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REVIEW

Diabetic Neuropathy: From Etiopathogenesis to Integrative Therapeutic Strategies with Traditional Chinese Medicine

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Abstract: Diabetic neuropathy is a common and disabling complication of diabetes leading to numbness, pain, sensory loss and reduced quality of life. This review summarizes its diagnosis, epidemiology, genetic basis, pathophysiological mechanisms and current treatment strategies, with a focus on the role of traditional Chinese medicine (TCM). Its current common diagnostic methods include nerve conduction studies and corneal confocal microscopy. The development of diabetic neuropathy has been closely linked to chronic hyperglycemia, metabolic disorders, oxidative stress, inflammation, and mitochondrial dysfunction, and the current treatment mainly relies on glycemic control, neuroprotective agents, pain relief, exercise, and physical therapy, despite clinical benefits remain limited in many patients. TCM has shown potential value through herbal formulas, active natural compounds, acupuncture, moxibustion, and external therapies such as herbal foot baths, which have shown efficacies in relieving symptoms and protecting nerve function through antioxidant, anti-inflammatory, and autophagy-related effects, as well as regulation of gut microbiota. This review also highlights current research gaps, including uneven study quality, insufficient mechanistic evidence, and lack of standardized evaluation. Overall, we integrate recent basic and clinical evidence to provide a clearer framework for future research and more standardized development of TCM-based strategies for diabetic neuropathy.

Keywords: diabetic neuropathy, hyperglycemia, oxidative stress, inflammation, TCM

Introduction

Diabetic neuropathy (DN) is one of the most common and burdensome complications of diabetes mellitus, often presenting with numbness, pain, paresthesia and progressive sensory loss that progressively reduce quality of life.[1] Recent evidence shows that the clinical burden of DN continues to grow, which can be associated with rise in diabetes worldwide, while current treatment remains largely focused on glycemic control and symptom relief rather than reversal of nerve injury.[2] The pathological development of DN is complex and involves chronic hyperglycemia, metabolic disturbance, oxidative stress, inflammation, mitochondrial dysfunction and microvascular damage, which together drive progressive nerve injury.[3]

Traditional Chinese medicine (TCM) has attracted increasing attention as a complementary approach because of its multi-target and whole-system characteristics. Recent clinical syntheses suggest that Chinese herbal medicine and acupuncture may improve pain scores and nerve conduction in some patients with DN, although the quality of evidence remains uneven and stronger trials are still needed.[4,5] Despite progress in this field in the recent years, several gaps remain in the current literature. Existing reviews often focus mainly on either mechanisms or clinical interventions, and few provide clear integrative discussion linking disease mechanisms, diagnostic progress, and the practical role of TCM in routine care.[6] In addition, heterogeneity in diagnostic criteria, study design, and outcome measures continues to limit comparison across studies and weakens translation into clinical practice.[2]

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Herein, we designed this narrative review through a targeted search of major Chinese and international databases on recent studies addressing DN pathogenesis, diagnosis, conventional management, and TCM-related interventions and merge them together in a clinically accessible way, so that readers can better understand not only where TCM may contribute, but also where the current evidence remains limited and what should be prioritized in future research.

Diagnosis

The clinical diagnosis of DN primarily relies on the evaluation of the patients' symptoms, physical signs, and relevant auxiliary examination findings. Characteristic symptoms typically include numbness, pain, paresthesia, and muscle weakness, which generally present symmetrically and progress from the distal to proximal segments of the limbs.[7] The common physical signs include diminished or absent tendon reflexes, hypoesthesia, and muscle atrophy. Nevertheless, an accurate diagnosis based solely on clinical manifestations can be challenging; therefore, a comprehensive assessment incorporating auxiliary diagnostic methods is essential.

Currently, there are no universally accepted clinical diagnostic criteria for DN. Frequently employed diagnostic modalities include nerve conduction velocity (NCV) testing, quantitative sensory testing (QST), and skin biopsy. NCV testing assesses the function of large nerve fibers, with reductions in conduction velocity indicative of potential neuropathic involvement.[8] The QST evaluates small fiber function by measuring patients' sensory thresholds to stimuli such as temperature and vibration, thereby detecting sensory impairments.[9] Skin biopsy allows for direct visualization of epidermal nerve fiber density and morphology, which is particularly valuable for diagnosing small fiber neuropathy.[10] Additionally, emerging diagnostic techniques, such as corneal confocal microscopy, offer non-invasive and reproducible means to indirectly assess peripheral nerve pathology by examining corneal nerve fiber morphology and density, thereby facilitating the early detection of DN.[11]

Among these modalities, NCV testing remains a cornerstone in the diagnosis and monitoring of DN, as it provides direct functional information on peripheral nerves. Patients with DN frequently exhibit slowed nerve conduction velocities, which correlate with the extent of nerve fiber damage. Empirical studies have demonstrated that both motor nerve conduction velocity (MCV) and sensory nerve conduction velocity (SCV) decline to varying degrees in diabetic individuals, with the magnitude of reduction being positively associated with neuropathy severity.[8] For instance, longitudinal investigations have revealed progressive decreases in MCV and SCV corresponding to diabetes duration, reflecting exacerbation of nerve injury.[12] Beyond diagnosis, NCV testing can be used to monitor disease progression and evaluate therapeutic efficacy. Nevertheless, because NCV testing predominantly reflects large-fiber dysfunction and has limited sensitivity for small-fiber pathology, it should be interpreted in conjunction with complementary diagnostic approaches.

Advances in imaging technologies have further expanded diagnostic options for DN. Corneal confocal microscopy enables noninvasive visualization of corneal nerve fiber density, length, and branching patterns, which are significantly reduced in diabetic patients and closely correlate with neuropathy severity.[11] Skin autofluorescence measurement provides an indirect assessment of advanced glycation end products (AGEs) accumulation and has been associated with neuropathy severity, supporting its potential role in early screening and risk stratification.[13] In addition, magnetic resonance imaging (MRI) can detect muscle atrophy, fatty infiltration, and structural nerve changes, offering valuable information for identifying complications such as diabetic myopathy and nerve compression syndromes.[14] Ultrasonography further complements these modalities by allowing evaluation of nerve morphology, thickness, and vascularity, thereby providing supplementary structural and hemodynamic information.[15]

Importantly, standardized clinical assessment combined with objective auxiliary diagnostic methods forms the foundation for epidemiological investigations and genetic association studies of DN. Consistent diagnostic definitions and phenotype classification are essential for accurately comparing disease prevalence, identifying population-level risk factors, and elucidating genetic susceptibility across different cohorts.

Epidemiology

Based on standardized clinical and auxiliary diagnostic criteria, epidemiological studies consistently demonstrate a global upward trend in the incidence and prevalence of DN. This increase closely parallels the rapid worldwide rise in diabetes

mellitus, as DN represents one of its most common chronic complications. Current projections indicate that the global burden of diabetes will continue to expand, which is expected to further increase the number of individuals affected by DN in the coming decades.[16,17]

Although the overall trend is consistent worldwide, substantial regional variation exists in the prevalence of DN. In many developing countries, the growing burden of neuropathy has been attributed to rapid urbanization, lifestyle changes, and population aging. Studies from several Asian and African regions report particularly high prevalence rates, imposing significant pressure on local healthcare systems.[18] Conversely, despite more advanced medical infrastructure and improved diabetes management in developed countries, DN remains highly prevalent and continues to exert a marked negative impact on patients' quality of life and long-term prognosis.[19] These observations suggest that improvements in healthcare access alone may be insufficient to offset the multifactorial drivers of neuropathy.

The incidence of DN varies markedly across populations and is influenced by multiple factors. Age is a significant factor; elderly individuals exhibit a higher incidence of diabetes, likely because of physiological decline and prolonged disease duration. Research indicates that diabetic patients over 60 years of age have a significantly greater incidence of neuropathy than younger cohorts, potentially linked to age-related neurodegeneration and cumulative nerve damage from chronic hyperglycemia.[20]

Sex- and ethnicity-related differences in DN have also been reported, although findings are not entirely consistent across studies. Some investigations suggest that women with diabetes may have a slightly higher risk of developing neuropathy than men, potentially related to hormonal factors, body composition, or lifestyle differences; however, the underlying mechanisms remain unclear.[21] Ethnic disparities are also evident, with African American and Latino populations demonstrating relatively higher neuropathy prevalence, which may reflect complex interactions among genetic susceptibility, socioeconomic status, environmental exposures, and disparities in healthcare access.[22] Additionally, regional economic disparities influence the incidence of neuropathy, with underdeveloped areas exhibiting higher rates, likely because of limited medical resources and insufficient health awareness.

From a risk factor perspective, DN is closely linked to chronic hyperglycemia and other components of metabolic dysfunction. Persistent hyperglycemia plays a central role by inducing metabolic and microvascular disturbances that damage peripheral nerves. Epidemiological and interventional studies consistently show that stringent glycemic control can delay neuropathy onset and slow disease progression, although it does not fully prevent neuropathy in all patients.[23,24] Beyond hyperglycemia, components of metabolic syndrome, including dyslipidemia, hypertension, and obesity, play critical roles in the development of neuropathy. Dyslipidemia promotes endoneurial microangiopathy, hypertension impairs vascular endothelial function and nerve perfusion, and obesity exacerbates insulin resistance and low-grade inflammation, collectively accelerating neural injury.[21,25]

In population-based studies, TCM interventions have also been explored for their potential role in alleviating neuropathy-related symptoms and disease burden. For example, a meta-analysis of 16 randomized controlled trials involving 1173 patients reported that Huangqi Guizhi Wuwu Decoction significantly improved clinical symptoms and NCV compared with control treatments.[26] However, the lack of significant effects on glycemic indices and the generally low methodological quality of the included studies warrant cautious interpretation and highlight the need for larger, rigorously designed trials. Experimental and clinical studies further suggest that certain TCM prescriptions, such as Danggui Sini Decoction, may attenuate neuropathic pain and inflammation, while external therapies including herbal foot baths may improve nerve conduction and symptom severity.[27,28] Although these interventions may not directly alter population-level prevalence, they may contribute to reducing disease burden and complications in affected individuals.

Collectively, the marked heterogeneity in prevalence, clinical presentation, and risk factor distribution across populations indicates that DN cannot be explained solely by environmental or metabolic factors. These population-level differences strongly suggest that genetic susceptibility, interacting with metabolic and lifestyle influences, contributes to the development and progression of DN, thereby providing a rationale for the genetic studies discussed in the following section.

Genetic Basis

Building on epidemiological observations of inter-individual and inter-population heterogeneity in the prevalence and clinical manifestations of DN, genetic susceptibility has emerged as an important area of investigation. Accumulating evidence suggests that genetic factors contribute to individual vulnerability to DN; however, compared with the extensive genetic studies on type 2 diabetes mellitus (T2DM) itself, the genetic architecture specifically underlying DN remains incompletely understood. Despite advances in sequencing technologies and candidate gene approaches, robust and reproducible genetic markers for DN have yet to be firmly established, reflecting the complex and multifactorial nature of the disease.[29]

Candidate gene studies have examined associations between specific genetic polymorphisms and susceptibility to DN, with variable and sometimes inconsistent results. For instance, research on GSTM1, GSTT1, and GSTP1 gene polymorphisms revealed that the GSTP1 Ile105Val variant correlates with an increased risk of T2DM but does not appear to influence the risk of DN, while GSTM1 and GSTT1 polymorphisms were likewise not consistently linked to neuropathy risk.[30] These findings suggest that genetic variants influencing diabetes susceptibility do not necessarily confer parallel risk for neuropathic complications. In contrast, a study focusing on the rs3746444 single nucleotide polymorphism (SNP) in MIR499A found that the GG genotype was associated with a heightened risk of cardiovascular autonomic neuropathy and diabetic polyneuropathy in T2DM patients, as well as poorer neurological outcomes.[31] Similarly, polymorphisms in the endothelial nitric oxide synthase (eNOS) gene, particularly the VNTR intron 4B/4B genotype and B allele, have been reported to occur more frequently in patients with both T2DM and diabetic polyneuropathy, suggesting a potential role of endothelial dysfunction–related genetic pathways in neuropathy development.[32]

Notably, the relationship between individual genetic polymorphisms and DN is often context-dependent and influenced by population characteristics. For instance, studies examining the aldose reductase (AR) gene C-106T polymorphism yielded mixed results: while the CC genotype was associated with a higher frequency of diabetic retinopathy in an Iranian cohort, its association with diabetic microvascular complications, including neuropathy, was not consistently observed across studies.[33] These findings underscore the difficulty of extrapolating genetic associations across different ethnic and clinical populations and highlight the need for cautious interpretation.

Research on vascular endothelial growth factor (VEGF) gene polymorphisms has yielded inconsistent results. Some studies report that the VEGF +405 and −460 polymorphisms are not significantly associated with diabetic peripheral neuropathy, although the VEGF +405 genotype appears more frequently among Indian Asians, potentially correlating with lower rates of ulcers and amputations in this population.[22,34] Conversely, another study identified an association between VEGF +936 C/T polymorphism and peripheral neuropathy in Mexican patients with T2DM, suggesting that the heterozygous CT genotype may confer a protective effect.[35] Such contradictory findings suggest that VEGF-related genetic effects on neuropathy may be modified by ethnic background, environmental exposures, and metabolic status rather than acting as universal risk determinants. Additional evidence linking MIR499a polymorphisms to mitochondrial DNA copy number further supports a potential role of mitochondrial dysfunction and oxidative stress in genetically mediated neuropathy susceptibility, although causal mechanisms remain to be clarified.[36]

Beyond single-gene polymorphisms, familial aggregation studies provide indirect but compelling evidence for a heritable component in DN. Individuals with a family history of diabetes appear to have a higher risk of developing neuropathic complications. A study involving 11,237 patients with type 1 diabetes mellitus (T1DM) in Taiwan reported an adjusted hazard ratio of 1.44 for DN among patients with a family history of T2DM, underscoring the significance of familial genetic factors as risk determinants.[37] Similar observations have been reported in Iranian and Chinese populations, where family history of diabetes was associated with increased rates of microvascular complications, including mononeuropathy and proliferative retinopathy.[38,39] However, familial clustering likely reflects the combined influence of inherited genetic variants, shared metabolic traits, and common environmental exposures.

Overall, current genetic evidence suggests that DN is a polygenic and heterogeneous condition in which genetic susceptibility interacts with metabolic, vascular, and inflammatory factors. The lack of consistent genetic markers across

studies highlights the limitations of candidate gene approaches and emphasizes the need for large-scale, multiethnic genome-wide association studies integrated with detailed phenotyping.

Pathophysiological Mechanisms

The pathophysiology of DN involves a complex and interconnected cascade of metabolic, oxidative, and inflammatory processes initiated by chronic hyperglycemia. These processes interact at molecular, cellular, and tissue levels, ultimately resulting in progressive structural and functional damage to peripheral nerves.

Mechanisms of Nerve Injury

Nerve injury in DN arises from multiple interrelated metabolic disturbances driven primarily by sustained hyperglycemia. One of the earliest and most extensively studied mechanisms is activation of the polyol pathway. Under hyperglycemic conditions, excess glucose is reduced to sorbitol by AR, leading to intracellular sorbitol accumulation. This osmotic imbalance increases cellular swelling and disrupts normal neuronal homeostasis, thereby contributing to nerve fiber injury.[40]

In parallel, hyperglycemia markedly enhances oxidative stress through excessive production of reactive oxygen species (ROS). Elevated ROS levels damage lipids, proteins, and nucleic acids within neuronal cells, impair membrane integrity, alter enzymatic activity, and disrupt gene expression, ultimately compromising neuronal viability and function.[41] Furthermore, the accumulation of AGEs represents another critical pathogenic mechanism. AGEs interact with their receptors on nerve and endothelial cells, activating downstream signaling pathways that amplify oxidative stress and inflammatory responses, promote neuronal apoptosis, and accelerate axonal degeneration.[40]

These pathological processes collectively affect both the structural and functional integrity of nerve fibers. The myelin sheath surrounding myelinated fibers undergoes thinning and loss, while axonal atrophy or fragmentation occurs, culminating in reduced NCV and deficits in sensory and motor function.

Effects of Hyperglycemia on the Nervous System

Beyond direct nerve injury, hyperglycemia exerts widespread deleterious effects on the nervous system at multiple biological levels. At the molecular level, hyperglycemia disrupts neuronal energy metabolism by impairing mitochondrial function and reducing adenosine triphosphate (ATP) production.[42] This energy deficit interferes with nerve impulse conduction and the synthesis and release of neurotransmitters.[43] Concurrently, hyperglycemia activates the protein kinase C (PKC) signaling pathway, which induces vasoconstriction, reduces blood flow to neural tissues, and exacerbates ischemic and hypoxic damage to neurons.[40]

At the cellular level, hyperglycemia induces apoptosis and necrosis in neuronal cells. Empirical evidence indicates that hyperglycemia promotes neuronal apoptosis through the activation of oxidative stress and inflammatory signaling cascades, leading to the upregulation of pro-apoptotic proteins and the downregulation of anti-apoptotic proteins.[44] Furthermore, hyperglycemia adversely affects glial cell function, diminishing their capacity to support and nourish neurons, which indirectly contributes to neuronal injury.

Functionally, these molecular and cellular abnormalities manifest as progressive impairment of sensory, motor, and autonomic nervous system function. Clinically, patients typically present with distal symmetric sensory neuropathy, characterized by numbness, pain, and paresthesia, accompanied in some cases by motor weakness and impaired coordination. Autonomic involvement may also occur, affecting cardiovascular, gastrointestinal, genitourinary, and other organ systems, thereby contributing to the systemic burden of DN.

Oxidative Stress and Inflammatory Reaction

Among the various pathogenic mechanisms involved in DN, oxidative stress and inflammation serve as central and mutually reinforcing hubs that amplify hyperglycemia-induced nerve injury. Hyperglycemia-driven metabolic abnormalities lead to mitochondrial dysfunction, resulting in excessive ROS production that overwhelms endogenous antioxidant defenses and initiates sustained oxidative stress.[41] This oxidative imbalance damages cellular macromolecules and disrupts neuronal signaling, ultimately promoting neuronal dysfunction and apoptosis.

Oxidative stress also acts as a potent activator of inflammatory pathways. The inflammatory milieu characteristic of DN is marked by the upregulation of multiple pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), which exacerbate neuronal injury and facilitate the progression of neuropathic pathology.[44] Inflammation further contributes to microvascular endothelial dysfunction within the endoneurium, increasing vascular permeability, impairing nerve perfusion, and worsening ischemic damage. Importantly, clinical and experimental studies indicate that interventions targeting oxidative stress and inflammation can partially alleviate neuropathic symptoms, underscoring these pathways as key therapeutic targets.

Collectively, these interconnected mechanisms—metabolic dysregulation, oxidative stress, inflammation, and impaired cellular homeostasis—form the biological basis of DN. Importantly, these pathways also provide critical molecular targets for therapeutic intervention. As discussed in the following sections, TCM exerts multi-target regulatory effects on these key mechanisms, including antioxidative, anti-inflammatory, and neuroprotective actions, thereby offering a mechanistic rationale for its clinical application.

Therapeutic Strategies for Diabetic Neuropathy

Medication

Based on the aforementioned pathophysiological mechanisms, current therapeutic strategies for DN primarily focus on controlling hyperglycemia, alleviating neuropathic pain, and preserving nerve function. Pharmacological treatment remains the cornerstone of disease management and typically includes agents for glycemic control, neurometabolic support, and symptomatic pain relief. Strict regulation of blood glucose levels is fundamental for both the prevention and treatment of DN. Clinical evidence indicates that the use of insulin and oral hypoglycemic agents can slow the progression of neuropathy to some extent, particularly when intensive glycemic control is achieved early in the disease course.[23]

Neurometabolic agents, such as mecobalamin, have been shown to promote the synthesis of nucleic acids, proteins, and lipids within neuronal cells, thereby contributing to the repair of damaged neural tissue and improvement of nerve function.[45] For patients experiencing neuropathic pain, commonly prescribed analgesics include antidepressants (eg, amitriptyline, duloxetine), anticonvulsants (eg, gabapentin, pregabalin), and opioids (eg, tramadol, oxycodone). These pharmacological agents exert analgesic effects via distinct mechanisms, but their use is associated with adverse effects. Antidepressants may induce somnolence and xerostomia, anticonvulsants can cause dizziness and peripheral edema, and opioids carry risks of constipation and dependence.[46]

Emerging pharmacological approaches, such as AR inhibitors, aim to target upstream pathogenic mechanisms by suppressing polyol pathway activation. Although these agents show theoretical promise in mitigating nerve damage, clinical trial results remain inconsistent, and their efficacy and safety profiles require further validation through well-designed studies. Collectively, these limitations underscore the need for complementary therapeutic strategies beyond pharmacological monotherapy.

Non-Drug Therapy

Given the limited efficacy of pharmacological treatments alone and the potential for adverse effects, non-pharmacological interventions constitute an essential complementary component of DN management. Exercise therapy plays a particularly important role, as regular physical activity improves peripheral circulation, enhances muscle strength, and supports neural function. Clinical studies indicate that sustained aerobic exercise, such as walking and cycling, can increase NCV and alleviate symptoms including pain and numbness in patients with diabetes.[47]

Furthermore, various physical therapies, including massage, hot compresses, acupuncture, and moxibustion, are extensively used in the treatment of DN. Massage therapy promotes localized blood flow and alleviates muscle tension and pain. Hot compresses induce vasodilation, thereby improving neural blood supply, while acupuncture and moxibustion modulate the nervous, endocrine, and immune systems through stimulation of specific acupoints, demonstrating efficacy in symptom relief for DN patients.[48] Psychological interventions are also vital as chronic illnesses often precipitate anxiety, depression, and other mental health challenges in this population. Psychotherapeutic approaches,

such as cognitive-behavioral therapy and psychological support, assist patients in adjusting their mental outlook, bolstering disease-coping confidence, and enhancing their overall quality of life. Concurrently, patient self-management, including adherence to a balanced diet, cessation of smoking, limitation of alcohol intake, and routine foot care, is essential for preventing and decelerating the progression of DN.

Integrated Management Programme

Given the multifactorial nature of DN, an integrated management programme that combines pharmacological treatment, non-pharmacological interventions, and long-term patient education is essential for achieving optimal therapeutic outcomes. Comprehensive metabolic control, including strict regulation of blood glucose, blood pressure, and lipid levels, forms the foundation of such an approach. Appropriate use of hypoglycemic, antihypertensive, and lipid-lowering agents can significantly reduce neuropathy risk and progression by maintaining these parameters within recommended targets.[49] In parallel, early identification and management of comorbid conditions, such as diabetic nephropathy and retinopathy, contribute to overall disease control and improved patient prognosis.

Pharmacological regimens should be individualized according to symptom severity, comorbidities, and patient tolerance, with careful consideration of drug interactions and adverse effects. In patients with severe neuropathic pain, combination therapy—for example, antidepressants in conjunction with anticonvulsants—may provide superior analgesia while allowing lower doses of individual agents and reducing side-effect burden.[50] Non-pharmacological interventions should likewise be tailored to patients' physical capacity and preferences to maximize safety and adherence. Importantly, patient education represents a central element of integrated management. By enhancing disease awareness and reinforcing self-care behaviors, including regular foot examinations and scheduled follow-up visits, educational interventions can help prevent complications and improve quality of life (Figure 1).

Despite these comprehensive strategies, a substantial proportion of patients continue to experience persistent symptoms or progressive nerve damage. This therapeutic gap has prompted increasing interest in complementary and

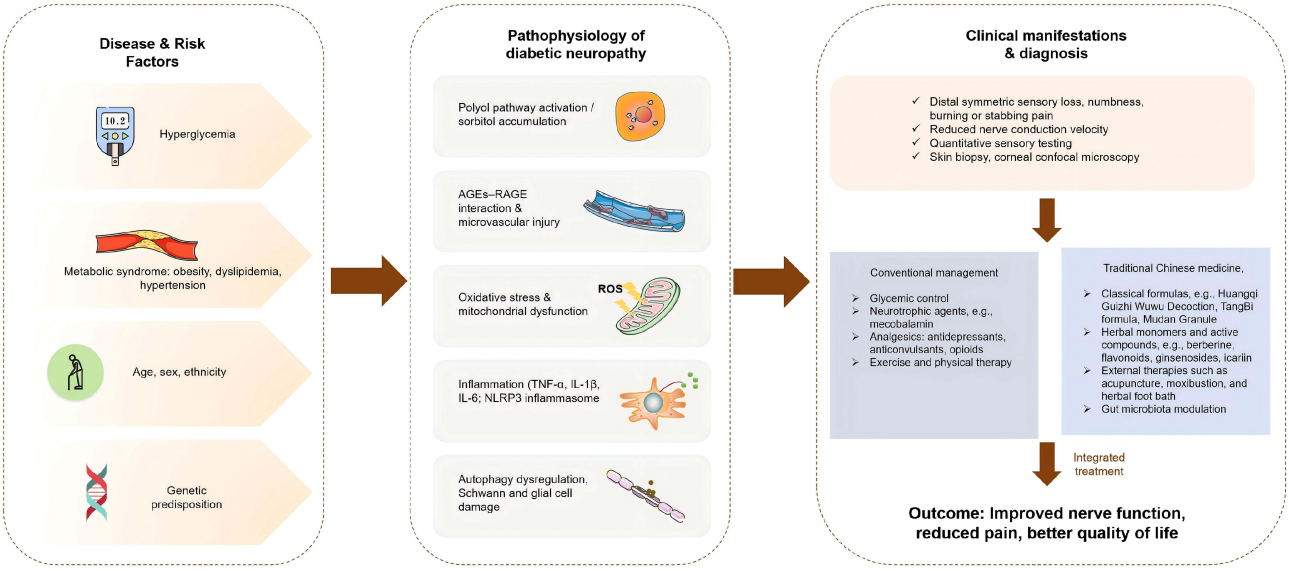

Figure 1 Disease and risk factors, pathophysiology, and integrated management of diabetic neuropathy. The left panel summarizes the main diseases and risk factors for diabetic neuropathy, including hyperglycemia, metabolic syndrome (obesity, dyslipidemia, and hypertension), age, sex, ethnicity, and genetic predisposition. The middle panel illustrates key pathophysiological mechanisms, such as polyol pathway activation and sorbitol accumulation, AGEs–RAGE interaction and microvascular injury, oxidative stress and mitochondrial dysfunction, inflammation (TNF-α, IL-1β, IL-6, and NLRP3 inflammasome activation), and autophagy dysregulation with Schwann and glial cell damage. The right panel shows clinical manifestations and diagnostic methods (distal symmetric sensory loss, numbness, burning or stabbing pain, reduced NCV, quantitative sensory testing, skin biopsy, and corneal confocal microscopy), together with conventional management (glycemic control, neurotrophic agents, analgesics, exercise, and physical therapy) and TCM interventions (classical formulas, herbal monomers and active compounds, acupuncture and moxibustion, herbal foot bath, and gut microbiota modulation). Directional arrows indicate the progression from risk factors to pathophysiological changes and subsequent clinical manifestations and management strategies. Integrated treatment may improve nerve function, reduce pain, and enhance patients' quality of life. (The figure is original and created by the authors).

Abbreviations: TCM, traditional Chinese medicine; AGEs, advanced glycation end products; RAGE, receptor for advanced glycation end products; TNF-α, tumor necrosis factor alpha; IL-1β, interleukin-1 beta; IL-6, interleukin-6; NLRP3, NOD-like receptor family pyrin domain containing 3.

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integrative approaches, particularly TCM, which offers multi-target regulation aligned with the complex pathophysiology of DN.

Basic Theory of TCM in Treating Diabetic Neuropathy

The pathogenesis of DN is multifactorial and dynamic, involving metabolic dysregulation, oxidative stress, inflammation, and impaired neural repair. Within the theoretical framework of TCM, DN is commonly attributed to a combination of "deficiency in origin and excess in superficiality", characterized by insufficiency of qi and yin, blood stasis, and obstruction of meridians.[51] Guided by this holistic perspective, TCM interventions aim to restore systemic balance through multi-target and multi-pathway regulation, rather than focusing on a single pathogenic factor.[52]

Accumulating evidence suggests that the accumulation of AGEs plays a central role in diabetic microvascular and neuropathic complications, providing a mechanistic bridge between traditional theories of "toxin accumulation" and modern biomedical concepts. Skin autofluorescence, a noninvasive surrogate marker of tissue AGE burden, has been increasingly used to assess diabetes-related complications. In a cohort study involving 118 patients with diabetic foot ulcers, the mean SAF value was 2.8 ± 0.2 arbitrary units (AU), demonstrating a significant correlation with diabetes duration and blood urea nitrogen levels. Logistic regression analysis further revealed that SAF was significantly associated with diabetic complications, such as retinopathy, nephropathy, and neuropathy.[53] These findings support the TCM view that chronic metabolic imbalance contributes to progressive nerve damage.

Experimental studies involving diabetic rats and Schwann cells cultured under high-glucose conditions revealed pathological morphological alterations in peripheral nerve tissues, accompanied by a reduction in autophagic structures and downregulation of Beclin1 expression. Treatment with Jinmaitong (JMT) significantly ameliorated these changes by enhancing autophagic activity. In vivo experiments showed that the integral optical density (IOD) of Beclin1 was markedly increased following JMT treatment, while in vitro studies demonstrated restoration of Beclin1 expression under high-glucose conditions.[54] These findings suggest that impaired autophagy contributes to DPN pathogenesis and that JMT may exert neuroprotective effects by restoring cellular homeostasis through autophagy regulation.

Similarly, Tang Bikang has been shown to improve metabolic and inflammatory parameters in diabetic rat models. Administration of Tang Bikang resulted in reduced fasting blood glucose levels, increased motor and sensory nerve conduction velocities, decreased serum malondialdehyde concentrations, and enhanced activities of antioxidant enzymes such as superoxide dismutase and glutathione peroxidase. Concomitant suppression of pro-inflammatory cytokines, including IL-6 and TNF-α, was also observed.[55]

At the molecular level, TCM-derived bioactive compounds further illustrate the multi-target characteristics of TCM therapy. Flavonoids, which are abundant in many TCM formulations, exhibit diverse antidiabetic and neuroprotective properties.[56] Hesperidin, for example, has demonstrated beneficial effects in experimental models of DN, potentially through antioxidative actions and modulation of intracellular signaling pathways; however, its precise molecular targets remain incompletely defined.[57] Icariin has been shown to improve renal function, autophagy, and fibrosis in type 2 diabetic nephropathy models, acting through androgen receptor–mediated regulation of the miR-192-5p/GLP-1R pathway.[58] Although these findings primarily derive from renal models, they underscore the broader relevance of autophagy and oxidative stress modulation in diabetic complications, including neuropathy.

Inflammation and immune dysregulation represent additional key targets of TCM intervention. Activation of the NOD-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome has been implicated in the progression of DN by promoting the release of pro-inflammatory cytokines and exacerbating neuronal injury.[59] Emerging evidence suggests that TCM formulations may attenuate neuropathic inflammation by modulating NLRP3 inflammasome activity and downstream signaling pathways.[60] Nevertheless, current pharmacological evidence remains limited, and comprehensive mechanistic studies are still lacking. As summarized in Figure 2, the ability of TCM to concurrently regulate oxidative stress, inflammation, and autophagy provides a plausible mechanistic basis for its therapeutic effects, while also highlighting the need for further rigorous experimental and clinical investigations.

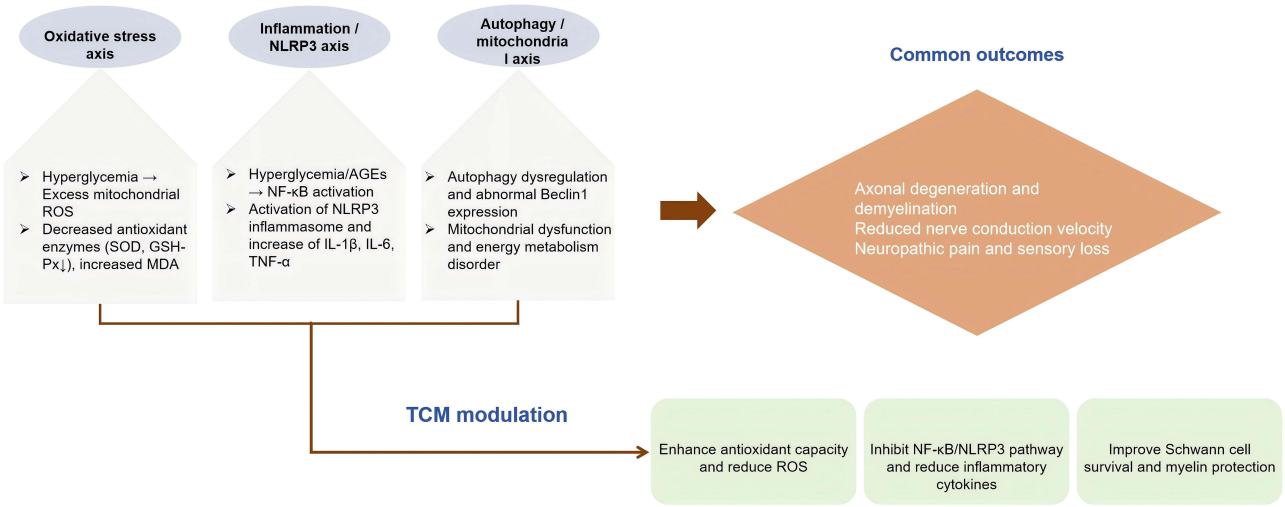

Figure 2 Key molecular axes and TCM modulation in diabetic neuropathy. From left to right, the figure depicts the oxidative stress axis, inflammation/NLRP3 axis, and autophagy/mitochondrial axis. In the oxidative stress axis, hyperglycemia leads to excessive mitochondrial ROS generation, accompanied by decreased activities of antioxidant enzymes, such as SOD and GSH-Px, and increased levels of MDA. In the inflammation/NLRP3 axis, hyperglycemia or AGEs trigger NF-κB activation, which induces NLRP3 inflammasome activation and upregulation of inflammatory cytokines, including IL-1β, IL-6, and TNF-α. In the autophagy/mitochondrial axis, autophagy dysregulation and abnormal Beclin1 expression result in mitochondrial dysfunction and energy metabolism disorders. These pathways converge on common downstream outcomes, including axonal degeneration and demyelination, reduced NCV, and neuropathic pain with sensory loss. The lower panel highlights that TCM interventions have been shown in experimental and early clinical studies to enhance antioxidant capacity, reduce ROS, inhibit the NF-κB/NLRP3 pathway and inflammatory cytokines, and improve Schwann cell survival and myelin protection, thereby exerting multi-pathway regulatory effects. Arrows indicate mechanistic interactions and convergence of these pathways, while inhibitory or modulatory effects of TCM are represented by reverse or blocking directional relationships. (The figure is original and created by the authors).
Abbreviations: ROS, reactive oxygen species; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; MDA, malondialdehyde; AGEs, advanced glycation end products; NF-κB, nuclear factor kappa B; NLRP3, NOD-like receptor family pyrin domain containing 3; IL-1β, interleukin-1 beta; IL-6, interleukin-6; TNF-α, tumor necrosis factor alpha.

Clinical Practice of TCM in the Treatment of Diabetic Neuropathy

Clinical Trial Evidence for TCM in Diabetic Neuropathy

An increasing number of clinical trials have evaluated the efficacy and safety of TCM in the management of DN, particularly as an adjunct to conventional Western therapies. In a multicenter, placebo-controlled, double-blind, randomized clinical trial involving 188 patients with distal symmetric polyneuropathy associated with T2DM,[61] the participants were randomly assigned to either a treatment group receiving tangbifang in combination with mecobalamin or a control group receiving placebo alongside mecobalamin for a duration of six months. After 24 weeks of intervention, the Michigan Diabetic Neuropathy Score (MDNS) significantly decreased. Additionally, statistically significant improvements were observed in both the Visual Analog Scale (VAS) and Toronto Clinical Scoring System (TCSS) scores relative to baseline measurements, suggesting potential additional benefit in symptom improvement; however, these findings should be interpreted cautiously given the limited sample size, short follow-up duration, and reliance on composite clinical scores rather than consistent electrophysiological improvement.

Evidence from other recent trials also suggests potential clinical value, although the findings are not entirely uniform. In addition, a randomized controlled trial of 62 patients with type 2 diabetes reported that acupuncture significantly reduced overall neuropathy-related complaints, pain, and neuropathic symptom burden compared with routine care, with benefits persisting during follow-up and only minor transient adverse effects.[62] However, not all studies have shown clear superiority over control procedures. A separate single-blind randomized trial of 60 patients found that adjunctive acupuncture did not produce a statistically significant advantage over sham acupuncture for pain or fatigue, indicating that the magnitude and reproducibility of benefit still require confirmation in more rigorous sham-controlled settings.[63]

In addition to completed trials, several large-scale, rigorously designed studies are currently underway. A 14-center, double-blind, randomized, placebo-controlled, parallel-group trial enrolling 402 patients has been initiated to evaluate the efficacy and safety of Mudan Granules combined with mecobalamin for type 2 diabetic peripheral neuropathy, with MDNS as the primary outcome measure. The results of this trial are expected to provide higher-quality clinical evidence regarding the role of standardized TCM formulations in DN management.[64]

Collectively, recent clinical trials suggest that TCM-based interventions may improve symptoms and, in some cases, neurological function in patients with DN. At the same time, variation in diagnostic criteria, comparator selection, treatment protocols and outcome measurescontinues to limit direct comparison across studies. Further large, well-controlled multicenter trials with standardized endpoints are still needed before these approaches can be more firmly positioned in routine clinical practice.

Evaluation of Therapeutic Effect of TCM in Patients with Diabetic Neuropathy

Clinical evaluation of TCM in DN has increasingly shifted toward a more multidimensional framework, ie, moving beyond simple symptom reporting to include validated clinical scales, electrophysiological parameters, and patient-reported outcomes, allowing for a more balanced assessment of whether observed benefits reflect true neurological improvement or primarily symptomatic relief.

Clinical evidence suggests that TCM interventions may exert therapeutic benefits in patients with DN, particularly in pain relief and functional improvement. Berberine, a bioactive alkaloid widely used in TCM, has demonstrated antioxidative and anti-inflammatory properties and has been applied in the management of DN and related metabolic disorders. Experimental and clinical studies indicate that berberine may improve insulin sensitivity and enhance insulin secretion, thereby indirectly contributing to neuropathy amelioration.[65]

In a single-center, randomized, single-blind, double-dummy, parallel-controlled clinical trial involving 68 patients with painful DN,[66] the efficacy of the Xiaoketongbi Formula was compared with that of pregabalin. After 10 weeks of treatment, both groups exhibited significant reductions in Brief Pain Inventory for Diabetic Peripheral Neuropathy (BPI-DPN) scores. Notably, a higher proportion of patients in the Xiaoketongbi group achieved a greater than 50% reduction in pain scores, and more patients reported moderate to marked symptom improvement. Additionally, improvements in NCV were observed in the Xiaoketongbi group, suggesting that certain TCM formulations may offer similar symptomatic benefit with potentially better tolerability profiles in selected patient.

More recent multicenter evidence further supports this trend. In a double-blind randomized trial,[61] adjunctive TangBi Formula improved composite clinical scores (MDNS, TCSS) and pain measures over 24 weeks, although electrophysiological indices did not show parallel improvement. This divergence highlights an important point: current TCM interventions may exert more consistent effects on symptom burden and clinical severity than on measurable nerve regeneration, at least within typical study durations.

Non-pharmacological TCM approaches, particularly acupuncture, have also been evaluated in recent controlled trials. A randomized clinical study in patients with type 2 diabetes and peripheral neuropathic symptoms showed that acupuncture significantly reduced overall symptom burden and pain-related scores compared with routine care, with sustained effects during follow-up.[62] However, sham-controlled studies have yielded less consistent results, with some trials reporting no significant differences between true and sham acupuncture, underscoring the need to better distinguish specific from non-specific treatment effects.[63]

At the evidence synthesis level, a systematic review and meta-analysis encompassing 21 randomized controlled trials with a total of 1737 participants reported that TCM interventions, whether used as monotherapy or adjunctive therapy, were associated with improvements in sensory and motor nerve conduction velocities, pain scores, and TCM syndrome scores; although substantial heterogeneity, variable study quality, and risk of bias limit the certainty of these pooled estimates. The incidence of adverse events was generally low, indicating a favorable safety profile. However, the authors also noted that the overall methodological quality of the included trials was moderate to low, highlighting the necessity for larger, high-quality randomized controlled trials to confirm these findings.[5]

Taken together, current evidence indicates that TCM may have a role in improving symptom control and overall clinical status in DN, especially as part of a combined management strategy. However, its effects on objective nerve recovery remain less certain. Future studies should focus on longer follow-up, standardized outcome measures, and clearer differentiation between symptomatic improvement and structural nerve repair to better define its clinical value.

Individualized and Syndrome-Differentiated TCM Approaches for Diabetic Neuropathy

A defining characteristic of TCM clinical practice is its emphasis on treatment based on syndrome differentiation and individualized therapeutic adjustment. In the management of DN and its complications, this pattern-based approach is considered particularly important because patients often present with different combinations of qi deficiency, yin deficiency, blood stasis, phlegm-dampness, or collateral obstruction,[67] which may influence symptom presentation and therapeutic response. Accordingly, individualized TCM strategies may contribute to differences in clinical outcomes.

For example, a retrospective analysis of 65 elderly patients with diabetic foot ulcers complicated by sepsis demonstrated that extensive debridement was associated with higher short-term mortality and elevated inflammatory and coagulation markers compared with limited debridement. Conservative approaches, such as small-incision drainage, appeared to attenuate systemic inflammatory responses and reduce early mortality risk, thereby creating more favorable conditions for subsequent comprehensive treatment.[68] Although this study was not designed specifically to evaluate syndrome differentiation, it supports the broader TCM principle of stage-specific and condition-adapted intervention in complex diabetic complications.

The value of individualized TCM treatment has also been explored more directly in patients with T2DM complicated by multiple microvascular disorders. In a randomized study, participants were assigned to receive either standardized treatment or individualized therapy guided by TCM syndrome differentiation. The study aimed to compare fixed versus personalized treatment strategies and to assess whether syndrome-based interventions could improve clinical outcomes in patients with complex diabetic complications.[69] These findings support the principle that individualized TCM management may offer potential advantages over uniform treatment approaches in heterogeneous patient populations, although current evidence remains limited and requires further validation in rigorously designed trials.

Moreover, external TCM therapies are increasingly being investigated as personalized adjunctive treatments. A multicenter, double-blind, randomized controlled trial involving 640 patients with diabetic peripheral neuropathy evaluated the efficacy of an external TCM foot bath compared with a control intervention, with changes in TCSS as the primary outcome.[28] From a TCM perspective, such external therapies may complement internal treatment by promoting meridian circulation, improving local symptoms, and providing an alternative option for patients who are intolerant to systemic pharmacotherapy.

Application of TCM in the Treatment of Diabetic Neuropathy

With advances in both clinical practice and biomedical research, the application of TCM in DN has expanded beyond conventional herbal prescriptions to encompass novel formulations, mechanistic innovations, and emerging technologies. These developments reflect a gradual transition from empirical use toward mechanism-informed and technology-assisted therapeutic strategies.

Recent clinical studies suggest that combined internal and external TCM therapies may provide additional benefits in the management of diabetic peripheral neuropathy. In a retrospective study involving 120 patients, a combined regimen consisting of Gubu Decoction foot baths and oral administration of Yiqi Huoxue Decoction was compared with conventional treatment alone. After one month of intervention, patients receiving the combined TCM therapy exhibited significant improvements in motor and sensory nerve conduction velocities of the common peroneal nerve, along with reductions in fasting blood glucose, postprandial glucose, and glycated hemoglobin levels.[70] Improvements in TCM symptom scores and overall clinical efficacy were observed without an increase in adverse events, suggesting that integrated TCM approaches may simultaneously improve metabolic control and neural function.

Beyond symptomatic treatment, emerging evidence highlights the role of gut microbiota dysbiosis in the pathogenesis of DN. Certain TCM formulations, including Shenqi Dihuang Decoction, Huangkui Capsule, and Qidi Tangshen Granule, have been shown to alleviate clinical manifestations of DN by modulating gut microbiota composition.[71] These findings raise the possibility that TCM interventions may indirectly influence neuropathy risk through microbiome regulation. Nevertheless, direct evidence linking microbiota modulation to improvements in diabetic peripheral neuropathy remains limited, and further mechanistic studies are required.

At the cellular level, preservation of Schwann cell viability under hyperglycemic conditions has emerged as a promising therapeutic target. Experimental research indicates that TCM monomers and herbal extracts can inhibit

Schwann cell apoptosis by regulating AGEs formation, oxidative stress, and endoplasmic reticulum stress pathways.[72] These findings provide mechanistic support for the neuroprotective potential of TCM and underscore its relevance in addressing key pathological processes underlying DN.

The integration of TCM with modern analytical and computational technologies has further advanced mechanistic research. For example, the therapeutic mechanisms of Buyang Huanwu Decoction in diabetic peripheral neuropathy were investigated using serum pharmacochemistry combined with network pharmacology approaches.[73] Ultra-performance liquid chromatography–quadrupole Orbitrap high-resolution mass spectrometry identified 101 chemical constituents, 30 of which were detected in systemic circulation. Subsequent construction of a compound–target–disease interaction network implicated the AGE/RAGE signaling pathway, and in vitro validation supported these predictions. Such integrative methodologies provide a systematic framework for elucidating the multi-component and multi-target mechanisms of classical TCM prescriptions.[73]

In parallel, emerging technologies are being explored to address complex DN-related complications, particularly diabetic foot ulcers. Nanomedicine has shown promise in targeting the hostile microenvironment of diabetic foot ulcers, characterized by hyperglycemia, ischemia, hypoxia, inflammation, and infection. Multifunctional nanosystems have demonstrated potential efficacy in promoting wound healing and controlling infection; however, comprehensive clinical validation and standardized evaluation frameworks remain lacking.[74] Similarly, machine-learning-based approaches offer opportunities to enhance diagnostic accuracy and optimize treatment planning for diabetic foot complications through large-scale data analysis.[75] Despite their promise, practical implementation is constrained by data quality, computational requirements, and ethical considerations.

Traditional external therapies continue to evolve alongside these technological advances. Moxibustion, a traditional TCM modality, has potential therapeutic effects on diabetic peripheral neuropathy. Experimental studies have shown that Moxibustion modulates the balance between nuclear factor erythroid 2–related factor 2 (Nrf2) and nuclear factor kappa B (NF-κB), improves sciatic NCV in diabetic rat models, and attenuates neuroinflammation. Specifically, moxibustion treatment was associated with decreased levels of pro-inflammatory cytokines and coordinated inhibition of NF-κB signaling alongside activation of Nrf2-mediated antioxidant responses, suggesting a mechanistic basis for its therapeutic effects.[76]

The external application of TCM formulations has also been employed in the management of diabetic foot infections. A multicenter, double-blind, randomized, placebo-controlled clinical trial evaluated a TCM foot bath decoction, assessing its effects on wound pathogen profiles, inflammatory markers, metabolic parameters, and wound healing outcomes. This study aims to establish evidence-based external TCM strategies for managing diabetic foot infections.[77] Furthermore, specific TCM-derived active constituents, such as ginsenoside Rg1, have been shown to promote diabetic foot ulcer healing by enhancing inducible NOS expression through modulation of the miR-23a/IRF-1 axis, further illustrating the translational potential of TCM compounds in DN-related complications.[78]

Taken together, these emerging applications illustrate the evolving role of TCM in DN management, ranging from combined clinical interventions and cellular protection to microbiome regulation and technology-assisted therapies. As summarized in Figure 3, the future development of TCM in DN is likely to depend on the integration of standardized clinical trials, mechanistic validation, and advanced technologies to establish robust, reproducible, and personalized therapeutic strategies.

Controversies and Future Prospects

Although TCM has demonstrated therapeutic potential in the management of DN, its clinical application remains subject to ongoing debate. One of the principal challenges lies in the substantial heterogeneity in study design, methodological quality, and intervention protocols across existing clinical investigations. For example, Mudan Granules have been reported to alleviate neuropathic symptoms, promote nerve tissue repair, and improve NCV in patients with type 2 diabetic peripheral neuropathy.[64] However, variations in trial design, sample size, and outcome assessment limit the strength and generalizability of these findings, thereby constraining their broader clinical endorsement. Consequently, there is an urgent need for rigorously designed, double-blind, randomized, placebo-controlled, multicenter trials to definitively establish the safety and efficacy of such TCM formulations.

From a mechanistic perspective, the multi-target and multi-pathway characteristics of TCM are widely recognized; nevertheless, the precise molecular and cellular mechanisms underlying its therapeutic effects remain incompletely elucidated. While emerging evidence suggests that certain TCM interventions may exert neuroprotective effects through modulation of key inflammatory pathways, such as NLRP3 inflammasome, comprehensive pharmacological validation and mechanistic dissection

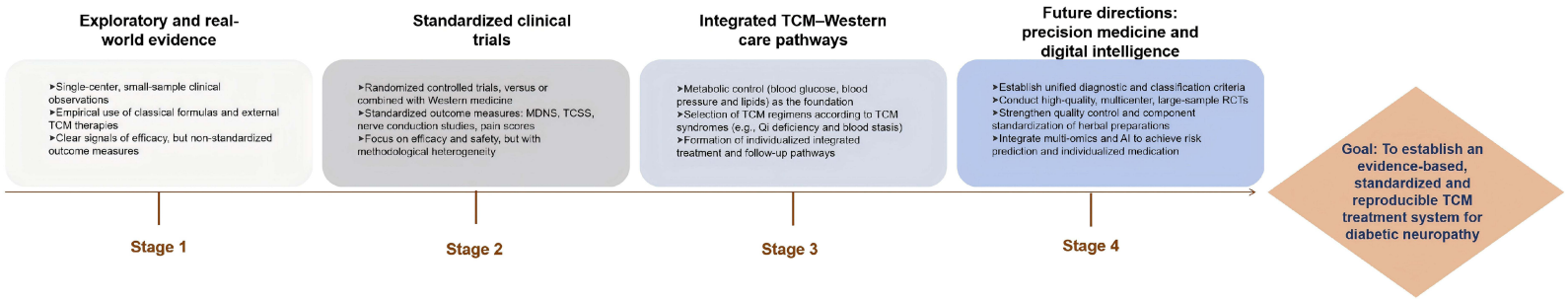

Figure 3 Evidence- and standardized development pathway of TCM for diabetic neuropathy. From left to right, the figure summarizes a four-stage pathway. Stage 1, "Exploratory and real-world evidence", consists of single-center, small-sample clinical observations and empirical use of classical formulas and external TCM therapies, providing signals of efficacy but lacking standardized outcome measures. Stage 2, "Standardized clinical trials", involves randomized controlled trials conducted alone or in combination with Western medicine, using standardized outcome measures such as MDNS, TCSS, nerve conduction studies, and pain scores, although methodological heterogeneity persists. Stage 3, "Integrated TCM–Western care pathways", is characterized by metabolic control (blood glucose, blood pressure, and lipids) as the foundation, syndrome-based TCM treatment (e.g, Qi deficiency and blood stasis), and the development of individualized integrated management and follow-up pathways. Stage 4, "Future directions: precision medicine and digital intelligence", emphasizes unified diagnostic and classification criteria, high-quality multicenter large-sample RCTs, strengthened quality control and standardization of herbal preparations, and integration of multi-omics and artificial intelligence for risk prediction and individualized therapy. The diamond on the right represents the ultimate goal of establishing an evidence-based, standardized, and reproducible TCM treatment system for diabetic neuropathy. Directional arrows indicate the progressive evolution across stages, and the diamond symbol summarizes the final integrative objective. (The figure is original and created by the authors).

Abbreviations: TCM, traditional Chinese medicine; MDNS, Michigan Diabetic Neuropathy Score; TCSS, Toronto Clinical Scoring System; RCTs, randomized controlled trials.

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are still lacking.[60] Future studies should focus on identifying specific molecular targets, signaling cascades, and interaction networks to provide a more robust and mechanistically grounded basis for clinical application.

Another major limitation of current clinical research on TCM for DN is the predominance of studies with relatively small sample sizes, which restricts statistical power and external validity. In addition, variability in diagnostic criteria, disease classification, and outcome measures across trials hampers direct comparison and synthesis of results. The absence of standardized evaluation systems complicates meta-analyses and impedes the formulation of evidence-based clinical guidelines. Addressing these methodological inconsistencies is essential for accurately assessing the overall efficacy and safety of TCM interventions in DN.

Future research directions should therefore emphasize both mechanistic refinement and clinical standardization. At the experimental level, studies should aim to clarify the active constituents of complex TCM formulations, delineate their molecular targets, and map relevant signaling pathways. For instance, although icariin has been implicated in modulating the miR-192-5p/GLP-1R pathway in DN models, its specific regulatory role and therapeutic relevance in neuropathic contexts require further investigation.[58] Such mechanistic insights may facilitate the development of more precise and reproducible therapeutic agents derived from TCM.

At the clinical level, large-scale, multicenter, high-quality randomized controlled trials are critically needed to enhance the reliability and generalizability of existing evidence. Standardization of diagnostic criteria, outcome measures, and treatment protocols is essential to enable cross-study comparisons and to promote the systematic integration of TCM into DN management. Harmonization of trial design would also facilitate regulatory evaluation and guideline development.

The integration of contemporary scientific and technological approaches offers promising opportunities to advance TCM research in DN. Metabolomics may be employed to characterize disease-associated metabolic alterations and to elucidate the modulatory effects of TCM on metabolic pathways, thereby identifying potential biomarkers and therapeutic targets. In parallel, artificial intelligence–based analyses of large clinical datasets may help uncover hidden patterns of treatment response, optimize individualized therapeutic strategies, and improve clinical outcomes.

Despite these prospects, several regulatory and policy challenges must be addressed. Quality control of Chinese materia medica remains a critical concern, given the complexity of herbal constituents and variability arising from differences in cultivation, processing, and manufacturing practices. Establishing standardized and stringent quality control systems covering the entire production chain—from raw material sourcing to final product inspection—is essential to ensure consistency, safety, and therapeutic reliability.

Furthermore, the regulatory framework for new TCM drug development poses unique challenges. The theoretical foundations and multi-component mechanisms of TCM differ fundamentally from those of conventional Western medicine, rendering existing regulatory pathways partially inadequate. Tailored approval standards and evaluation criteria that account for TCM characteristics are therefore needed to accelerate the development and clinical translation of novel TCM therapies while ensuring safety and efficacy.

Conclusion

In conclusion, TCM has demonstrated potential as a complementary and integrative approach in the management of DN through its multi-target effects on symptom control, nerve protection, and related pathogenic pathways. However, its broader and more standardized clinical application still requires sustained policy support, professional training, and stronger regulatory coordination. Thus, improving the training of TCM practitioners is important for enhancing diagnostic accuracy and provide more consistent syndrome differentiation and treatment selection. At the same time, greater efforts are needed to standardize herbal formulations, dosages, treatment duration, and combination regimens, while minimizing irrational or inappropriate use. Public education should also be strengthened to improve patients' understanding and rational use of TCM therapies. With continued progress in standardization, mechanistic research, and high-quality clinical evaluation, TCM may be more effectively and safely integrated into comprehensive management strategies for DN.

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