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REVIEW

Review of the Efficacy and Mechanisms of Traditional Chinese Medicine for Treating Multi-Organ Damage in Wilson's Disease

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Abstract: Wilson's disease (WD) is an autosomal recessive disorder characterized by abnormal copper metabolism. Disruptions in copper metabolism lead to excessive copper deposition in the liver, nervous system, kidneys, heart, and other organs, thereby inducing a range of pathological manifestations and clinical symptoms. Traditional Chinese Medicine (TCM) has demonstrated significant therapeutic efficacy and excellent safety profiles. When integrated with effective Western anti-copper therapies, it can yield superior therapeutic outcomes. Consequently, TCM has exhibited unique advantages in managing WD, particularly when combined with multiple systemic damages. This paper discusses the pathological mechanisms and TCM etiology and pathogenesis of WD combined with multiple organ damage. It also summarizes the clinical efficacy and mechanism of TCM in treating WD combined with multiple organ damage, aiming to provide a reference for further studies on the role and potential mechanisms of TCM interventions in WD.
Keywords: Wilson's disease, copper, traditional Chinese medicine, multiple organ damage, mechanism

Introduction

Wilson's disease (WD), also known as hepatolenticular degeneration, is a rare autosomal recessive disorder characterized by mutations in the ATP7B gene, leading to abnormal copper metabolism. The disease was first identified by Wilson in March 1912 and was named after him.[1] Subsequent studies have revealed excessive copper accumulation in the liver and brain of patients who died from WD, indicating that copper plays a crucial role in its pathogenesis.[2–4] Since 1968, numerous western researchers have conducted epidemiological surveys on the incidence of WD, with initial estimates at 5/1 million[5] and later adjustments to 17/1 million.[6] A gene sequencing study from the UK reported that the frequency of individuals carrying two mutant ATP7B alleles was approximately 1/7026.[7] In 2008, an epidemiological study conducted in Hong Kong, China, reported an incidence rate of WD at 1/5400.[8] However, an epidemiological study conducted among the Han population in southern China identified 9 cases of WD within a cohort of 153,370 individuals.[9] Such findings imply that the prevalence of WD in China might be greater than that observed in Western nations.

Due to the disorder of copper metabolism caused by ATP7B gene mutation, a large amount of copper is deposited in various organs such as the liver, brain, kidney, heart, and cornea. This leads to a range of clinical features including liver diseases (eg, hepatitis, cirrhosis), neurological (including extrapyramidal syndromes, drooling, dysphagia and dysarthria) or psychiatric disorders (such as mood disorders, psychosis and cognitive impairments, and personality and behavioral disturbances),[10,11] renal diseases, cardiac dysfunction, and the presence of a Kayser-Fleischer (K-F) ring in the cornea.[12] Among these, hepatic and neurological symptoms are considered the most common.[13] It has been reported that up to 60% of patients exhibit neurological or psychiatric symptoms at the onset, even when accompanied by hepatic involvement.[6] In recent years, the exploration of diagnostic and therapeutic biomarkers for WD has witnessed substantial advancements.

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Studies have revealed that non-ceruloplasmin copper (NCC) constitutes more than 30–50% of the total copper content in WD, suggesting its potential utility as a biomarker for both the diagnosis and management of WD. Moreover, direct NCC (dNCC), labile copper, and ceruloplasmin-bound copper (CP-Cu), serve as pivotal biomarkers in evaluating systemic copper status, thereby playing a vital role in the diagnostic assessment and therapeutic surveillance of WD patients.[14] The primary treatment modalities for this condition encompass a low-copper diet, zinc supplementation, copper chelating agents (such as tetrathiomolybdate, penicillamine (PCA), trientine, sodium dimercaptosuccinate (Na DMPS)), and traditional Chinese medicine (TCM). It is worth noting that approximately 14% of WD patients and nearly one-quarter of initial WD cases may experience neurological deterioration in the early stages of copper chelation therapy, warranting further investigation and research.[15] For those with severe hepatic impairment, options like splenectomy and liver transplantation can be considered.[16,17] Moreover, gene therapy and cellular therapies, including stem cell transplantation, exhibit promising long-term efficacy and hold extensive potential for widespread applications.[18–20]

TCM emphasizes individualized syndrome differentiation and treatment centered around the holistic concept.[21] Since the last century, guided by TCM theories, numerous experts in China have pioneered investigations into the etiology and pathogenesis of WD within the framework of TCM,[22] proposing corresponding principles and schemes for its treatment. Numerous studies have validated that TCM treatment regimens are relatively flexible, safe, and effective, playing an indispensable role in the management of WD.[23–25] However, given the multitude of active components in TCM and its complex mechanisms involving multi-level, multi-channel, and multi-target actions, further exploration is warranted. This paper provides a comprehensive overview of the pathological mechanisms underlying WD complicated by multiple organ dysfunctions, systematically reviews the TCM perspectives on the pathogenesis of WD, various TCM formulations and their active components, and advances in the clinical efficacy and pharmacological mechanisms of TCM compounds in treating WD with concurrent multiple organ dysfunctions, aiming to offer a more robust foundation for TCM-based interventions in WD. The diagram of comprehensive research ideas was illustrated in Figure 1.

Pathological Mechanisms of WD with Multi-Organ Dysfunction

The ATP7B gene is situated on chromosome 13q14.3, spanning a total genome length of 80 KB and comprising 21 exons interspersed with 20 introns.[26] Currently, mutations and dysfunctions within this gene are recognized as the predominant

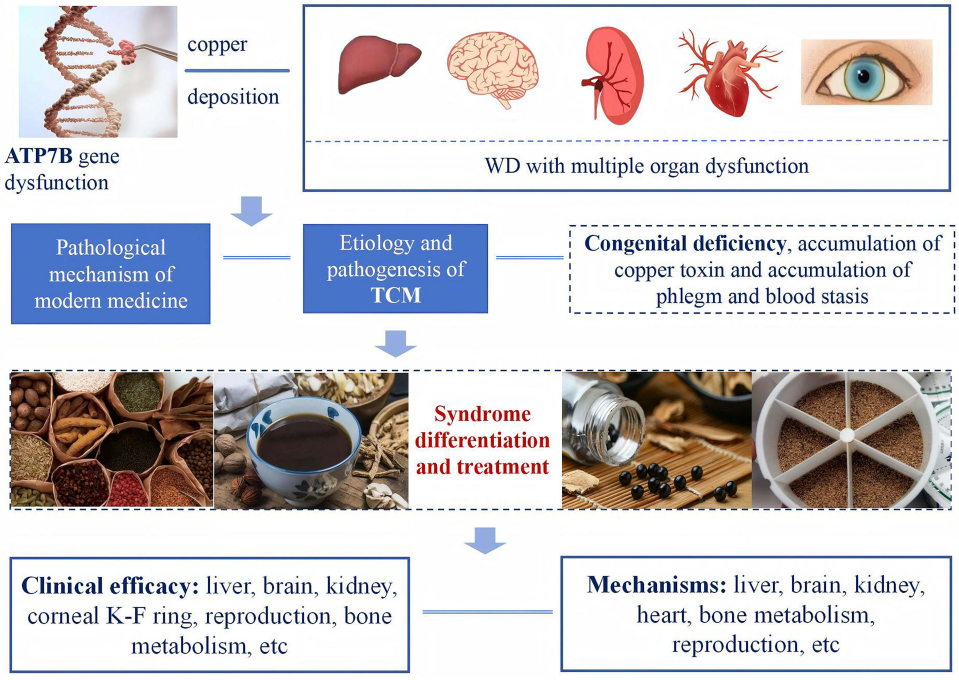

Figure 1 Diagram of comprehensive research ideas.

causes underlying the onset and progression of WD. To date, over 1200 distinct ATP7B mutations have been identified, among which missense mutations represent the most frequent type associated with WD, followed by frameshift, nonsense, promoter mutations, and others.[27] Notably, the missense R778L variant was reported to be the most prevalent in East Asia,[28] whereas the H1069Q missense variant predominates in Europe.[29] In India, the C271* nonsense variant appears most frequently.[30] A recent genetic analysis encompassing 115 Chinese WD patients revealed that the Arg778Leu mutation was the foremost high-frequency mutation detected in the Chinese cohort upon examining the genotype-phenotype correlation in WD. Patients harboring this mutation exhibited elevated ALT levels, and those with a homozygous P.Arg778Leu mutation were prone to developing neurological manifestations of WD.[31] This revelation augments the mutational spectrum of the ATP7B gene and constitutes a significant advancement in ATP7B genotype-phenotype association studies. The ATP7B gene is predominantly expressed in the liver but is also present in the kidney, brain, placenta, and breast.[32–35] Consequently, the pathogenesis of the disease is multi-organ involving hepatic, nervous, renal, cardiac, and reproductive system impairments. The multi-organ damage mechanism involved in WD was shown in Figure 2.

Liver

Mitochondrial damage is an early pathological manifestation of WD in the liver,[36] characterized by impaired cholesterol synthesis, leading to hepatic steatosis. Apoptosis plays a pivotal role in the pathological mechanism of WD-related liver damage. Oxidative stress, induced by copper accumulation, can trigger apoptosis by disrupting mitochondrial function and releasing cytochrome c.[37,38] Furthermore, research has indicated that copper deposition can influence the release of acid sphingomyelinase (Asm) and ceramide, contributing to hepatocyte apoptosis.[39,40] Persistent liver injury activates hepatic stellate cells (HSCs) due to inflammatory responses, oxidative stress products, apoptotic bodies, and transforming growth factors. This activation leads to the transformation of HSCs into contractile, proliferative, and fibrogenic myofibroblasts,[41,42] along with the accumulation of extracellular matrix and remodeling of liver tissue architecture, ultimately resulting in liver fibrosis and cirrhosis.[43] By observing the biochemical characteristics and morphological changes of the liver of atp7b-/- mice, Huster et al discovered significant copper accumulation, with focal hepatocyte swelling, necrosis, inflammation, and glycogen storage depletion evident at 6 weeks. Between 12–20 weeks, there was

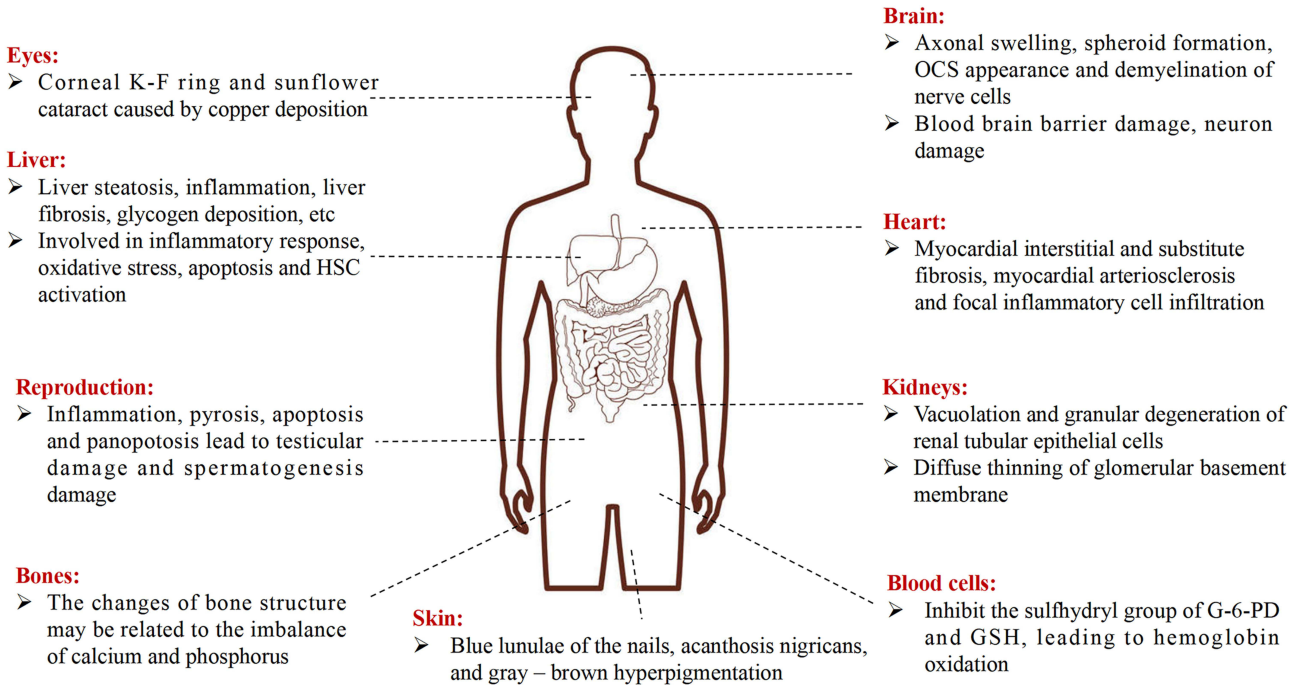

Figure 2 Schematic diagram of the mechanisms of WD-related multi-organ damage.

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pronounced hepatocellular damage, inflammation, and extensive necrosis, along with nuclear enlargement, prominent nucleoli, and vacuolization.[44] Furthermore, Pronicki[45] identified through pathological examination of WD livers that WD hepatic pathology encompasses steatosis, acute or chronic inflammation, fibrosis, cirrhosis, glycogen accumulation, hepatocyte necrosis, ballooning degeneration, and Mallory-Denk bodies. These insights enhance our understanding of the pathogenesis of WD-related liver damage. As research progresses, further specific manifestations and underlying mechanisms of WD liver involvement warrant investigation.

Brain

By measuring the copper content in the brains of WD patients, it has been observed that the copper levels in various brain regions are elevated.[46,47] Furthermore, there is a correlation between copper content and the extent of neuronal damage.[48] Astrocytes play a crucial role in mitigating copper toxicity due to their robust copper storage capacity.[49] However, when the accumulation of copper surpasses the storage capabilities of astrocytes, it continues to accumulate in different brain areas. This copper accumulation disrupts the blood-brain barrier and leads to further neuronal damage. Pathological examinations have revealed axonal swelling, spheroid formation,[50,51] the presence of characteristic Opalski cells (OCs), and significant demyelination.[52] These findings may be linked to oxidative stress resulting from excessive copper's impairment of the antioxidant defense system.[53] The lesion primarily affects the basal ganglia, encompassing regions such as the thalamus, brainstem, and cerebellum.[54] Impairment to neurons within the basal ganglia can disrupt the transmission of multiple neural pathways between different brain areas, leading to dystonia and a range of movement disorders.[55] This disruption is due to the destruction of fiber bundle conduction between the basal ganglia and the cerebral cortex, resulting in an imbalance of neurotransmitter release. Consequently, patients may exhibit a variety of psychiatric symptoms, including emotional, personality, and cognitive changes.[56] Previous research has indicated varying degrees of iron accumulation in the basal ganglia of patients with WD, suggesting that iron metabolism plays a crucial role in the pathogenesis of the WD nervous system.[57,58] Moreover, a recent 7T SWI study identified high signal intensity at the periphery of the globus pallidus in WD, revealing a distinctive metal deposition pattern in the brain, which could serve as a potential biomarker for neuroimaging diagnosis.[59] However, given the complexity of the nervous system, its precise mechanisms are still under investigation.

Kidneys

In addition to the liver, the kidney is also one of the organs with high copper content in the body. Patients with WD-related kidney damage may exhibit symptoms such as hematuria, proteinuria, aminoaciduria, and glucosuria.[60] The study found that the copper content in the kidney of WD patients was significantly higher than that of normal patients.[61,62] Excessive copper can interfere with the cell respiratory process or free radical defense mechanism, causing a series of pathological manifestations, mainly renal tubular epithelial damage. This includes cell vacuolation, granular degeneration, cell volume increase, tubular expansion, cell morphological changes (such as pyknosis), nuclear fragmentation, and proximal renal tubular injury and necrosis.[12,63] Studies have demonstrated significant copper granular deposits in the cytoplasm of both proximal and distal tubular cells in patients with WD.[64] However, glomerular and vascular damage were not pronounced.[65] Nonetheless, some researchers have also observed the deposition of granular material in the renal segmental capillary wall, foot process fusion of glomerular visceral epithelial cells, scattered electron-dense material deposition in the segmental subendothelial layer, and diffuse thinning of the glomerular basement membrane.[63] The continuous deposition of copper can cause a series of oxidative stress reactions and even lead to renal fibrosis by affecting lysine oxidase-mediated matrix crosslinking.[66]

Heart

Early prospective studies from the UK identified four types of WD-related cardiac dysfunction: arrhythmia, cardiomyopathy, cardiac death, and autonomic nerve dysfunction.[67] Additionally, a clinical study involving 463 WD cases revealed an increased risk of atrial fibrillation and heart failure among these patients.[68] Prior autopsy and cardiac biopsy results in WD patients confirmed excessive copper deposition in the heart.[69,70] However, the precise correlation between copper deposition levels and the extent of myocardial injury remains unclear.[67] Early electron microscopy examinations noted

mitochondrial damage and reduced ceruloplasmin associated with copper deficiency.[71] Subsequent pathological examinations uncovered interstitial and substitutional fibrosis, arteriosclerosis, and focal inflammatory cell infiltration in WD myocardium.[72] Research has shown that exposure to copper sulfate significantly elevates plasma levels of inflammatory cytokines such as ischemia modified albumin(IMA), heart-type fatty acid-binding protein (HFABP), cardiac troponin-I (cTn-I), and Brain Natriuretic Peptide (BNP), increasing the risk of myocardial injury and ischemia. This suggests a potential mechanism for WD-related cardiac injury.[73] Currently, there is a paucity of studies on WD-induced cardiac damage, and its specific mechanisms require further investigation and discussion.

Other Organs

In WD, copper deposition can manifest as a corneal Kayser-Fleischer (K-F) ring, impacting the reproductive system, bone, and blood cell functions. When hepatic copper storage becomes saturated, a greenish-brown ring emerges in the cornea, known as the K-F ring.[74] Harry et al observed electron-dense copper deposits of varying sizes on Descemet's membrane using an electron microscope, suggesting these deposits contribute to the formation of the K-F ring.[75] However, these deposits may not be readily apparent during the early stages of the disease. Research indicated that nearly all patients exhibiting neurological symptoms present with a K-F ring, and its magnitude may correlate positively with disease severity.[76] Following copper chelation therapy, the prominence of the K-F ring may diminish or vanish in tandem with treatment efficacy.[77] Consequently, the presence of a corneal K-F ring holds significant diagnostic and evaluative value in WD. In addition, sunflower cataract is a relatively rare ocular manifestation, occurring in only 2–17% of untreated WD patients. This condition is believed to be caused by the deposition of copper in the anterior capsule.[78–80]

Research has shown that male patients with WD often exhibit reproductive system dysfunctions, such as hypogonadism, erectile dysfunction, and hypoasthenozoospermia.[81,82] The sperm count and vitality are directly correlated with copper concentration levels.[83] The underlying mechanism may involve the TLR4/NF-κB signaling pathway, which induces an inflammatory response, pyroptosis, apoptosis, and PANoptosis. These processes lead to toxic testicular damage in WD and affect the release of reproductive neuroendocrine hormones, thereby impairing spermatogenesis.[84,85] Additionally, Golding et al observed alterations in bone structure among WD patients, including an increased incidence of osteomalacia, osteoporosis, and spontaneous fractures. These changes are believed to be associated with calcium and phosphorus imbalances resulting from renal dysfunction.[86] When a large amount of liver copper is released into the bloodstream, it can lead to copper toxicity, which may result in hemolytic anemia or thrombocytopenia.[87,88] Furthermore, copper can inhibit glucose-6-phosphate dehydrogenase (G-6-PD) and the thiol group of glutathione (GSH), affecting the clearance of free radicals and causing pathological changes in hemoglobin oxidation.[89,90] According to reports, patients with WD may present with skin changes such as blue lunulae of the nails, acanthosis nigricans, and gray–brown hyperpigmentation mostly on their lower limbs.[91,92] Further research is warranted to investigate the damage to other tissues and organs associated with WD.

The Study of TCM on the Etiology and Pathogenesis of WD

In the realm of TCM, WD possesses a unique nomenclature. Based on clinical manifestations, it can be classified as "Jiju", "Zhengjia" or "Guzhang" due to cirrhosis and ascites; or as "Chanbing", "Chizong", "Jingzheng" etc., according to the motor disorders presented; or as "Diankuang", "Chidai" and other TCM diseases based on mental symptoms. As a genetic disorder, congenital deficiency is the underlying cause of its manifestation.

As early as the 1970s, many scholars from China have been at the forefront of discussing the pathogenesis of WD in TCM. Yang et al believed that the etiology and pathogenesis of WD were related to congenital endowment deficiency and kidney yin deficiency.[93–96] Similarly, some scholars have proposed that the disease primarily affects the liver and kidney, with its pathogenesis varying across different periods. In the early stage, it is mainly due to liver and kidney deficiency and Qi and blood deficiency, while in the clinical stage, it is primarily characterized by damp heat accumulation syndrome.[97,98] Specifically, due to congenital deficiencies, the kidney may be deficient in essence and qi. Moreover, as the liver and kidney share a homologous relationship, kidney diseases can affect the liver. The liver serves as a focal point for the accumulation of copper-related toxins, which can impair its ability to facilitate the excretion of these toxins through bile. Copper toxicity is often associated with damp-heat syndrome. Furthermore, the deficiency of kidney essence can disrupt the functional circulation of the spleen and stomach, leading to compromised health of these organs. This results in the internal generation of dampness and

pathogenic factors. Prolonged exposure to damp-heat can lead to the formation of phlegm, obstruction of the qi mechanism, and the formation of blood stasis and phlegm turbidity. These factors can penetrate into the bloodstream and accumulate beneath the ribcage, manifesting as "Jiju" and "Zhengjia". Long-term exposure to toxins and pathogens can lead to sustained illness and damage to physiological pathways, resulting in impaired energy flow (Qi stagnation), blood circulation issues (blood stasis), and fluid accumulation (water stagnation) in the abdominal cavity, manifesting as "Guzhang". Furthermore, the accumulation of copper toxins and the stagnation of dampness, turbidity, and blood in the limbs and meridians can result in conditions such as "Chanbing", "Chizong", and "Jingzheng". If the pathological factors persist in the brain and impede the orifices, it is referred to as "Diankuang" or "Chidai". In summary, the primary cause of WD is congenital deficiency, leading to poor excretion of copper turbidity and subsequent accumulation of copper toxins.

Therefore, the pathogenesis of WD in TCM generally pertains to "liver and kidney deficiency, phlegm and blood stasis", characterized by a mix of deficiency and excess, with both manifestation and root causes of the disease. The key points of the etiology and pathogenesis of WD in TCM have been visualized (Figure 3).

Clinical Efficacy Evaluation of TCM in the Treatment of WD with Multi-Organ Dysfunction

Guided by the holistic approach and syndrome differentiation and treatment concept from TCM, and based on a summary of the fundamental etiology and pathogenesis of WD, numerous scholars have employed Chinese medicine with "tonifying the liver

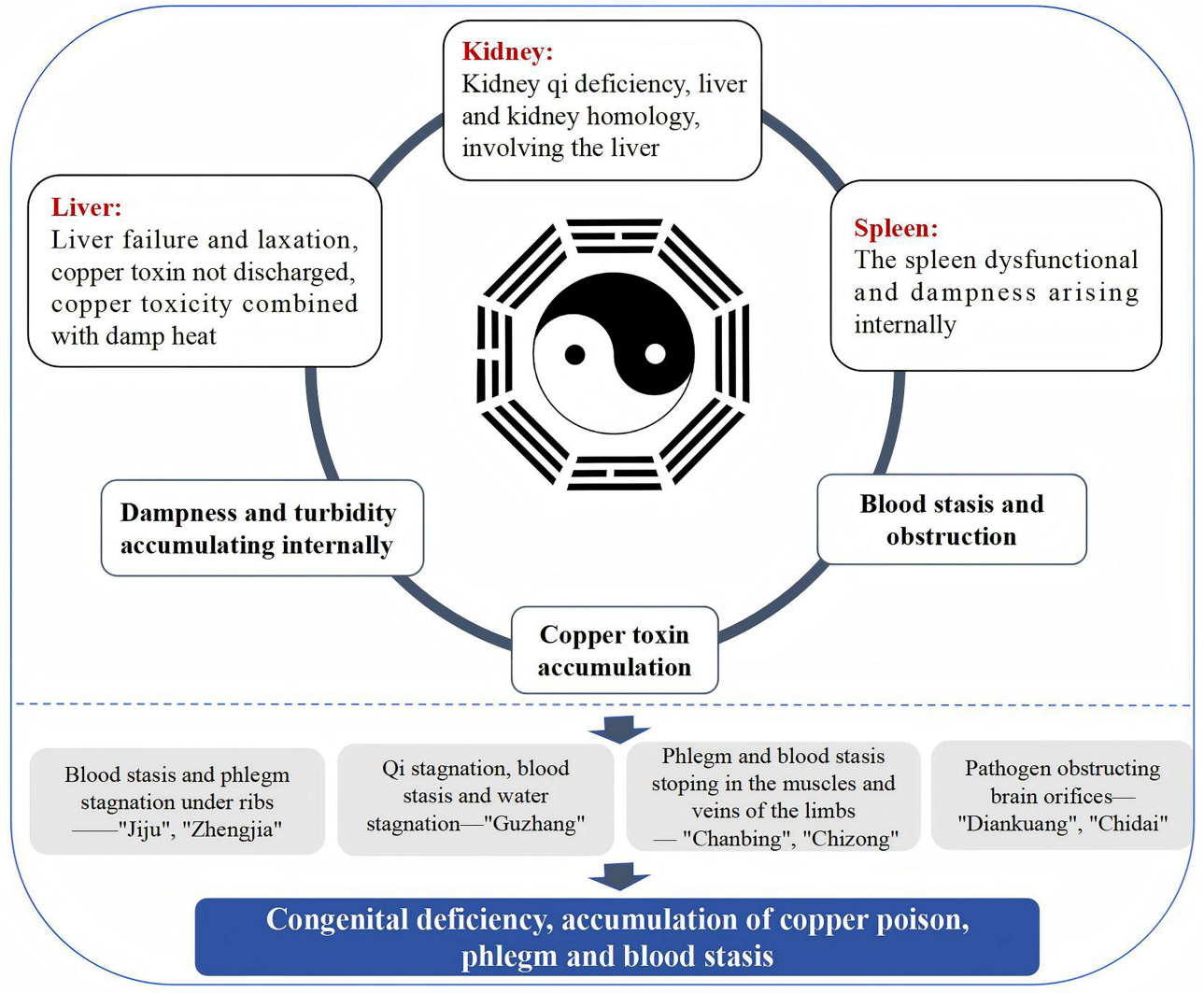

Figure 3 Diagram of etiology and pathogenesis of WD in TCM.

and kidney, resolving phlegm and blood stasis" effects (such as Gandoutang, Gandouling, Gandou Fumu decoction, Bushen Huoxue Huazhuo formula, etc.) to treat WD with multi-organ dysfunction, achieving favorable therapeutic outcomes. Chinese medicine has gradually emerged as an indispensable treatment modality for WD by adjusting the body's internal environment, restoring physiological equilibrium, and enhancing patient organ function. These effects substantially enhance both the quality of life and survival rates, highlighting the significant role in managing WD-related multi-organ dysfunctions of TCM.

Clinical Efficacy of TCM in Treating WD-Related Liver Damage

As an important complementary treatment method, the combination of traditional Chinese medicine and Western medicine has demonstrated more significant efficacy in treating Wilson's disease-related liver damage compared to Western medicine alone in clinical practice. Reports indicated that the TCM compound, Gandoutang (GDT), comprised of Rhubarb, Scutellaria baicalensis, Coptis chinensis, Andrographis paniculata, Barbed skullcap, Bixie, when used in conjunction with DMPS therapy, demonstrated a marked improvement in liver function and liver fibrosis markers in WD patients with Damp Heat Type.[99–101] Xue et al observed that the administration of Gandou decoction IV (GDD IV), which includes ingredients such as Rhubarb, Salvia miltiorrhiza, Sophora flavescens, Astragalus membranaceus, Alisma, etc., in combination with DMPS, resulted in significant enhancements in serum liver function parameters and liver fibrosis markers in WD patients.[102] The study revealed that the Chinese patent drug, Gandouling (GDL), composed of Rhubarb, Coptis chinensis, Turmeric, Salvia miltiorrhiza, Zedoary, etc., in conjunction with DMPS substantially improved liver function in WD patients and enhanced clinical outcomes.[103] Furthermore, in comparison to monotherapy with conventional Western medicine, the combination therapy involving GDL have been shown to significantly improve TCM syndrome scores, liver fibrosis, and liver function metrics in WD patients, while also reducing portal vein diameter, spleen length, and thickness.[104] Gandou Fumu decoction (GDFMD), a formula composed of Polygonum multiflorum, Bupleurum chinense, Radix curcumae, the fruit of Chinese wolfberry, Paeonia lactiflora, Poria cocos, and Panax notoginseng, when administered as a combined therapeutic approach, has been shown to significantly improve serum markers of liver function, reduce spleen diameter values, and enhance liver ultrasound scores in patients with WD, thereby reversing liver fibrosis to some extent.[105,106] The Tonifying the kidney, promoting blood circulation, and eliminating turbidity formula (Bushen Huoxue Huazhuo formula, BSHXHZF), which includes Rehmannia glutinosa, Schisandra chinensis, Morinda officinalis, Rhubarb, Coptis chinensis, Turmeric, Salvia miltiorrhiza, and other ingredients, effectively improved the liver function level of WD patients when used as a combination therapy. It has significant anti fibrotic effects by affecting the indicators of type III procollagen peptide (PIIIP), type IV collagen (CIV), laminin (LN), and hyaluronic acid (HA).[107] In an observational study by Zhang et al, the integration of Nourishing Qi, Promoting Blood Circulation, and Removing Turbidity TCM (YQHXHZ), consisting of Astragalus membranaceus, Peach kernel, Red peony, Safflower, Ligusticum wallichii, White peony, Zedoary, and other components—with DMPS demonstrated significant therapeutic benefits for WD patients. The combination therapy has been shown to effectively reduce Traditional Chinese Medicine Syndrome scores, improve liver symptoms as assessed by the Unified Wilson Disease Rating Scale (UWDRS), alleviate markers of liver fibrosis, decrease serum CXCL10 concentrations, and lower liver shear wave elastography (p-SWE) measurements.[108]

Clinical Efficacy of TCM in Treating WD-Related Neurological Damage

Similarly, TCM holds a significant position in the integrative approach when combined with Western medicine. The combination of GDT and DMPS has been shown to significantly enhance neurological function in patients compared to DMPS monotherapy, with demonstrated safety.[101] In conjunction with standard Western medical treatments, administration of GDT has been shown to effectively enhance cognitive function in patients,[109] mitigate dysphagia and equilibrium disturbances in WD patients exhibiting a damp-heat syndrome,[110] and reduce overall clinical symptomatology.[111] Studies have indicated that GDL can markedly improve the neurological function scores of WD patients, enhancing clinical outcomes, improving patients' quality of life, and exhibiting good safety profiles when administered as a combination therapy.[112–114] Specifically, the combination therapy of GDL have been found to significantly ameliorate cognitive and executive functions in WD patients with phlegm stasis type compared to single Western medicine treatment.[115] Furthermore, GDL combination therapy demonstrated a more significant effect on gait disorders in patients with WD.[116] The synergistic approach of combining GDFMD with olanzapine, predicated on the therapy of copper chelation, has demonstrated efficacy in alleviating anxiety and depressive symptoms associated with WD, enhancing overall clinical outcomes without a concomitant rise in adverse effects.[117] The combination of BSHXHZF and DMPS increased 24-hour

urinary copper excretion in patients. Furthermore, as a combinatory therapy, it has been shown to alleviate neurological and psychiatric manifestations.[118] The application of this formula, which combines copper chelation therapy with transcranial magnetic stimulation (TMS), has demonstrated a significant improvement in the scores of patients with WD on the Modified Young's Scales, HAMA, HAMD, MoCA, and four specialized cognitive domain scales. This finding suggests that the combination therapy of traditional Chinese medicine has a more significant improvement effect on patients' neurological function, mental and cognitive status compared to Western medicine alone.[119] Additionally, the integration of this TCM compound with DMPS has been shown to notably improve muscle tone abnormalities in WD patients diagnosed with liver and kidney deficiency and phlegm blood stasis syndrome.[120]

Clinical Efficacy of TCM in Treating WD-Related Other Organ Damage

Regarding renal effects, the combination of GDL and DMPS treatment has been demonstrated to significantly decrease urinary microalbumin levels in patients with WD, thereby ameliorating early renal damage, as compared to DMPS monotherapy.[121] Moreover, an enhanced formulation, known as improved Gandouling decoction (GDLD), which comprises Radix curcumae, Lysimachia christinae, Alisma, Salvia miltiorrhiza, Coptis chinensis, Chicken Blood Vine, Curcuma, Turmeric, and Rhubarb, in combination with DMPS, effectively mitigated symptoms associated with early renal impairment in phlegm blood stasis type of WD. The combinational administration of this formulation more effectively enhanced copper excretion and preserves renal function.[122] Resveratrol, a notable component in TCMs such as Polygonum multiflorum,[123,124] has demonstrated efficacy when combined with DMPS. This combination significantly improved the grading of the corneal K-F ring, patient symptoms, and related indicators.[125]

In the realm of clinical research on WD reproduction, the combination therapy of Gandou Bushen decoction (GDBSD), composed of Salvia miltiorrhiza, Coptis chinensis, Curcuma, Turmeric, Chicken Blood Vine, Eucommia ulmoides, the fruit of Chinese wolfberry, Rehmannia glutinosa, Leonurus japonicus, etc., with Western medicine has demonstrated significantly superior clinical efficacy in treating male patients with WD complicated by reproductive damage compared to monotherapy with Western medicine.[126] Furthermore, the Tonifying the kidneys, resolving phlegm, and removing blood stasis formula (BSHTQYF), which includes Radix curcumae, Coptis chinensis, Salvia miltiorrhiza, Eucommia ulmoides, the fruit of Chinese wolfberry, Rehmannia glutinosa, Cuscuta chinensis, etc., combined with DMPS significantly improved semen quality in patients with Wilson's disease complicated by oligozoospermia and asthenospermia, thereby increasing the fertility rate among spouses.[127] Additionally, the combination of GDL with DMPS treatment can ameliorate blood markers such as Ca, 1.25-(OH)2D3, IGF-1, IL-4, BGP, BAP, and TNF-α in WD patients to a certain extent. This improvement was achieved by modulating cytokines involved in bone metabolism and facilitating copper excretion, thereby correcting bone metabolic disorders.[128] Currently, there are no published reports on the clinical evaluation of TCM for addressing damage to other tissues and organs, such as the heart, in WD. The key points of the clinical observational studies included in the article were summarized and presented in Table 1.

The Potential Mechanisms of TCM in the Treatment of WD with Multi-Organ Dysfunction

In previous studies, numerous TCM formulas have been employed clinically under the guidance of TCM theory, demonstrating definite therapeutic effects. However, the complex mechanisms underlying TCM, which involve multiple levels, targets, and pathways, pose challenges for researching drug mechanisms. With the continuous advancements in modern molecular biology and scientific technology, the investigation into the mechanism of TCM intervention in WD is progressively deepening. The key mechanisms of TCM in treating WD with associated damage to the liver, nervous system, heart, and reproductive system, among others, are gradually being uncovered and understood. This provides an important scientific foundation and basis for the treatment of WD using TCM.

Mechanisms of TCM in Treating WD-Related Liver Dysfunction

Gandou decoction (GDD), a formula composed of Rhubarb, Rhizoma alismatis, Coptis chinensis, Turmeric, Lysimachia christinae, and Panax notoginseng, has been shown to promote copper excretion. It improved oxidative stress and protects

Table 1 Summary of the Clinical Studies on the Treatment of Multi-Organ Damage in WD with Different TCMs

TCM	Ingredient	Site of Action	Clinical Efficacy Indicators	References
GDT + DMPS	Rhubarb, Scutellaria baicalensis, Coptis chinensis, Andrographis paniculata, Barbed skullcap, Bixie	Liver	Liver function and liver fibrosis indicators	[98–100]
GDT + DMS/DMPS	Ditto	Nervous system	Neurological function, intelligence level, swallowing function, and balance disorder scores	[100, 108–110]
GDD IV + DMPS	Rhubarb, Salvia miltiorrhiza, Sophora flavescens, Astragalus membranaceus, Alisma, etc.	Liver	Liver function and liver fibrosis indicators	[101]
GDL + DMPS	Rhubarb, Coptis chinensis, Turmeric, Salvia miltiorrhiza, Zedoary, etc.	Liver	Liver function and hepatic fibrosis, portal vein width, spleen length and thickness	[102, 103]
GDL + DMPS/PCA	Ditto	Nervous system	Neurological function scores, gait disturbances	[111–115]
GDL+DMPS	Ditto	Kidneys	Urinary microalbumin level	[120]
GDL+DMPS	Ditto	Bones	Cytokines involved in bone metabolism	[127]
GDFMD + DMPS	Polygonum multiflorum, Bupleurum chinense, Radix curcumae, the fruit of Chinese wolfberry, Paeonia lactiflora, etc.	Liver	Liver function, spleen diameter value, and liver ultrasound scores	[104, 105]
Modified GDFMD + Olanzapine	Ditto	Nervous system	Anxiety and depression symptoms	[116]
BSHXHZF + DMPS	Rehmannia glutinosa, Schisandra chinensis, Morinda officinalis, Rhubarb, Coptis chinensis, Turmeric, etc.	Liver	Liver function indicators and liver fibrosis indicators	[106]
BSHXHZF + DMPS	Ditto	Nervous system	Neurological and psychiatric symptoms	[117]
BSHXHZF + DMPS	Ditto	Nervous system	Muscle tone disorder score	[119]
BSHXHZF+DMPS+TMS	Ditto	Nervous system	Modified Young Scale, HAMA, HAMD, MoCA, and four specialized cognitive domain scales	[118]
YQHXHZ + DMPS	Astragalus membranaceus, Peach kernel, Red peony, Safflower, Ligusticum wallichii, etc.	Liver	Liver fibrosis indicators and serum CXCL10 expression levels, liver p-SWE values, and UWDRS liver symptom scores	[107]
GDLD + DMPS	Radix curcumae, Lysimachia christinae, Alisma, Salvia miltiorrhiza, Coptis chinensis, etc.	Kidneys	Renal function	[121]
GDBSD + DMPS	Salvia miltiorrhiza, Coptis chinensis, curcuma zedoary, Curcuma, Turmeric, etc.	Reproductive system	Male reproductive impairment indicators	[125]
BSHTQYF + DMPS	Radix curcumae, Coptis chinensis, Salvia miltiorrhiza, Eucommia ulmoides, the fruit of Chinese wolfberry, etc.	Reproductive system	Semen quality and spousal fertility rate in oligoasthenozoospermia	[126]
Resveratrol	/	Eyes	Corneal K-F ring grading	[124]

WD liver cells from damage by regulating the expression of GS, GLS1, and GLS2 proteins.[129] Furthermore, GDD can regulate metabolic disorders in rat livers by enhancing lipid and oxidative stress metabolism.[130] In WD model mice, GDD modulated hepatic lipid metabolism through the PPARγ-CD36 pathway, thereby protecting liver function.[131] Dong et al discovered that GDD can facilitate copper excretion and safeguard liver cells by modulating the expression of copper metabolism-related proteins such as ATP7b, ATOX1, CCS, and COX17 in liver cells.[132] The recipe of GDD enhanced copper excretion and upregulated proteins associated with the lipoic acid pathway, mitigating liver cuproptosis in WD models and provided an auxiliary synergistic effect in WD treatment.[133] Gandou decoction II (GDD II), which contains ingredients such as Astragalus membranaceus, Peony bark, Red peony, White peony, Ligusticum wallichii, Zedoary, and Peach kernel, has been shown to downregulate the expression of Collagen I, α-smooth muscle actin (α-SMA), and Transforming Growth Factor-β1 (TGF-β1) by modulating the TGF-β1/Smad signaling pathway. This action inhibited liver fibrosis in mice with WD and alleviated copper accumulation-induced liver pathological damage.[134]

Many scholars have explored the therapeutic mechanisms of TCM, such as GDL, GDFMD, and BSHXHZF, in treating liver damage. Research has demonstrated that GDL can inhibit WD-related liver fibrosis through the Wnt-1/β-catenin signaling pathway.[135] By suppressing Bax and promoting the expression of Bcl-2, caspase-3, caspase-8, and NF-κB, GDL effectively regulated apoptosis in WD liver cells,[136–138] and also enhanced HSC apoptosis.[139] Additionally, GDL has been found to significantly modulate small molecule metabolites in copper-loaded rats, with its restorative effect on metabolic abnormalities potentially serving as one of the mechanisms for treating WD liver fibrosis.[140] Furthermore, GDL can mitigate liver fibrosis in copper-loaded mice by inhibiting the P38/JNK signaling pathway.[141] Utilizing transcriptomic techniques, Wei et al identified multiple mechanisms of GDFMD in treating WD liver fibrosis, encompassing metabolic pathways, immune and inflammatory responses, liver fibrosis, cell death, among others. The constructed RNA interaction network lays the groundwork for TCM interventions in WD liver fibrosis.[142] Cellular studies revealed that GDFMD can inhibit Erastin-induced ferroptosis in HepG2 liver cancer cells by modulating the SLC7A11/GPX4 axis, thereby offering hepatoprotection.[143] Moreover, GDFMD ameliorated WD liver injury by curtailing autophagy via the PI3K/Akt/mTOR pathway.[144] Subsequent research indicated that GDFMD could regulate ULK1-mediated autophagy by upregulating miR-29b-3p, thereby exerting anti-fibrotic effects against WD liver fibrosis.[145] BSHXHZF can ameliorate WD liver failure by addressing metabolic disorders, deterring hepatic failure and hepatocyte apoptosis.[146] Moreover, BSHXHZF promoted BMP-7 expression and curbs TGF-β1 expression in the liver tissue of WD TX mice, diminishing collagen fiber generation and exerting anti-fibrotic effects through regulation of the liver regeneration process.[147] The detoxification, turbidity removal, and blood stasis elimination formula (JDHZQYF), which comprises Rhubarb, Coptis chinensis, Salvia miltiorrhiza, Zedoary, Turmeric, and Lysimachia christinae, has been found to suppress liver inflammation and vascular proliferation. It also regulated the cell cycle and inhibited the activation and proliferation of HSCs, thereby improving WD-related liver fibrosis.[148]

Moreover, certain monomeric components derived from TCM have demonstrated effects on WD-related liver fibrosis. Curcumin, a bioactive compound present in TCMs such as Yujin, Curcuma, and Atractylodes macrocephala, exhibits beneficial therapeutic properties for the liver, respiratory system, and skin.[149–151] Studies have revealed that curcumin can mitigate iron deposition, diminish copper accumulation, facilitate copper efflux, and counteract WD-related oxidative stress via the Nrf2/HO-1/GPX4 signaling pathway, offering protection against WD-related hepatic damage.[152] Furthermore, treatment with subcutaneous liposome-encapsulated curcumin (LEC) has been shown to ameliorate copper-induced hepatic injury in WD murine models by suppressing HMGB1-mediated hepatic and systemic inflammation.[153]

Mechanisms of TCM in Treating WD-Related Neurological Damage

Regarding the neural damage mechanism, GDD has been found to mitigate the inflammatory damage of nerve cells in WD models by inhibiting the activation of NLRP3 inflammasomes induced by copper accumulation.[154] The modified GDD formula, which consists of Rhubarb, Rhizoma alismatis, Coptis chinensis, Turmeric, Lysimachia christinae, Panax notoginseng, Red peony, Evodia rutaecarpa, among others, elevated the expression of XIAP while diminishing that of Caspase-9 and Caspase-3 in brain tissues. This modulation mitigated oxidative stress injury induced by copper accumulation in neural cells, consequently inhibiting neuronal apoptosis.[155]

Numerous studies have been conducted on the mechanism of GDL in treating WD-related neural damage, primarily focusing on pathways such as autophagy, inflammation, cell apoptosis, and ferroptosis. By modulating the ERK signaling pathway and

enhancing ERK1/2 phosphorylation levels, GDL has demonstrated a beneficial effect on spatial memory function in WD model mice.[156] Research indicated that GDL can stimulate the proliferation and differentiation of neural stem cells in WD model mice, elucidating a potential mechanism by which GDL enhances WD neural function.[157] Through regulation of the pink1/Parkin pathway in the brains of TX mice with WD, GDL can suppress excessive mitochondrial autophagy, thereby exerting neuroprotective effects.[158] GDL has been shown to inhibit autophagy and mitigate nerve damage in WD model rats via the PI3K/Akt/FoxO1 and Sirt1/FoxO1 signaling pathways.[159] By upregulating Beclin-1 and LC3-II expression while downregulating P62 expression, GDL induced neuronal autophagy and exhibited a positive effect on cognitive impairment in WD model TX mice.[160] Chen et al employed network pharmacology and metabolomics to identify five pivotal targets for GDL in treating neural damage in WD rats: UGT1A1, CYP2E1, CYP2E2, PIK3CB, and LPL. These findings elucidate the mechanism by which GDL counteracts WD-related neural damage.[161] Furthermore, GDL has been shown to ameliorate cognitive impairments in WD by inducing methylation of the GSK3β promoter.[162] By modulating the TLR4/NF-κB/NLRP3 signaling pathway, GDL mitigated inflammatory damage in the hippocampal tissue of TX mice and suppressed CuCl2-induced overactivation of BV2 cells.[163] Zhao et al, utilizing network pharmacology methods and molecular docking technology, discovered that GDL regulated the PI3K-AKT, AGE-RAGE, and other signaling pathways through core targets such as JUN, STAT3, and TP53. This regulation reduced reactive oxygen species levels, alleviated neuroinflammatory responses, inhibited neuronal apoptosis, and thereby exerted a protective effect on nerve cells and enhanced cognitive function.[164] Moreover, GDL has been found to alleviate iron death in the hippocampal tissue of TX mice and inhibit CuCl2-induced iron death in HT22 cells. The underlying mechanism may involve downregulation of the PKCβII/ASCL4/ALOX5 signaling pathway and a decrease in intracellular lipid peroxidation.[165]

The recipe of BSHXHZF exerted a regulatory effect on metabolites such as glycolytic, taurine, valine, and tyrosine metabolisms in the striatum tissue of WD copper-loaded rats, demonstrating a certain degree of repair on neural damage in these WD copper-loaded rats.[166] The traditional Chinese patent medicine Huangpu Tongqiao Capsule (HPTQ), comprised of Acorus tatarinowii, Alpinia oxyphylla, Polygonum multiflorum, Ligusticum wallichii, Rhubarb, and Ginseng, can inhibit endoplasmic reticulum stress-induced apoptosis by regulating the expression levels of GRP78, CHOP, caspase-12, cleaved caspase-9, and cleaved caspase-3, and have neuroprotective effects on WD copper loaded rat models.[167]

Furthermore, emodin, an active compound derived from the TCM Rhubarb, has been shown to mitigate cognitive impairments associated with WD by modulating the expression of apoptosis-related proteins. Specifically, emodin downregulated Bax and cleaved Caspase-3 while upregulating Bcl-2, p-PI3K/PI3K, and p-AKT/AKT, thereby inhibiting apoptosis.[168] Another active component, ferulic acid, found in TCMs like Ligusticum wallichii and Angelica sinensis, has demonstrated potential in alleviating hippocampal neuronal damage through the activation of Sirt1-mediated ferroptosis, which may also contribute to the improvement of cognitive impairments in WD.[169]

Mechanisms of TCM in Treating WD-Related Other Organ Damage

Reports indicated that GDL may exert a cardioprotective effect by enhancing the expression of Heme Oxygenase-1 (HO-1) in the cardiac tissue of WD model rats.[170] In the context of bone metabolism, BSHTQYF has been shown to promote the growth and development of femoral tissue in TX mice, elevate the expression levels of Bone Gla Protein (BGP) and Osteoprotegerin (OPG) proteins in TX mouse bone tissue, and ameliorate bone metabolic disorders in these mice.[171] Currently, there is a paucity of research on the mechanisms underlying TCM treatments for WD in combined with cardiac damage and bone metabolism. Further investigations and refinements are warranted.

The team from Dr. Han in China has been pioneering research on the mechanism of TCM for treating WD-related reproductive damage, achieving significant phased results. Their findings suggested that GDBSD and the TCM monomer Berberine can ameliorate ovarian tissue damage in TX mice with WD by suppressing iron death and endoplasmic reticulum stress.[172,173] Additionally, BSHTQYF has been shown to increase ovulation numbers in copper-loaded mice, foster follicular development, enhance mitochondrial ultrastructure, and improve the proliferative capacity of the cumulus complex granulosa cells.[174] While TCM has demonstrated promising clinical efficacy in addressing WD-related renal damage, its underlying mechanisms remain unreported and warrant further exploration. The key findings from the studies on mechanisms discussed within this article were shown in Table 2.

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Table 2 Summary of the Mechanisms Underlying the Treatment of Multi-Organ Damage in WD with Different TCMs

TCM	Ingredient	Site of Action	Mechanisms	References
GDD	Rhubarb, Rhizoma alismatis, Coptis chinensis, Turmeric, Lysimachia christinae, etc.	Liver	GS, GLS1, and GLS2 proteins and oxidative stress; Lipid and oxidative stress metabolism; PPAR γ - CD36 pathway; Copper metabolism related proteins	[128–131]
GDD	Ditto	Nervous system	NLRP3 inflammasome, neuronal inflammation	[153]
GDD	Ditto	Liver	Lipoic acid pathway related proteins, liver cuproptosis	[132]
GDDII	Astragalus membranaceus, Peony bark, Red peony, White peony, Ligusticum wallichii, etc.	Liver	TGF - β 1/Smad pathway, Col I, α - SMA, and TGF - β 1 proteins	[133]
Modified GDD	Rhubarb, Rhizoma alismatis, Coptis chinensis, Turmeric, Lysimachia christinae, etc.	Nervous system	XIAP, Caspase-9, and Caspase-3 proteins, oxidative stress, apoptosis	[154]
GDL	Rhubarb, Coptis chinensis, Turmeric, Salvia miltiorrhiza, Zedoary, etc.	Liver	Wnt-1/β - catenin signaling pathway; Bax, Bcl-2, caspase-3, caspase-8, and NF - κ B proteins; HSC apoptosis; P38/JNK signaling pathway; small molecule metabolites	[134–140]
GDL	Ditto	Nervous system	ERK signaling pathway; Proliferation and differentiation of mouse neural stem cells; Pink1/Parkin pathway, autophagy; PI3K/Akt/FoxO1 and Sirt1/FoxO1 signaling pathways; Beclin-1, LC3-II, and P62; The five key targets include UGT1A1, CYP2E1, CYP2E2, PIK3CB, and LPL; Methylation of GSK3 β promoter; TLR4/NF - κ B/NLRP3 signaling pathway, hippocampal inflammation; PI3K-AKT, AGE-RAGE and other signaling pathways, apoptosis; PKC β II/ASCL4/ALOX5 signaling pathway, ferroptosis	[155–164]
GDL	Ditto	Heart	HO-1 protein	[169]
GDFMD	Polygonum multiflorum, Bupleurum chinense, Radix curcumae, the fruit of Chinese wolfberry, Paeonia lactiflora, etc.	Liver	Metabolic pathways, immune and inflammatory responses, liver fibrosis, cell death, etc; SLC7A11/GPX4, ferroptosis PI3K/Akt/mTOR, Autophagy; miR-29b-3p, autophagy	[141–144]
BSHXHZF	Rehmannia glutinosa, Schisandra chinensis, Morinda officinalis, Rhubarb, Coptis chinensis, Turmeric, etc.	Liver	Metabolic disorders, inhibiting liver fibrosis and hepatocyte apoptosis	[145]
BSHXHZF	Ditto	Liver	BMP-7 and TGF - β 1 proteins	[146]
BSHXHZF	Ditto	Nervous system	Glycolytic, taurine, valine, and tyrosine metabolisms	[165]
JDHZQYF	Rhubarb, Coptis chinensis, Salvia miltiorrhiza, Zedoary, Turmeric, etc.	Liver	The process of liver inflammation, vascular proliferation, cell cycle, activation and proliferation of HSCs	[147]
HPTQ	Acorus tatarinowii, Alpinia oxyphylla, Polygonum multiflorum, Ligusticum wallichii, etc.	Nervous system	GRP78, CHOP, caspase-12, cleaved caspase-9, cleaved caspase-3 proteins, endoplasmic reticulum stress, apoptosis	[166]
BSHTQYF	Radix curcumae, Coptis chinensis, Salvia miltiorrhiza, Eucommia ulmoides, the fruit of Chinese wolfberry, etc.	Bones	BPG, OPG proteins	[170]
GDBSD/Berberine	Salvia miltiorrhiza, Coptis chinensis, curcuma zedoary, Curcuma, Turmeric, etc.	Reproductive system	Ferroptosis, endoplasmic reticulum stress; Mitochondrial ultrastructure and proliferation ability of cumulus complex granulosa cells	[171–173]
Curcumin	/	Liver	Nrf2/HO-1/GPX4 signaling pathway, iron deposition; HMGB1, inflammation	[151, 152]
Chrysophanol	/	Nervous system	Bax, Cleaved Caspase-3, Bcl-2, p-PI3K/PI3K, p-AKT/AKT proteins, apoptosis	[167]
Ferulic	/	Nervous system	Sirt1, ferroptosis	[168]

Limitation

However, there are still some issues that need to be addressed. Firstly, although TCM has demonstrated certain therapeutic effects in treating WD, the complex and varied components of TCM necessitate enhanced quality control to prevent any adverse impact on clinical efficacy and fundamental research due to lax oversight. Secondly, there is a paucity of research on the treatment of WD with individual TCM monomers. Therefore, it is imperative to actively screen for active ingredients within TCM and conduct targeted research on these monomer components, which is crucial for elucidating the potential mechanisms underlying the efficacy of TCM in treating WD. Thirdly, while there is relatively extensive clinical and mechanistic research on the use of TCM for liver and neural system involvement in WD, research on organ damage such as kidney and heart impairment remains limited. This may be attributed to other systemic symptoms being more readily overlooked. Fourthly, this study primarily focuses on the impact of TCM on multi-organ damage in WD. Given that TCM is widely used in China, there remains a lack of information regarding its application in other countries internationally. Future research should aim to gradually improve and supplement these data to validate the conclusions. Fifth, there is still a need for additional biomarkers, standardized scales, brain MRI examinations, and other diagnostic results to further investigate the underlying mechanisms. Moreover, numerous clinical and basic studies have combined TCM with Western medicine for treatment. Although the superiority of integrating TCM and Western medicine over Western medicine alone has been confirmed, the precise mechanism through which TCM exerts its effects cannot be conclusively determined. Future studies should independently examine and investigate the effects of TCM to mitigate the confounding influence of Western medical practices.

Conclusion

In summary, this article delves into the clinical efficacy and potential mechanisms of TCM in treating WD with multi-organ damage, including the liver, neurological system, heart, reproductive system, and other tissues and organs, based on a comprehensive review and analysis of both modern medical pathological mechanisms and TCM etiology and pathogenesis. The study not only highlights the significance of TCM as an effective treatment for WD accompanied by multi-organ damage but also enhances our understanding of the complex mechanisms underlying TCM interventions in WD. This provides a crucial foundational and molecular basis for the treatment of WD using TCM.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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