Bcl-2 ratio (*93*). Acorus and its active compound α-asarone protect hippocampal neurons by suppressing PERK-mediated endoplasmic reticulum stress and reducing ROS accumulation (*94*). Polysaccharides from Dendrobium exhibit potent antioxidant effects and promote neurotrophic factor expression (*95*). In microglial-neuronal co-cultures, pentosidine B significantly inhibited LPS-induced neuroinflammatory responses: decreased the release of inflammatory factors such as NO, TNF-α, IL-1β, and IL-6, and reduced ROS by inhibiting the TLR4/MyD88/NF-$_k$B pathway and NADPH oxidase activity (*96*). Cistanoside, a major active compound from Cistanche tubulosa, has potential therapeutic effects on neurodegenerative diseases, including ALS, through multiple mechanisms such as preserving mitochondrial function, scavenging ROS, and suppressing neuroinflammation (*97*). Catalpol is a core bioactive compound derived from Rehmannia glutinosa. Catalpol reduces neuronal apoptosis and promotes motor function recovery after spinal cord injury by inhibiting CHOP/GRP78-mediated endoplasmic reticulum stress and modulating the Caspase3/Bax/Bcl-2 pathway (*98*). Lv *et al*. found that cinnamaldehyde pretreatment effectively reduced oxidative damage, maintained mitochondrial membrane potential, reduced ROS generation and cytochrome c release, and inhibited the caspase-mediated apoptotic pathway by up-regulating Bcl-2 and down-regulating Bax (*99*).

3.3. Different treatments for the same disease and the same treatment for different diseases

TCM emphasizes the therapeutic principles of "different treatments for the same disease" and the "same treatment for different diseases". In treating ALS, TCM adopts distinct therapeutic approaches based on syndrome differentiation: patients with spleen "Qi" deficiency are treated with Jiawei Sijunzi decoction to tonify "Qi" and strengthen the spleen (*100*), while those with yin and yang deficiency receive Dihuang Yinzi (*77*). The use of different essential formulas for the same disease exemplifies the principle of personalized treatment based on pattern differentiation in TCM.

Conversely, Western-defined diseases such as ALS and myasthenia gravis may be classified under the same TCM syndrome pattern such as spleen-kidney yang deficiency, and thus can be treated with similar herbal formulas like Shenqi Fuzheng Injection (SFI). Animal experiments also further proved the correctness of the approach involving the Same Treatment for Different Diseases. SFI significantly delays disease onset, prolongs survival, and protects motor neurons in a mouse model of ALS by reducing oxidative stress and activating the Nrf2 antioxidant pathway (*86*). SFI also effectively reduces the severity and duration of transient worsening in myasthenia gravis patients receiving high-dose steroid therapy, with minimal adverse effects (*101*).

4. Research approaches and techniques

Currently, researchers are use multi-scale approaches and techniques to elucidate the mechanisms by which multi-component TCM formulas act on rare and intractable diseases (Table 2). Multi-omics studies of Huanglian Jiedu decoction have shown that it may ameliorate Alzheimer's disease-like pathology by modulating gut microbiota, lipid metabolism, and inflammatory pathways. Its mechanisms include suppressing gut dysbiosis and related Aβ deposition, alleviating neuroinflammation, and reversing cognitive impairment (*102*). Network pharmacology allows for the construction of "herb-active compound-target-disease" interaction networks. One example is research on *Astragalus membranaceus* in the treatment of lupus nephritis, which revealed approximately 200 shared key genes between the herb and the disease and which identified the PI3K/AKT/mTOR signaling pathway as the core mechanism (*103*). Animal experiments play an important role in validating mechanisms and evaluating the efficacy of TCM. Lycium barbarum polysaccharides demonstrated significant anti-inflammatory effects in a mouse model of Sjögren's syndrome by effectively reducing glandular inflammation (*104*). In addition, the clinical translation of TCM therapeutic strategies is steadily progressing. A typical example is an ongoing

Table 2. Research pathways and technical approaches

Path/Technology	Content	Examples of use in TCM
Multi-omics	Multi-level biological networks regulated by TCM	Huanglian Jiedu decoction for the treatment of Alzheimer's disease
Network pharmacology	Compound-target-disease interaction network	Astragali radix for the treatment of lupus nephritis
Animal models	Rare diseases using disease-specific mouse models	Lycium barbarum polysaccharide for the treatment of primary Sjögren's syndrome
Multicenter clinical trial	Phase II clinical trial	Shenrong granules for the treatment of ALS

multicenter phase II clinical trial evaluating the efficacy and safety of Shenrong granules (*105*) in the treatment of ALS, marking a significant step toward evidence-based validation of TCM interventions in the management of rare diseases.

In addition to these conventional methods, emerging tools such as computational modeling and phenomics are currently being introduced. Machine learning algorithms can be used to analyze the clustering of TCM components based on cellular phenotypes, thus revealing their multi-targeting mode of action (*106*). Transcriptome-based linkage profiling, which utilizes 102 TCM components for gene expression profiling, provides a phenotype-oriented research tool for mechanisms of the effects of TCM (*107*). Comprehensive research techniques from computational prediction and high-throughput screening to traditional component separation and systems biology modeling are gradually revealing the multi-targeted and networked effects of TCM in the treatment of rare and complex diseases.

5. Discussion

In 2018, China released its first Catalogue of Rare Diseases, covering 121 rare diseases, including neurodegenerative, metabolic, and hematologic disorders (*108*). TCM has gradually demonstrated clinical value and potential in the treatment of multiple rare diseases (*26,110-112*). Diseases listed in the catalogue, such as ALS, SLE, AA, and WD, have become key focus areas for TCM research and clinical interventions. TCM, based on the theoretical framework of syndrome differentiation and combined with modern pharmacological mechanisms, possesses advantages of multi-component, multi-target, and multi-pathway interventions. It has displayed a certain level of efficacy and safety in the treatment of these rare diseases.

In recent years, several Chinese herbal compound preparations have been approved for clinical use in rare diseases through "expanded indications" or the expedited "green channel" regulatory mechanism. Gandouling Capsule, used to treat WD, has been approved by the National Medical Products Administration; Kunxian Capsule, Tripterygium Glycoside Tablets, and Kunming Shanhaitang Tablets, commonly used in the treatment of SLE and rheumatoid arthritis, are also being gradually incorporated into clinical pathways for rare autoimmune diseases. These medications reflect the potential and translational value of TCM. The integrative potential of TCM is also being increasingly recognized. A cohort study in Taiwan involving 1,188 patients with SLE and chronic kidney disease found that those who used 17 types of Chinese herbal compound prescriptions had significantly lower rates of progression to renal failure and all-cause mortality compared to non-users (*112*). Another cross-sectional survey conducted in Shanghai indicated that over 90% of ALS patients had received TCM interventions (*113*).

China currently faces multiple challenges in the development of orphan drugs. A study reported that between 2013 and 2022, a total of 481 clinical trials related to rare diseases were conducted in China, which was significantly fewer than in the United States, Europe, and Japan during the same period (*114*). This gap is largely attributed to the absence of a comprehensive patient registry, clinical research infrastructure, and an inclusive framework for reimbursement of rare disease treatment. Moreover, many rare diseases, such as mitochondrial disorders, inherited metabolic conditions, and rare genetic dermatological diseases, remain unexplored territories in TCM research and require urgent scientific attention.

In contrast, the United States leads globally in the development of therapies for rare diseases such as ALS, supported by the FDA's Orphan Drug Designation program, the ClinicalTrials.gov registry, and a robust national patient database system (*4,115,116*). Japan classifies rare and intractable diseases under the umbrella term "Nanbyo" (intractable and rare diseases) and has established the Nanbyo Information Center and a national disease registry to facilitate multi-center clinical studies. The Ministry of Health, Labour and Welfare also supports the development of targeted therapies through the Database of Drug Development for Rare Diseases database and a rare disease biobank (*117,118*). The Japanese Government has made significant investments in healthcare expenditures for intractable diseases. According to the "Act on medical care for patients with intractable diseases". patients diagnosed with "designated intractable diseases" are typically required to cover only

10% of their medical expenses, substantially alleviating their financial burden (*119*). Of the 165 rare disease drugs approved for marketing in China, approximately 70% have been included in the national medical insurance catalog as of February 2024. Seventeen of these drugs are fully reimbursed, while the remaining 95 drugs are partially reimbursed (*120*). Although reimbursement efforts have intensified in recent years, the long-term treatment costs remain relatively high, imposing a considerable financial burden on patients.

To enhance the international competitiveness of TCM in the treatment of rare diseases, China has continued to strengthen its collaboration with the World Health Organization (WHO) in the field of traditional medicine. In 2024, the Chinese government pledged USD 5 million to support the WHO Traditional, Complementary, and Integrative Medicine Programme, aimed at facilitating the implementation of the WHO Traditional Medicine Strategy 2025–2034 (*121*). In December of the same year, China hosted the World Traditional Medicine Conference in Beijing, where representatives from 85 countries adopted the "Beijing Declaration", calling for strengthened evidence-based research and international cooperation to integrate traditional medicine into global health systems (*122*).

In summary, TCM has begun to establish a foundation for clinical translation in selected rare diseases and, supported by national policies, international collaboration, and scientific practice, holds promise for further development. However, advance mechanistic studies need to be conducted and the number of high-level, randomized multi-center trials needs to be increased to enhance TCM's reputation and academic recognition globally in the treatment of rare and intractable diseases.

Funding: This work was supported by a grant from the Qinghai Provincial Department of Science and Technology, a Demonstration Study of the Natural Population Cohort on the Tibetan Plateau (Grant No.2024-0204-SFC-0019).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Plaiasu V, Nanu M, Matei D. Rare disease day - At a glance. Maedica. 2010; 5:65-66.
2. Sequeira AR, Mentzakis E, Archangelidi O, Paolucci F. The economic and health impact of rare diseases: A meta-analysis. Health Policy Technol. 2021; 10:32-44.
3. European Union. Medicines for rare diseases - orphan drugs. *https://eur-lex.europa.eu/EN/legal-content/summary/medicines-for-rare-diseases-orphan-drugs.html* (accessed May 8, 2025).
4. U.S. Food and Drug Administration. Rare diseases at FDA. *https://www.fda.gov/patients/rare-diseases-fda* (accessed May 12, 2025).
5. Lu Y, Han J. The definition of rare disease in China and its prospects. Intractable Rare Dis Res. 2022; 11:29-30.
6. Wang Y, Liu Y, Du G, Liu Y, Zeng Y. Epidemiology and distribution of 207 rare diseases in China: A systematic literature review. Intractable Rare Dis Res. 2024; 13:73-88.
7. The State Council of the People's Republic of China. Progress made in rare disease treatment. *https://english.www.gov.cn/statecouncil/ministries/202211/04/content_WS63647e18c6d0a757729e249f.html* (accessed May 8, 2025).
8. Ministry of Science and Technology of the People's Republic of China. The project for "China Rare Disease Prevention Research and Demonstration " under the National Science and Technology Support Program of the 12th Five-Year Plan has passed final acceptance. *https://www.most.gov.cn/kjbgz/201607/t20160726_126785.html* (accessed May 12, 2025)
9. Xu HP, Zhu C, Gong MC, Zhang SY. Research of rare diseases in China: From the past to the future. Med J Peking Union Med Coll Hosp. 2018; 9:5-9. (in Chinese)
10. Beijing Association of Rare Disease Diagnosis, Treatment and Security. About us. *https://www.chard.org.cn/about* (accessed May 8, 2025).
11. China Pharmaceutical Innovation and Research Development Association. Bright Prospects for the big health industry: Traditional Chinese medicine sales to account for 32.4% of the pharmaceutical market by 2020. *https://www.phirda.com/about_19001.html* (accessed May 12, 2025).
12. Somekawa L, Maegawa H, Tsukada S, Nakamura T. Establishment of application guidance for OTC non-kampo crude drug extract products in Japan. J Intercult Ethnopharmacol. 2017; 6:333-338.
13. The Central People's Government of the People's Republic of China. Notice of the General Office of the State Council on Issuing the "14th Five-Year Plan for the Development of Traditional Chinese Medicine". *https://www.gov.cn/zhengce/zhengceku/2022-03/29/content_5682255.htm* (accessed May 12, 2025).
14. The Central People's Government of the People's Republic of China. Notice of the General Office of the State Council on issuing the implementation plan for major projects in the revitalization and development of traditional Chinese medicine. *https://www.gov.cn/zhengce/zhengceku/2023-02/28/content_5743680.htm* (accessed May 12, 2025).
15. Feldman EL, Goutman SA, Petri S, Mazzini L, Savelieff MG, Shaw PJ, Sobue G. Amyotrophic lateral sclerosis. Lancet. 2022; 400:1363-1380.
16. Napattharin V, Natkitta S, Han XJ, Li R, Zhang HH, Wang CH, Pan WD. New progress in the etiology and treatment of amyotrophic lateral sclerosis with traditional Chinese and Western medicine. J Neurol Neurorehab. 2024; 20:47-57. (in Chinese)
17. Liu X, Qin T, Li T, Shan L, Lei X, Xu X, Wen B, Feng Y, Yin P, Fan D. "Huoling shengji granule" for amyotrophic lateral sclerosis: Protocol for a multicenter, randomized, double-blind, riluzole parallel controlled clinical trial. Front Aging Neurosci. 2023; 15:1153973.
18. Zhou Q, Wang Y, Zhang J, Shao Y, Li S, Wang Y, Cai H, Feng Y, Le W. Fingerprint analysis of Huolingshengji Formula and its neuroprotective effects in SOD1G93A mouse model of amyotrophic lateral sclerosis. Sci Rep. 2018; 8:1668.

19. Huang GC, Lee CJ, Wang KT, Weng BC, Chien TY, Tseng SH, Wang CC. Immunomodulatory effects of hedysarum polybotrys extract in mice macrophages, splenocytes and leucopenia. Molecules. 2013; 18:14862-14875.
20. Han R, Tang F, Lu M, Xu C, Hu J, Mei M, Wang H. Astragalus polysaccharide ameliorates H2O2-induced human umbilical vein endothelial cell injury. Mol Med Rep. 2017; 15:4027-4034.
21. Lin S, Ye S, Huang J, Tian Y, Xu Y, Wu M, Wang J, Wu S, Cai J. How do Chinese medicines that tonify the kidney inhibit dopaminergic neuron apoptosis? Neural Regener Res. 2013; 8:2820-2826.
22. Raman C, McAllister SD, Rizvi G, Patel SG, Moore DH, Abood ME. Amyotrophic lateral sclerosis: Delayed disease progression in mice by treatment with a cannabinoid. Amyotroph Lateral Scler Other Motor Neuron Disord. 2004; 5:33-39.
23. Bilsland LG, Dick JR, Pryce G, Petrosino S, Di Marzo V, Baker D, Greensmith L. Increasing cannabinoid levels by pharmacological and genetic manipulation delay disease progression in SOD1 mice. FASEB J. 2006; 20:1003-1005.
24. Kiriakidou M, Ching CL. Systemic lupus erythematosus. Ann Intern Med. 2020; 172:ITC81-96.
25. Wang H, Li M, Zou K, Wang Y, Jia Q, Wang L, Zhao J, Wu C, Wang Q, Tian X, Wang Y, Zeng X. Annual direct cost and cost-drivers of systemic lupus erythematosus: A multi-center cross-sectional study from CSTAR registry. Int J Environ Res Public Health. 2023; 20:3522.
26. Wang Y, Han M, Pedigo CE, Xie ZM, Wang WJ, Liu JP. Chinese herbal medicine for systemic lupus erythematosus: A systematic review and meta-analysis of randomized, placebo-controlled trials. Chin J Integr Med. 2021; 27:778-787.
27. Li D, Pan B, Ma N, Wang X, Deng X, Lai H, Ge L, Niu J, Yang K. Efficacy and safety of shenqi dihuang decoction for lupus nephritis: A systematic review and meta-analysis. J Ethnopharmacol. 2024; 323:117602.
28. Chen HQ, Zhang N, Li CX, Zhang HX. Effects of astragalus membranaceus on systemic lupus erythematosus in a mouse model of pregnancy. Immun Inflammation Dis. 2022; 10:e624.
29. Chae BS, Yang JH. Regulatory effect of fresh Rehmanniae Radix extract on the *in vitro* production of proinflammatory cytokines in pristane-induced lupus mice. Nat Prod Sci. 2007; 13:322-327.
30. Li M, Ma JJ, Zhao XL, Zhu Y. Treating lupus nephritis by a drug pair of Radix Astragali and Rehmanniae Radix combined with glucocorticoid: A preliminary clinical study. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2014; 34:956-959. (in Chinese)
31. Pollard KM, Cauvi DM, Toomey CB, Morris KV, Kono DH. Interferon-γ and systemic autoimmunity. Discov Med. 2013; 16:123-131.
32. Billiau A. Interferon-gamma: Biology and role in pathogenesis. Adv Immunol. 1996; 62:61-130.
33. Hu H, Chen E, Li Y, Zhu X, Zhang T, Zhu X. Effects of arsenic trioxide on INF-gamma gene expression in MRL/lpr mice and human lupus. Biol Trace Elem Res. 2018; 184:391-397.
34. Chen C, Zhu R, Liu M, Yang H, Guo F, Du Q, Wang X, Li M, Song G, Qin R, Liu S. Kunxian capsule alleviates renal damage by inhibiting the JAK1/STAT1 pathway in lupus nephritis. J Ethnopharmacol. 2023; 310:116349.
35. Chen Y, Wang YF, Song SS, Zhu J, Wu LL, Li XY. Potential shared therapeutic and hepatotoxic mechanisms of tripterygium wilfordii polyglycosides treating three kinds of autoimmune skin diseases by regulating IL-17 signaling pathway and Th17 cell differentiation. J Ethnopharmacol. 2022; 296:115496.
36. DiMauro S, Hirano M. Mitochondrial encephalomyopathies: An update. Neuromuscul Disord. 2005; 15:276-286.
37. Lorenzoni PJ, Werneck LC, Kay CSK, Silvado CES, Scola RH. When should MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) be the diagnosis? Arq Neuropsiquiatr. 2015; 73:959-967.
38. Long H, Huang L, Wang J, Li Y, Fu X, Wen C. Mitochondrial encephalomyopathy involves ophthalmology, otorhinolaryngology, neurology and their clinical features. Lin Chuang Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2021; 35:529-534. (in Chinese)
39. Li Y, Gu X, Li J. Clinical analysis of the opposite and complementary method for treating mitochondrial encephalomyopathy. Chin J Clin Pharmacol. 2015; 31:890-892. (in Chinese)
40. Qiu Q. Neuroprotective effects of salidroside on GSK-3β in rats with cerebral ischemia/reperfusion. Chin Pharmacol Bull. 2020; 665-669.
41. Huang B. Research progress on Traditional Chinese medicine treatment of Parkinson's disease. Hans J Med Chem. 2019; 7:57-63. (in Chinese)
42. Su X, Guo C, Ying Q, Zhou D. Differentiation and treatment of mitochondrial encephalomyopathy based on the theory of Rong Qi deficiency. Clin J Trad Chin Med. 2021; 33:2266-2269. (in Chinese)
43. Chen ZG, Wang Y, Li NN, Ren S, Chen L, Kang SH, Ran WZ, Zhang XN, Zhao D. Treatment of mitochondrial encephalomyopathy based on the theory of "brain Qi - brain spirit - brain marrow." Chin J Integrative Med Cardio/Cerebrovasc Dis. 2023; 21:3649-3652. (in Chinese)
44. Young NS. Aplastic anemia. N Engl J Med. 2018; 379:1643-1656.
45. Marsh JC. Treatment of aplastic anaemia: First do no harm. Lancet. 2000; 356:1536-1537.
46. Bacigalupo A. How I treat acquired aplastic anemia. Blood. 2017; 129:1428-1436.
47. Hu ZJ, Zhang XM, Lan HX, Wu J, Zhu LL. Efficacy and safety of therapy of tonifying kidney and promoting blood circulation combined with cyclosporine plus androgen for the treatment of aplastic anemia: A meta-analysis. J Guangzhou Univ Tradit Chin Med.. 2024; 41:1919-1926. (in Chinese)
48. Song XY, He DD, Wang JH, Sun WZ. Meta-analysis of traditional Chinese medicine combined with IST regimen in the treatment of aplastic anemia. Yunnan J Trad Chin Med and Materia Medica. 2025; 46:63-69. (in Chinese)
49. Zhu C, Gao Y, Jiang T, Hao C, Gao Z, Sun Y. Meta-analysis of huangqi injection for the adjunctive therapy of aplastic anemia. Int J Clin Exp Med. 2015; 8:10256-10264.
50. Deng P, Li X, Wei Y, Liu J, Chen M, Xu Y, Dong B, Zhu L, Chai L. The herbal decoction modified Danggui Buxue Tang attenuates immune-mediated bone marrow failure by regulating the differentiation of T lymphocytes in an immune-induced aplastic anemia mouse model. PLoS One. 2017; 12:e0180417.
51. Wang MS, Li J, Di HX, Li ZL, Yang SL, Hou W, Yan JY, Zhao XM. Clinical study on effect of Astragalus Injection and its immuno-regulation action in treating chronic aplastic anemia. Chin J Integr Med. 2007; 13:98-102.

52. Chiu ML, Hsu YL, Chen CJ, Li TM, Chiou JS, Tsai FJ, Lin TH, Liao CC, Huang SM, Chou CH, Liang WM, Lin YJ. Chinese herbal medicine therapy reduces the risks of overall and anemia-related mortalities in patients with aplastic anemia: A nationwide retrospective study in Taiwan. Front Pharmacol. 2021; 12:730776.
53. Jiang ZY, Yu FQ, Gao RL, Kuang YM, Zhu Y, Chen YH, Li LJ, Ouyang GF, Hu J, Wu XL. Treatment of chronic aplastic anemia with Chinese patent medicine Pai-Neng-Da capsule for replacing androgen partially: A clinical multi-center study. Chin J Integr Med. 2022; 28:20-27.
54. Wen WW, Sun X, Zhuang HF, Lin XJ, Zheng ZY, Gao RL, Yin LM. Effects of panaxadiol saponins component as a new Chinese patent medicine on proliferation, differentiation and corresponding gene expression profile of megakaryocytes. Chin J Integr Med. 2016; 22:28-35.
55. Zheng ZY, Yu XL, Dai TY, Yin LM, Zhao YN, Xu M, Zhuang HF, Chong BH, Gao RL. Panaxdiol saponins component promotes hematopoiesis and modulates T lymphocyte dysregulation in aplastic anemia model mice. Chin J Integr Med. 2019; 25:902-910.
56. Bandmann O, Weiss KH, Kaler SG. Wilson's disease and other neurological copper disorders. Lancet, Neurol. 2015; 14:103-113.
57. Wright LM, Huster D, Lutsenko S, Wrba F, Ferenci P, Fimmel CJ. Hepatocyte GP73 expression in Wilson disease. J Hepatol. 2009; 51:557-564.
58. Hedera P. Update on the clinical management of Wilson's disease. Appl Clin Genet. 2017; 10:9-19.
59. European Association for Study of Liver. EASL clinical practice guidelines: Wilson's disease. J Hepatol. 2012; 56:671-685.
60. Xu MB, Rong PQ, Jin TY, Zhang PP, Liang HY, Zheng GQ. Chinese herbal medicine for Wilson's disease: A systematic review and meta-analysis. Front Pharmacol. 2019; 10:277.
61. Fang X, Jin S, Yang W, Chen H, Fu Y. Clinical study of Gandou Decoction combined with copper-removal therapy for balance disorder in patients with interior retention of damp-heat type Wilson's disease. Chinese General Practice. 2020; 23:3094-3098. (in Chinese)
62. Hwang JK, Noh EM, Moon SJ, Kim JM, Kwon KB, Park BH, You YO, Hwang BM, Kim HJ, Kim BS, Lee SJ, Kim JS, Lee YR. Emodin suppresses inflammatory responses and joint destruction in collagen-induced arthritic mice. Rheumatology (Oxford). 2013; 52:1583-1591.
63. Shia CS, Juang SH, Tsai SY, Chang PH, Kuo SC, Hou YC, Chao PD. Metabolism and pharmacokinetics of anthraquinones in rheum palmatum in rats and ex vivo antioxidant activity. Planta Med. 2009; 75:1386-1392.
64. Jin H, Sakaida I, Tsuchiya M, Okita K. Herbal medicine rhei rhizome prevents liver fibrosis in rat liver cirrhosis induced by a choline-deficient L-amino acid-defined diet. Life Sci. 2005; 76:2805-2816.
65. Yi J, Wu S, Tan S, Qin Y, Wang X, Jiang J, Liu H, Wu B. Berberine alleviates liver fibrosis through inducing ferrous redox to activate ROS-mediated hepatic stellate cells ferroptosis. Cell Death Discov. 2021; 7:374.
66. Chai FN, Zhang J, Xiang HM, Xu HS, Li YF, Ma WY, Li XG, Ye XL. Protective effect of coptisine from rhizoma coptidis on LPS/D-GalN-induced acute liver failure in mice through up-regulating expression of miR-122. Biomed Pharmacother. 2018; 98:180-190.
67. Chen Y, Zhang B, Cao S, Huang W, Liu N, Yang W. GanDouLing combined with penicillamine improves cerebrovascular injury *via* PERK/eIF2α/CHOP endoplasmic reticulum stress pathway in the mouse model of Wilson's disease. Biosci Rep. 2018; 38:BSR20180800.
68. Fang S, Yang W, Zhang K, Peng C. Gandouling mitigates CuSO4-induced heart injury in rats. Animals (Basel). 2022; 12:2703.
69. Cheng C, Wang Q, Huang Y, Xue Q, Wang Y, Wu P, Liao F, Miao C. Gandouling inhibits hepatic fibrosis in Wilson's disease through wnt-1/β-catenin signaling pathway. J Ethnopharmacol. 2023; 311:116445.
70. Zhou Y, Wu R, Cai FF, Zhou WJ, Lu YY, Zhang H, Chen QL, Sun MY, Su SB. Development of a novel anti-liver fibrosis formula with luteolin, licochalcone a, aloe-emodin and acacetin by network pharmacology and transcriptomics analysis. Pharm Biol. 2021; 59:1594-1606.
71. Luo Y, Huo Y, Song P, Zhang X, Liao M. Validation and functional analysis of the critical proteins in combination with taurine, epigallocatechin gallate and genistein against liver fibrosis in rats. Biomed Pharmacother. 2019; 115:108975.
72. Jiang J, Wang Y, Deng M. New developments and opportunities in drugs being trialed for amyotrophic lateral sclerosis from 2020 to 2022. Front Pharmacol. 2022; 13:1054006.
73. Blair HA. Tofersen: First approval. Drugs. 2023; 83:1039-1043.
74. Aschenbrenner DS. New drug approved for ALS. Am J Nurs. 2023; 123:22-23.
75. Neurologylive. Amylyx pharmaceuticals discontinues AMX0035 after failing primary end point in phase 3 PHOENIX trial. *https://www.neurologylive.com/view/amylyx-pharmaceuticals-discontinues-amx0035-after-failing-primary-end-point-phase-3-phoenix-trial* (accessed May 12, 2025).
76. Balendra R, Al Khleifat A, Fang T, Al-Chalabi A. A standard operating procedure for King's ALS clinical staging. Amyotroph Lateral Scler Front Degener. 2019; 20:159-164.
77. Qiu H, Li JH, Yin SB, Ke JQ, Qiu CL, Zheng GQ. Dihuang yinzi, a classical Chinese herbal prescription, for amyotrophic lateral sclerosis: A 12-year follow-up case report. Medicine (Baltimore). 2016; 95:e3324.
78. de Carvalho M, Swash M, Pinto S. Diaphragmatic neurophysiology and respiratory markers in ALS. Front Neurol. 2019; 10:143.
79. Wanfangdata. Clinical assessment of bulbar palsy in amyotrophic lateral sclerosis and therapeutic effect of spleen-strengthening and lung-tonifying formula. *https://d.wanfangdata.com.cn/thesis/Y3144311* (accessed May 12, 2025).
80. Bao J, Fu M, Shen B, Zhu X. Clinical study of Jiawei Sijunzi Decoction in the treatment of amyotrophic lateral sclerosis. Herald Med. 2016; 35:43–45. (in Chinese)
81. Yang Z, Sun R, Tian Y, Zhang Y, Li Y, Wang Q. The correlation study between traditional Chinese medicine constitutions and immunology. Immunol Stud. 2014; 2:23-32. (in Chinese)
82. Deng YF, Li MD, Liu DY, Zhao HM, Zhou W. A review on immunopharmacological mechanism and clinical application of the Buzhong Yiqi decoction. Clin J Chin Med. 2023; 15:68-72. (in Chinese)
83. Wu YL. Correlation analysis of Qi collateral–NEI network. J Trad Chin Med. 2005; 16:723-726. (in Chinese)
84. Cui C, Ingre C, Yin L, Li X, Andersson J, Seitz C, Ruffin N,

Pawitan Y, Piehl F, Fang F. Correlation between leukocyte phenotypes and prognosis of amyotrophic lateral sclerosis. Elife. 2022; 11:e74065.
85. McCombe PA, Lee JD, Woodruff TM, Henderson RD. The peripheral immune system and amyotrophic lateral sclerosis. Front Neurol. 2020; 11:279.
86. Sugimoto K, Liu J, Li M, Song Y, Zhang C, Zhai Z, Gao Y. Neuroprotective effects of shenqi fuzheng injection in a transgenic SOD1-G93A mouse model of amyotrophic lateral sclerosis. Front Pharmacol. 2021; 12:701886.
87. Cai M, Lee SH, Yang EJ. Bojungikgi-tang improves muscle and spinal cord function in an amyotrophic lateral sclerosis model. Mol Neurobiol. 2019; 56:2394-2407.
88. Zhang WB, Tian YY, Li H, Tian JH, Luo MF, Xu FL, Wang GJ, Huang T, Xu YH, Wang RH. A discovery of low hydraulic resistance channel along meridians. J Acupunct Meridian Stud. 2008; 1:20-28.
89. Yang J, Zuo, Shi Y. Research progress on physiological basis and physical characteristics of meridians. Tradit Chin Med. 2022; 11:641-647. (in Chinese)
90. Deng WL. Advances in research on traditional Chinese medicine for amyotrophic lateral sclerosis (part II). Pharmacol Clinics Chin Materia Medica. 2016; 32:233-243. (in Chinese)
91. Taylor JP, Brown RH, Cleveland DW. Decoding ALS: From genes to mechanism. Nature. 2016; 539:197-206.
92. Van Damme P, Robberecht W, Van Den Bosch L. Modelling amyotrophic lateral sclerosis: progress and possibilities. Dis Models Mech. 2017; 10:537-549.
93. Tian W, Zhao J, Lee JH, Akanda MR, Cho JH, Kim SK, Choi YJ, Park BY. Neuroprotective effects of cornus officinalis on stress-induced hippocampal deficits in rats and H2O2-induced neurotoxicity in SH-SY5Y neuroblastoma cells. Antioxid (basel Switz). 2019; 9:27.
94. Mikami M, Takuya O, Yoshino Y, Nakamura S, Ito K, Kojima H, Takahashi T, Iddamalgoda A, Inoue S, Shimazawa M, Hara H. Acorus calamus extract and its component α-asarone attenuate murine hippocampal neuronal cell death induced by l-glutamate and tunicamycin. Biosci Biotechnol Biochem. 2021; 85:493-501.
95. Xu X, Zhang C, Wang N, Xu Y, Tang G, Xu L, Feng Y. Bioactivities and mechanism of actions of *Dendrobium officinale*: A comprehensive review. Oxid Med Cell Longev. 2022; 2022:6293355.
96. Zeng KW, Zhang T, Fu H, Liu GX, Wang XM. Schisandrin B exerts anti-neuroinflammatory activity by inhibiting the toll-like receptor 4-dependent MyD88/IKK/NF-κB signaling pathway in lipopolysaccharide-induced microglia. Eur J Pharmacol. 2012; 692:29-37.
97. Li J, Yu H, Yang C, Ma T, Dai Y. Therapeutic potential and molecular mechanisms of echinacoside in neurodegenerative diseases. Front Pharmacol. 2022; 13:841110.
98. Huang Z, Gong J, Lin W, Feng Z, Ma Y, Tu Y, Cai X, Liu J, Lv C, Lv X, Wu Q, Lu W, Zhao J, Ying Y, Li S, Ni W, Chen H. Catalpol as a component of rehmannia glutinosa protects spinal cord injury by inhibiting endoplasmic reticulum stress-mediated neuronal apoptosis. Front Pharmacol. 2022; 13:860757.
99. Lv C, Yuan X, Zeng HW, Liu RH, Zhang WD. Protective effect of cinnamaldehyde against glutamate-induced oxidative stress and apoptosis in PC12 cells. Eur J Pharmacol. 2017; 815:487-494.
100. Pan W, Su X, Bao J, Wang J, Zhu J, Cai D, Yu L, Zhou H. Open randomized clinical trial on JWSJZ decoction for the treatment of ALS patients. Evid-based Complement Altern Med. 2013; 2013:347525.
101. Qi GY, Liu P, Gao BL. Shenqi fuzheng injection alleviates the transient worsening caused by steroids pulse therapy in treating myasthenia gravis. Evid-based Complement Altern Med. 2013; 2013:816829.
102. Gu X, Zhou J, Zhou Y, Wang H, Si N, Ren W, Zhao W, Fan X, Gao W, Wei X, Yang J, Bian B, Zhao H. Huanglian jiedu decoction remodels the periphery microenvironment to inhibit Alzheimer's disease progression based on the 'brain-gut' axis through multiple integrated omics. Alzheimer's Res Ther. 2021; 13:44.
103. Zhan K, Chen S, Ji L, Xu L, Zhang Y, Zhang Q, Dai Q, Wu S. Network pharmacology to unveil the mechanism of astragali radix in the treatment of lupus nephritis *via* PI3K/AKT/mTOR pathway. Sci Rep. 2024; 14:25983.
104. Wang Y, Xiao J, Duan Y, Miao M, Huang B, Chen J, Cheng G, Zhou X, Jin Y, He J, Li Z, So KF. Lycium barbarum polysaccharide ameliorates Sjögren's syndrome in a murine model. Mol Nutr Food Res. 2021; 65:e2001118.
105. Drug Clinical Trial Registration and Information Disclosure Platform. Shenrong Granules. *http://www.chinadrugtrials.org.cn/clinicaltrials.searchlist.dhtml?keywords=CTR20240243* (accessed May 12, 2025)
106. Guo F, Tang X, Zhang W, Wei J, Tang S, Wu H, Yang H. Exploration of the mechanism of traditional Chinese medicine by AI approach using unsupervised machine learning for cellular functional similarity of compounds in heterogeneous networks, XiaoErFuPi granules as an example. Pharmacol Res. 2020; 160:105077.
107. Lv C, Wu X, Wang X, Su J, Zeng H, Zhao J, Lin S, Liu R, Li H, Li X, Zhang W. The gene expression profiles in response to 102 traditional Chinese medicine (TCM) components: A general template for research on TCMs. Sci Rep. 2017; 7:352.
108. National Health Commission. Notification on the release of the first list of rare diseases. *https://www.gov.cn/zhengce/zhengceku/2018-12/31/content_5435167.htm* (accessed May 12, 2025).
109. Suh WJ, Seo Y, Jin C, Cho SY, Park SU, Jung WS, Moon SK, Park JM, Ko CN, Kwon S, Cho KH. Traditional East Asian herbal medicine for amyotrophic lateral sclerosis: A scoping review. Evid-based Complement Altern Med. 2021; 2021:5674142.
110. Guan J, Zhao Y, Wang T, Fu R. Traditional Chinese medicine for treating aplastic anemia. J Pharm Pharm Sci: Publ Can Soc Pharm Sci Soc Can Sci Pharm. 2023;26:11863.
111. Chen H, Wang X, Tang L, Pu Y, Ma Y, Ye H, Zhang J. Review of the efficacy and mechanisms of traditional Chinese medicine for treating multi-organ damage in wilson's disease. Drug Des Dev Ther. 2025; 19:2453-2471.
112. Chen HT, Tung CH, Yu BH, Chang CM, Chen YC. Renal and survival benefits of seventeen prescribed Chinese herbal medicines against oxidative-inflammatory stress in systemic lupus erythematosus patients with chronic kidney disease: A real-world longitudinal study. Front Pharmacol. 2023; 14:1309582.
113. Pan W, Chen X, Bao J, Bai Y, Lu H, Wang Q, Liu Y, Yuan C, Li W, Liu Z, Liu J, Zhu X, Qin B, Cai D, Zhou H. The use of integrative therapies in patients with amyotrophic lateral sclerosis in Shanghai, China. Evid-based

Complement Altern Med: Ecam. 2013; 2013:613596.
114. Peng A, Fan X, Zou L, Chen H, Xiang J. Trend of clinical trials of new drugs for rare diseases in China in recent 10 years. Orphanet J Rare Dis. 2023; 18:114.
115. National Institutes of Health, National Library of Medicine. Clinical Trials. *https://clinicaltrials.gov/* (accessed May 12, 2025).
116. National Organization for Rare Disorders. Understanding Rare Disease *https://rarediseases.org/understanding-rare-disease/* (accessed May 12, 2025).
117. National Institutes of Biomedical Innovation, Health, and Nutrition. Laboratory of Rare Disease Information and Resource Library. *https://www.nibn.go.jp/en/activities/disease-resources.html* (accessed May 12, 2025).
118. Japan Intractable Diseases Information Center. List of Designated Intractable Diseases. *https://www.nanbyou.or.jp/entry/5461* (accessed May 12, 2025).
119. Ministry of Health, Labour and Welfare of Japan. Act on Medical Care for Patients with Intractable Diseases. *https://www.mhlw.go.jp/file/05-Shingikai-10601000-Daijinkanboukouseikagakuka-Kouseikagakuka/0000060761.pdf* (accessed May 12, 2025).
120. Yicai Global. 70% of China's rare disease drugs have been added to medical insurance plan. *https://www.yicaiglobal.com/news/70-of-chinas-rare-disease-drugs-have-been-added-to-medical-insurance-plan* (accessed May 12, 2025).
121. World Health Organization. China and WHO deepen strategic partnership to lead global traditional medicine advancements. *https://www.who.int/news/item/09-11-2024-china-and-who-deepen-strategic-partnership-to-lead-global-traditional-medicine-advancements* (accessed May 12, 2025).
122. World Health Organization. Beijing declaration calls for strengthened global collaboration on traditional medicine. *https://www.who.int/news/item/23-12-2024-beijing-declaration-calls-for-strengthened-global-collaboration-on-traditional-medicine*(accessed May 12, 2025).

Received March 16, 2025; Revised May 20, 2025; Accepted May 28, 2025.

**Address correspondence to:*
Yanming Ren, Department of Public Health, Qinghai University Medical College, No. 16 Kunlun Rd, Xi-ning, China 810008.
E-mail: btyqh@126.com

Peipei Song, Center for Clinical Sciences, Japan Institute for Health Security, Tokyo, 1-21-1 Toyama Shinjuku-ku, Tokyo, Japan 162-8655.
E-mail: psong@jihs.go.jp

Released online in J-STAGE as advance publication May 30, 2025.