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Review Article

Micro Zhēngjiǎ as a reversible microstructural lesion network in diabetic myocardial fibrosis: mechanistic insights and therapeutic implications of Huoxue-Tongluo therapy

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Abstract: Diabetic myocardial fibrosis (DMF) is a prominent pathological process that leads to the progression of diabetic heart disease, and yet the underlying mechanisms have not been properly clarified. Recently, a new paradigm called Micro Zhēngjiǎ lesion has been implicated, with microstructural changes in the myocardial capillaries being indicated as critical factors in the development of diabetic fibrosis. The purpose of the review is to investigate the mechanistic basis of the Micro Zhēngjiǎ lesion in DMF and its implications across tissue, cellular, and molecular levels. This article summarizes findings from histological and imaging studies, which show the structural and functional impairments of the myocardial extracellular space, as well as dysregulation of fibrosis-related signaling pathways, in the diabetic heart. Moreover, potential treatment interventions are reviewed, especially Huoxue-Tongluo therapy. This approach, which aims to activate blood circulation and dredge collaterals, combines traditional Chinese medicine with modern pharmacological principles to reverse the development of DMF. By targeting major inflammatory mediators, improving microcirculation, and regulating fibroblast activation, Huoxue-Tongluo therapy has the potential to be used as an alternative or complementary approach to conventional therapy. The review proves the translational potential of the given therapeutic paradigm and suggests future research directions to investigate the multifaceted interplay of microstructural lesions, metabolic dysfunction, and fibrosis in the diabetic heart in depth.

Keywords: Diabetic myocardial fibrosis, micro Zhēngjiǎ lesion, Huoxue-Tongluo therap, microstructural remodeling, cardiometabolic mechanism

Introduction

The central pathological substrate of diabetic cardiomyopathy (DCM) is diabetic myocardial fibrosis (DMF), defined by excessive deposition of extracellular matrix (ECM), microvascular rarefaction, and progressive ventricular stiffness, which results in heart failure with preserved ejection fraction [1]. Notwithstanding the progress in glucose-lowering and hemodynamic therapies, there is currently no treatment that can stop or reverse myocardial fibrogenesis during diabetes. The majority of modern models focus on systemic metabolic derangements (hyperglycemia, oxidative stress, lipotoxicity, and chronic inflammation), yet they fail to describe the etiology of fibrosis and how it develops to become spatially structured in the diabetic myocardium. Hence, it is imperative to develop a finer pathological paradigm that incorporates the heterogeneity of microenvironments and the local sensitivity of tissues.

To overcome the abovementioned drawbacks, a new conceptual and mechanistic paradigm is proposed, the Micro Zhēngjiǎ lesion, which may suggest that DMF is caused by spatially restricted domains of structural organization, microvascular hypoxia, and impaired cellular communication [2]. This paradigm, based on the concept of Zhēngjiǎ in traditional Chinese medicine (TCM), which is defined as pathologi-

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cal nodules due to stagnant circulation and metabolic obstruction, reframes DMF from a diffuse process into an interconnected system of dynamic, potentially reversible fibrotic foci, characterized by biochemical, biomechanical, and microcirculatory imbalances [3]. High-resolution imaging, single-cell transcriptomics, and spatial omics support the presence of these microlesions and demonstrate local fibroblast activation, uncoupling of endothelial and pericyte, redox disequilibrium of the mitochondria, and impaired perfusion, which together cause fibrotic remodeling on the microscale [4-7]. Nevertheless, very little has been done to explore the translational value of these findings, especially their potential to be applied in specific interventions.

In this novel pathophysiological theoretical model, Huoxue-Tongluo treatment, an original TCM approach that aims to activate blood and dredge collaterals, provides a mechanistically coherent treatment. Evidence is building in support of Huoxue-Tongluo as a multimodal anti-fibrotic agent, which exerts its multifactorial anti-fibrotic effect by restoring microvascular perfusion, balancing fibroblast-immune interactions, and normalizing ECM turnover; these effects are achieved through the coordinated control of the Transforming Growth Factor-beta/Mothers Against Decapentaplegic homolog (TGF-β/Smad), AMP-activated Protein Kinase (AMPK) and Nuclear factor erythroid 2-related factor 2 (NRF2) pathways [8-10]. Since it possesses a multitarget pharmacological effect, the treatment is specifically appropriate in reducing the interconnected metabolic, inflammatory, and structural dysfunctions in the Micro Zhēngjiǎ lesion.

This review integrates mechanistic and microstructural data to explain the biological basis of the Micro Zhēngjiǎ paradigm, and to provide a conceptual framework for understanding how Huoxue-Tongluo therapy interacts with the microenvironmental agents in DMF. The therapeutic repair of microdomains, which bridges a critical gap in cellular pathophysiology, is best understood within the frameworks of microcirculatory biology and molecular cardiology - despite its conceptual origins in traditional medicine. Finally, we advocate a paradigm shift away from viewing DMF as a helpless, diffuse process, and toward understanding it as a dynamic network of microstructural lesions with inherent reversibility. This reframing paves the way for more accurate therapeutic strategies.

Biological basis of "Micro Zhēngjiǎ": from metabolic disturbance to microstructural reorganization

Initiation - metabolic soil and the pre-fibrotic microenvironment

The pathogenesis of DMF starts in an already metabolically diseased land which serves as the soil in which the microlesional fibrosis develops [11]. Chronic hyperglycemia, lipid overload, and insulin resistance - by dysregulating cardiomyocyte and vascular metabolism - create a pro-inflammatory and redox-imbalanced microenvironment [12]. In this area of biochemistry, there is extra accumulation of advanced glycation end products (AGEs) on the extracellular and intracellular proteins, which increase cross-linkage and reduce matrix plasticity [13, 14]. At the same time, generation of reactive oxygen species (ROS) by dysfunctional mitochondria and Nicotinamide Adenine Dinucleotide Phosphate oxidases in excess interferes with cellular redox signaling, negates the bioavailability of nitric oxide, and facilitates endothelial activation [15]. These events convert the myocardium from a metabolically adaptive organ to a fibrogenic bioreactor, where the first molecular seeds of the "Micro Zhēngjiǎ" lesion are sown.

In addition to the oxidative damage, the cellular energy hierarchy is also reorganized with diabetic metabolism. The substrate shift (from glucose to fatty-acid oxidation) increases oxygen consumption and places substantial strain on mitochondria, which leads to Adenosine Triphosphate (ATP) inefficiency and overproduction of electron-leak-created superoxide [16, 17]. The resulting redox imbalance triggers the activation of key transcriptional regulators, including Nuclear factor kappa-B (NF-κB), Hypoxia-Inducible Factor 1-Alpha, and NRF2; these factors coordinate a pathogenic gene expression program that drives inflammation, angiogenic regression, and ECM deposition [18]. Exposed endothelial cells lose junctional integrity and anchoring of pericytes, resulting in microvascular leakage and hypoperfusion. This creates spatially delimitative areas of isch-

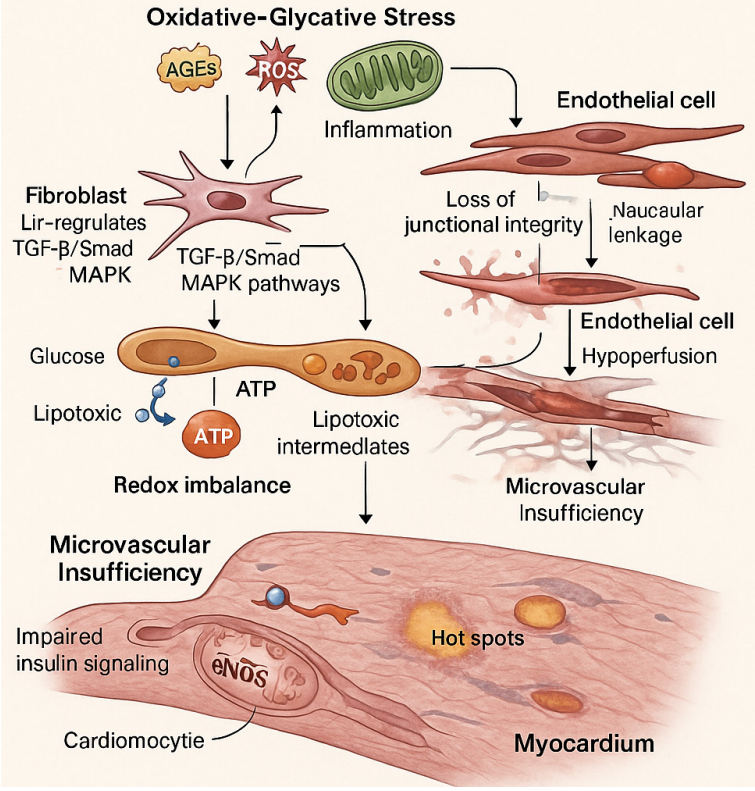

Figure 1. Metabolic terrain in diabetic myocardial fibrosis. This diagram illustrates the molecular mechanisms underpinning the genesis of diabetic myocardial fibrosis within a dysregulated metabolic environment. Chronic hyperglycemia, lipid overload, and insulin resistance create a redox-imbalanced, pro-inflammatory microenvironment that fosters the accumulation of AGEs and ROS. These stressors trigger endothelial dysfunction, microvascular insufficiency, and fibroblast activation through the TGF-β/Smad and MAPK pathways, culminating in fibrosis. Altered myocardial metabolism, marked by a switch from glucose to fatty acid oxidation, exacerbates mitochondrial dysfunction, ATP inefficiency, and oxidative stress. Impaired insulin signaling further disrupts microvascular function and cardiomyocyte survival, establishing localized "hot spots" of fibrotic susceptibility. This complex interplay between metabolic injury and cellular responses highlights the critical role of a dysregulated metabolic landscape in initiating and perpetuating diabetic cardiomyopathy. Note: AGEs, Advanced Glycation End-products; ROS, Reactive Oxygen Species; TGF-β/Smad, Transforming Growth Factor-beta/Mothers Against Decapentaplegic homolog; MAPK, Mitogen-Activated Protein Kinase; ATP, Adenosine Triphosphate; eNOS, Endothelial Nitric Oxide Synthase.

endoplasmic-reticulum stress and pro-fibrotic secretomes [19, 20]. This creates microscale metabolic heterogeneity in the myocardium, resulting in microdomains with pronounced glycative, oxidative, and lipotoxic gradients that spatially dictate fibrogenic susceptibility. From this perspective, the topologically patterned metabolic landscape acts as the pathogenic soil, generating discrete foci of cellular vulnerability that nucleate the formation of Micro Zhēngjiǎ lesions.

Finally, disrupted insulin signaling is a critical dysfunction that unleashes fibrosis via disrupted metabolic-vascular interactions. The loss of insulin-mediated endothelial nitric oxide synthase (eNOS) activation inhibits microvascular dilation. Concurrently, the lessening of Protein Kinase B (Akt)-AMPK activity suppresses the recruitment of cardiomyocyte survival signals and autophagic clearance of harmed organelles [21, 22]. The combination of these defects promotes inflammatory responses of low grade and extracellular redox cycles, and forms a self-perpetuating metabolic feedback mechanism of converting acute metabolic stress into structural pathology (**Figure 1**).

emic stress, which indicate the future sites of fibrotic foci.

The most important factor is the glycolipotoxic signaling axis, which further propagates the metabolic damage into the paracrine regulation of fibroblast activities. AGEs-Receptor for Advanced Glycation End-products interaction of cardiac fibroblasts up-regulates TGF-β/Smad and MAPK signaling, while lipotoxic intermediates, ceramides and diacylglycerols activate

Propagation - cellular crosstalk and the microdomain of dysregulated dialogue

Upon the beginning of metabolic injury, DMF progresses via a cascade of maladaptive cellular interactions that increases fibrogenesis under specified microdomains. The Micro Zhēngjiǎ lesion propagation is not a simple accumulation of the ECM components but a distorted multicellular signaling network. This network arises from aberrant crosstalk among

cardiomyocytes, fibroblasts, endothelial cells, and immune cells, which collectively reinforce fibrotic remodeling. This interaction is an important process in myocardial fibrosis progression, with each cell type playing a role in amplifying and localizing the pathological remodeling.

Primary damage to cardiomyocytes, which is motivated by oxidative stress, mitochondrial dysfunction, and metabolic disruptions, preconditions the activation of fibroblasts. The paracrine signals released by the exposed cardiomyocytes such as TGF-β1, angiotensin II (Ang II) and Connective Tissue Growth Factor, not only activate the resident fibroblasts but also bring in circulating fibroblast progenitors to the injury site by exposing them to chronic hyperglycemia and lipotoxicity [23, 24]. The cardiomyocyte-fibroblast interaction leads to a cascade of fibrotic events, which are typified by myofibroblast differentiation, ECM deposition, and the acquisition of a contractile/matrix-producing phenotype. This creates a self-perpetuating cycle wherein fibroblast-derived cytokines amplify cardiomyocyte stress, which then feeds back to further stimulate fibroblast activation, culminating in progressive tissue stiffening [25].

The immune system is the essential component of the spread of fibrosis, as it is capable of regulating the activation of fibroblasts and ECM remodeling [26]. Low grade inflammation caused by persistent macrophage, neutrophil, and T-cell exposure is also a contributing factor to a fibrotic phenotype in diabetes in several ways. Macrophages undergo polarized responses, in which the M1 (pro-inflammatory) macrophage phenotype promotes fibroblast activation by cytokines like Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1 Beta (IL-1β) and C-C Motif Chemokine Ligand 2 (CCL2), while the M2 (anti-inflammatory) macrophage phenotype endorses the resolution of fibrosis by anti-inflammatory cytokines and tissue repair cues [27]. The inability to overcome the M1/M2 imbalance in the diabetic myocardium results in chronic inflammation and prolongs fibroblast activation and ECM deposition.

Endothelial dysfunction and microvascular rarefaction contribute to fibrosis propagation equally because both hypoxia and progressive accumulation of the ECM depend on the vascular component of the microdomain. Endothelial cells of diabetic hearts experience dysfunction caused by oxidative stress and endothelial-to-mesenchymal transition, a process that degrades the endothelial monolayer and converts endothelial cells into mesenchymal-like fibroblast precursors [28]. This transition not only increases the proportion of fibroblasts in the site of lesion, but also interferes with the microvascular network, thereby undermining oxygen and nutrient delivery to cardiomyocytes and creating hypoxic regions [29]. The disintegration of the endothelial glycocalyx and the loss of pericyte support exacerbate these deficiencies, thus creating an ischemic microdomain that triggers the accretion of fibrotic matrix proteins [30].

Mitochondrial dysfunction is central to the propagation of fibrosis and connects metabolism to cellular signaling. In the diabetic myocardium, impaired mitochondrial oxidative phosphorylation and excessive production of the ROS are not only the aggravators of the oxidative damage but also the triggers of mitochondrial-nuclear signaling pathways. These pathways converge on key fibrotic mediators, including TGF-β/Smad2/3 [31]. Moreover, the recently discovered form of intercellular communication, mitochondrial-derived vesicles, has been demonstrated to deliver signaling molecules, which propagate inflammatory and fibrotic responses [32, 33]. This signaling pathway, involving mitochondria, provides a distinct cell-cell communication axis that conveys fibrotic signals throughout the microdomain, facilitating the diffusion of the fibrotic phenotype across cellular compartments. Therefore, mitochondrial malfunction is the central node, connecting metabolic stress and oxidative damage to fibrotic signaling and driving the propagation network.

Mechanotransduction, the cellular translation of ECM mechanical signals into biochemical activity, is also involved in fibrosis perpetration in the context of the Micro Zhēngjiǎ lesion. Accelerated ECM deposition leads to myocardial stiffening, which in turn subjects resident cells - including cardiomyocytes, fibroblasts, and endothelial cells - to increased mechanical stress. This rigidity acts as a potent signal, powerfully transduced by the Yes-associated protein/Transcriptional coactivator with PDZ-binding motif (YAP/TAZ) and focal adhesion

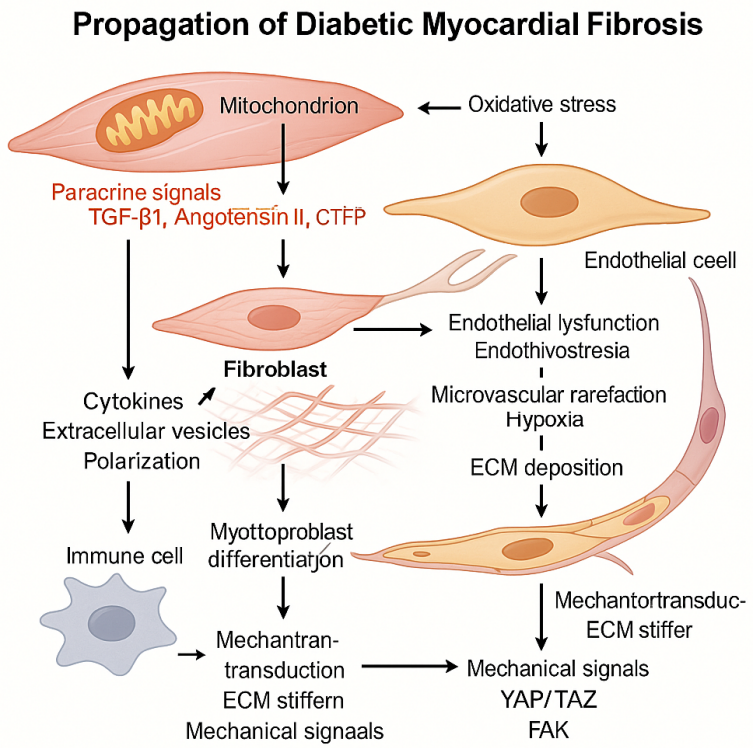

Figure 2. Propagation of diabetic myocardial fibrosis ("Micro Zhēngjiǎ" Lesion). This schematic illustrates the multicellular and multi-signal propagation phase of diabetic myocardial fibrosis within the "Micro Zhēngjiǎ" lesion. Cardiomyocytes exposed to oxidative and metabolic stress release paracrine mediators - including TGF-β_1, angiotensin II, and CTFP - that activate cardiac fibroblasts and promote their differentiation into myofibroblasts. Activated fibroblasts, in turn, secrete cytokines and extracellular vesicles that further exacerbate cardiomyocyte injury and metabolic stress. Immune cells, particularly polarized macrophages, further amplify fibroblast activation and ECM deposition through chronic inflammatory signaling. Endothelial dysfunction and endothelial-to-mesenchymal transition contribute additional fibroblast precursors and microvascular rarefaction, aggravating local hypoxia and fibrosis. Mitochondrial ROS production and mitochondrial-derived vesicle signaling link metabolic injury to fibrogenic transcriptional programs (TGF-β/Smad2/3). Finally, ECM accumulation increases tissue stiffness, activating mechanotransductive pathways such as YAP/TAZ and FAK that perpetuate fibroblast activation and fibrotic expansion. Together, these metabolic, inflammatory, and mechanical feedback loops drive the spatially confined propagation of fibrosis within diabetic myocardium. Note: TGF-β_1, Transforming Growth Factor-beta 1; CTFP, Connective Tissue Fibrosis Promoter; ECM, Extracellular Matrix; YAP/TAZ, Yes-associated protein/Transcriptional coactivator with PDZ-binding motif; FAK, Focal Adhesion Kinase; TGF-β/Smad2/3, Transforming Growth Factor-beta/Mothers Against Decapentaplegic homolog 2/3.

kinase (FAK), which then drive fibroblast activation and collagen production [34, 35]. Increased tissue stiffness also enhances fibroblast stimulation, forming a mechanical cycle that leads to the growth of the lesion and expansion of fibrosis within the microdomain. Such mechanical feedback amplifies the fibrotic process, and shifts the lesion's primary driver from a biochemical to a biomechanical stimulus.

The transmission of the Micro Zhēngjiǎ can therefore be explained as a multicellular, multi-signal feedback system that accelerates the fibrotic process in the diabetic myocardium. The propagation of the lesion is, in essence, a dysregulated cellular communication. Cardiomyocytes, fibroblasts, immune cells, and endothelial cells engage in synergistic crosstalk via multimodal signaling (cytokines, extracellular vesicles, and mechanical cues) to reinforce their profibrotic activities, culminating in enhanced fibrotic remodeling. It is this complex network of signals that creates a pathophysiological microdomain, where metabolic, inflammatory and biomechanical signals converge to accelerate fibrosis (**Figure 2**). Notably, this spatially localized propagation is not random but organized, tracking the initial patterns of metabolic and microvascular stress. This reveals that the fibrotic process within the Micro Zhēngjiǎ lesion is targetable and potentially reversible at the cellular and microdomain levels.

Based on the synthesized evidence, we assert that diabetic myocardium fibrosis propagates not as a linear cascade, but as a spatially confined feedback network operating at the microdomain level. This explanation highlights that cellular crosstalk, (particularly fibroblast-endothelial-immune responses) constitutes self-reinforcing fibrotic niches whose spatial frames determine lesion progression. This point of view goes beyond current accounts of individual signaling pathways by providing a spatial-system interpretation of DMF progression.

The structural manifestation of "Jié": pathological reorganization of the ECM

As the metabolic and cellular disruptions within the Micro Zhēngjiǎ lesion advance, they culminate in the Jié phase - a state of structural entrapment achieved through pathological ECM reorganization, where dynamic fibrotic signals become crystallized into fixed structural deformation. This represents the critical transition from a state of reversible microdomain dysfunction to a biomechanically consolidated fibrotic network. The remodeled ECM is not merely a cumulative product of upstream molecular injury but also a dynamic determinant of disease persistence, acting as a pool of mechanical, biochemical and topologic memory in the diabetic myocardium.

Under physiological conditions, a precise balance between ECM synthesis and degradation - fine-tuned by matrix metalloproteinases (MMPs) and their inhibitors - is crucial for maintaining myocardial compliance and microvascular integrity. This balance fails in diabetes. While activated pathways such as TGF-β/Smad, Ang II/Ang II type 1 receptor and Wnt/β-catenin drive fibroblast hyperproliferation and collagen synthesis, concurrent oxidative and glycative stress paradoxically stabilize the ECM by crosslinking proteins, rendering them resistant to proteolytic degradation [36]. This leads to a state of matrix lock-in, characterized by increased deposition of fibrillar collagens (preponderantly types I and III) and fibronectin, coupled with a decline in turnover and remodeling plasticity [37]. Such imbalance promotes fibrosis through two mechanisms: it stiffens the myocardial tissue and sequesters signaling molecules (e.g., latent TGF-β, growth factors) within the matrix. Together, these effects create a feed-forward fibrotic niche that sustains fibroblast activity autonomously.

A defining feature of the Jié phase is the abnormal crosslinking of collagen, both enzymatic and non-enzymatic. Enzymatic crosslinking, mediated by lysyl oxidase, originates as a physiological repair response to microinjury; however, under chronic hyperglycemic and oxidative stress, this mechanism becomes dysregulated and pathological [38]. Simultaneously, non-enzymatic crosslinking by AGEs increases inter-fibrillar crosslinks, impairing their sliding capacity and promoting tissue rigidity [39]. This effect aids in the provision of a stiff, hierarchically stacked ECM that fails to deform within physiologic limits and dissipates contractile energy inefficiently. Mechanotransduction pathways, such as integrin-FAK, YAP/TAZ, and RhoA-ROCK, sense elevated stiffness and reciprocally regulate fibroblast contractility and matrix production [40]. Therefore, the matrix becomes both its own product and propagator, embodying the concept of Jié as a biomechanical self-entrapment within the myocardial interstitium.

The spatial disorganization of the microcirculatory network is also a result of the structural restructuring of the ECM. Capillaries are surrounded by thickened basement membranes, perivascular collagen cuffs, and microfibrillar aggregates, which collectively reduce the luminal diameter and impair endothelial-pericyte communication [41]. This not only slows down oxygen and nutrient diffusion but also creates perfusion heterogeneities in the form of microzones, thereby intensifying local hypoxia and redox stress. On the ultrastructural scale, imaging shows a complex network of collagen bundles and amorphous deposits around degenerated microvessels - morphology remarkably consistent with the micro-nodules mentioned in the Micro Zhēngjiǎ paradigm. The ECM is thus a structural framework that not only underlies microvascular disintegration but also transduces molecular injuries into topological deformations [42].

The acquisition of biochemical inertia is a defining characteristic that distinguishes the Jié phase from earlier stages of fibrogenesis. The high crosslinked and glycated ECM resists proteolytic remodeling. Concurrently, fibroblasts trapped within this rigid scaffold develop a senescence-associated secretory phenotype [43]. This population of senescent fibroblasts releases proinflammatory cytokines, MMP inhibitors, and other fibrotic mediators, which collectively drive the tissue into a state of erratic and exacerbated remodeling. As a result, even after the initial metabolic or inflammatory insults subside, the structural substrate is mechanically and biochemically frozen. This perpetuates diastolic dysfunction and poor compliance - the mechanical phenotype of DCM.

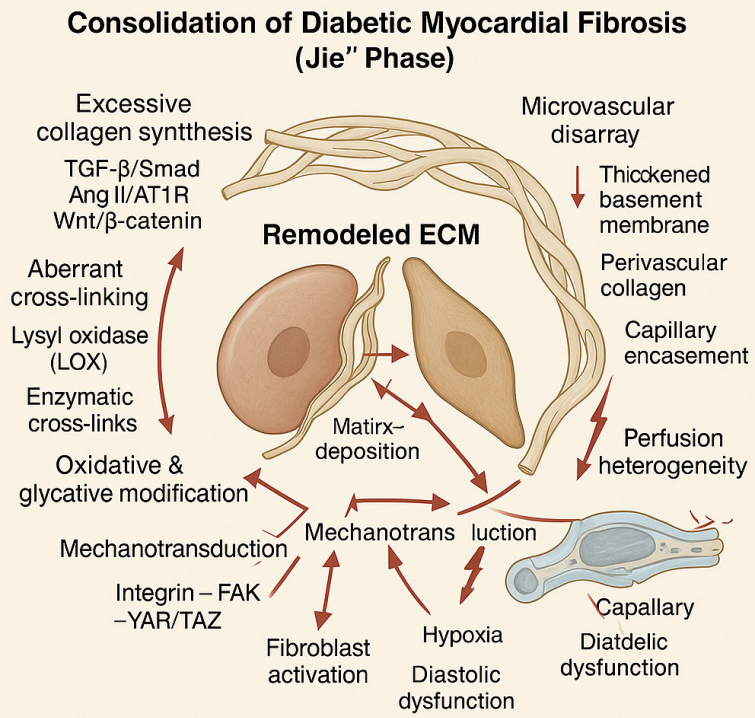

Figure 3. Structural entrapment ("Jié" Phase) in diabetic myocardial fibrosis. This schematic illustrates the consolidation phase of diabetic myocardial fibrosis - termed the "Jié" phase - representing the transition from reversible microdomain remodeling to irreversible structural entrapment. Persistent activation of profibrotic signaling pathways (TGF-β/Smad, Ang II/AT1R, and Wnt/β-catenin) drives excessive collagen I/III and fibronectin synthesis, while oxidative and glycative stress stabilize ECM proteins, reducing their degradation. Aberrant enzymatic (LOX-mediated) and non-enzymatic (AGEs-induced) collagen crosslinking produces a stiff, hierarchically rigid matrix that traps growth factors and reinforces fibroblast activation via integrin-FAK-YAP/TAZ and RhoA/ROCK mechanotransduction. Progressive ECM accumulation thickens basement membranes and encases capillaries, causing microvascular rarefaction, hypoxia, and perfusion heterogeneity. Fibroblasts entrapped within this stiffened scaffold develop a senescence-associated secretory phenotype, perpetuating chronic inflammation and remodeling arrest. Collectively, these biochemical and biomechanical feedback loops entrench the myocardium in a self-sustaining state of fibrosis, converting transient metabolic injury into enduring architectural deformation - the structural signature of diabetic cardiomyopathy. Note: TGF-β/Smad, Transforming Growth Factor-beta/Mothers Against Decapentaplegic homolog; Ang II/AT1R, Angiotensin II/Angiotensin II Type 1 Receptor; Wnt/β-catenin, Wingless-related integration site/Beta-catenin; ECM, Extracellular Matrix; LOX, Lysyl Oxidase; AGE, Advanced Glycation End-product; FAK-YAP/TAZ, Focal Adhesion Kinase - Yes-associated protein/Transcriptional coactivator with PDZ-binding motif; RhoA/ROC, Ras homolog gene family member A/Rho-associated protein kinase.

The Jié stage of the Micro Zhengjiang lesion represents the culmination of diabetic myocardial fibrogenesis - a pathophysiological state characterized by the biophysical codification of prolonged cellular miscommunication. What began as a cluster of metabolic and microvascular injuries evolves into an organized, load-bearing pathology - a material memory of diabetes imprinted within the myocardial ECM [44]. Recognizing the transition from reversible matrix remodeling to irreversible architectural entrapment reframes DMF as a hierarchical systems disorder, sustained by mutually reinforcing biochemical and biomechanical feedback loops (**Figure 3**). This theoretical framework highlights an urgent therapeutic imperative: to intervene before the Jié phase becomes irreversibly established, while microcirculatory function and ECM plasticity remain amenable to antifibrotic modulation. It is upon this mechanical premise that a strategy such as Huoxue-Tongluo therapy becomes viable - a strategy designed not only to suppress fibrosis but also to arouse the latent potential of myocardial tissue for structural and functional self-renewal.

Mechanistic pathways of Huoxue-Tongluo therapy: a multidimensional strategy targeting "Jié" formation

"Huoxue Yiqing" - restoring the metabolic microenvironment to prevent "Jié" formation

As a therapeutic principle, Huoxue Yiqing (invigorating blood and resolving metabolic turbidity) takes up a central mechanistic place in Huoxue-Tongluo therapy. It focuses on the early biochemical derangements that precondition the diabetic myocardium for fibrotic entrapment. Unlike traditional interventions intended to regulate the systemic glucose or lipid levels, Huoxue Yiqing acts locally within the myocardial microenvironment. It neutralizes the redox, energetic, and microvascular disequilibria that constitute the pathological soil for Jié formation. This therapeutic axis aims at

reprogramming the fibrogenic niche by reducing oxidative overload and restoring endothelial-cardiomyocyte coupling - thereby intervening before the microenvironment switches into an irreversible phase of matrix reorganization.

The molecular basis of Huoxue Yiqing involves restoring the redox imbalance underlying early-stage diabetic myocardial injury. Evidence-based experiments shows that components of the canonical formulae - such as *Salvia miltiorrhiza* (Danshen), *Panax notoginseng* (Sanqi), and *Ligusticum chuanxiong* (Chuanxiong) - enhance mitochondrial respiration and reduce superoxide leakage via activation of the AMPK-PGC-1α-NRF2 axis. By re-initiating mitochondrial biogenesis, enhancing mitochondrial antioxidant enzymes (e.g., SOD2, HO-1), and attenuating the AGEs-Receptor for Advanced Glycation End-products interaction, this signaling cascade alleviates the oxidative-glycative burden on cardiomyocytes and fibroblasts [45]. Mitochondrial integrity facilitates ATP production efficiency, thereby mitigating ROS-induced damage while also restoring the mitochondrial function essential for contractile activity [46]. From this perspective, Huoxue Yiqing transforms the oxidative entropy of the metabolic microenvironment into redox homeostasis, thereby arresting the initial biochemical inertia that drives fibrogenesis.

In addition to its role in redox regulation, Huoxue Yiqing controls the use of metabolic substrates, which is typically dysregulated in diabetic hearts. Excessive fatty acid oxidation, mitochondrial overload, and impaired glucose oxidation are characteristic metabolic features of the diabetic myocardium, leading to oxygen wastage and inefficient utilization [47]. Huoxue Yiqing enhances AMPK-dependent metabolic switching to stimulate glucose use and restore fatty acid β-oxidation balance, thereby reinstating the metabolic flexibility necessary for myocardial resilience. Preclinical models also show that this intervention helps improve insulin signaling by promoting Akt-GLUT4 recruitment, resulting in greater substrate uptake and reduced levels of lipotoxic intermediates such as ceramides and diacylglycerols [48]. In turn, Huoxue Yiqing transforms the metabolic landscape of the diabetic heart - characterized by rigidity and overload - into a state of dynamic adaptability. This prevents the bioenergetic collapse that would otherwise trigger ECM remodeling and the subsequent consolidation into Jié.

Huoxue Yiqing is unique in its ability to maintain the structural and functional integrity of the microcirculation - a determinant of diabetic fibrosis that is frequently ignored. By promoting the activity of eNOS and inhibiting endothelin-1 receptors, Huoxue Yiqing restores endothelial-mediated vasodilation and reduces microvascular tone. Simultaneously, its antioxidant and anti-inflammatory effects inhibit endothelial apoptosis, enhance pericyte stability, and improve basement membrane elasticity. All these effects are able to rebuild the endothelial-pericyte interface and enhance capillary perfusion and nutrient supply within susceptible myocardial microdomains. The resultant normalization of local oxygen tension blocks the activation of hypoxia-inducible TGF-β and the transdifferentiation of fibroblasts - an obligatory phase of preventing the establishment of the Micro Zhēngjiǎ lesion.

The inflammatory milieu that underpins fibrogenic propagation is also restructured through the metabolic correction achieved by Huoxue Yiqing. By polarizing macrophages through inhibition of NF-κB and activation of PPARγ signaling, Huoxue Yiqing inhibits proinflammatory cytokines (e.g., TNF-α, IL-1β, CCL2) and stimulates the M2 phenotype [48]. This reconstituted immune profile reprograms paracrine fibroblast activation and restores the natural resolution phase of tissue repair - thereby turning a chronically inflamed interstitium into a regulated remodeling microenvironment. Furthermore, the decrease in local oxidative stress suppresses the activation of NLRP3 inflammasomes, thereby inhibiting the sterile inflammation that would otherwise promote ECM deposition.

Collectively, Huoxue Yiqing is considered a microenvironmental metabolic treatment that intercepts the progression from metabolic disequilibrium to structural fibrosis. By ensuring mitochondrial efficiency, minimizing the oxidative-glycative load, promoting efficient use of substrates, and maintaining microvascular homeostasis, this intervention prevents the biochemical preconditioning that leads to Jié formation. Within the Micro Zhēngjiǎ paradigm, Huoxue Yiqing modulates fibrotic fate by target-

ing its underlying metabolic and microcirculatory determinants. This paradigm shift is exemplified by a convergence of traditional pharmacology and contemporary metabolic cardiology at a mechanistic level, shifting the therapeutic goal from a reactive anti-fibrotic response to preventive microenvironmental reconstitution. This integration forms the conceptual and translational basis of an integrative therapy for diabetic cardiac fibrosis.

"Tongluo Pohuai" - directly targeting the fibrotic core of "Zhēngjiǎ"

When the diabetic myocardium enters the consolidated Jié stage, the fibrotic structure becomes the embodiment and the driver of the pathology. The second strategic axis of Huoxue-Tongluo therapy is embodied in the principle of Tongluo Pohuai (unblocking the collaterals and breaking pathological nodules). Its goal is not merely to stop fibrosis but to actively reverse the entrenched microstructural rigidity of the Micro Zhēngjiǎ lesion. Theoretically, this approach is consistent with the current antifibrotic paradigm, which aims to remodel the ECM, restore mechanosignalling, and recover microcirculatory connections. Tongluo Pohuai operates at three interconnecting levels - cellular, matrix, and vascular - to convert a fixed lesion into a dynamic and repairable tissue network.

The cellular core of the Zhēngjiǎ lesion is the myofibroblast, a persistently activated cell whose survival and contractile activity maintain ECM tension and stiffness. Components of Tongluo Pohuai (especially *Carthamus tinctorius*, Honghua) have been reported to inhibit myofibroblast activation by regulating TGF-β/Smad2-3, ERK1/2, and YAP/TAZ mechanotransductive signaling [49]. Through these pathways, they inhibit β-catenin signaling, induce fibroblast reversion to a quiescent state, and restore ECM susceptibility to regulated degradation through reactivation of MMP-2 and MMP-9. This two-fold process - inhibiting matrix synthesis while restoring physiological remodeling of the fibrotic core - converts lesions from a stiff scaffold into a softer, dynamically regulated microenvironment [50]. Notably, the mechanistic process of lesion softening prevents uncontrolled tissue destruction and, instead, re-establishes the natural homeodynamic balance between matrix production and degradation.

The Tongluo Pohuai principle also targets the biophysical pathology of the ECM, specifically the pathological crosslinking that establishes the Jié state. Preclinical studies have shown that Salvianolic acid B and Tanshinone IIA have the potential to block the activity of lysyl oxidase and can effectively disrupt AGE-mediated non-enzymatic crosslinks, thereby reducing collagen fiber density and stiffness. By breaking down excessive crosslinks, these agents reduce the local Young's modulus and restore viscoelastic compliance to the myocardial interstitium. This mechanical normalization reduces the transmission of aberrant mechanical signals to resident cells, leading to attenuated integrin-FAK-RhoA signaling and decreased fibroblast traction forces [51]. On a biophysical level, Tongluo Pohuai functions as a biomechanical reset. It releases the myocardium from the mechanical memory of chronic metabolic stress and restores synchronized contraction and perfusion at the microvascular level.

A key distinction of Tongluo Pohuai is its capacity to restore microvascular connectivity within fibrotic areas. Angiogenesis and endothelial recovery are promoted by active constituents such as ferulic acid and ligustilide, which stimulate the VEGF/VEGFR2 and PI3K/Akt/eNOS pathways while inhibiting endothelin-1-induced vasoconstriction [52]. Restoring capillary density reverses microregional hypoxia, attenuates HIF-1α-mediated fibrogenic signaling, and improves local nutrient delivery. These microcirculatory benefits further enhance ECM remodeling by improving the diffusion of proteases and the clearance of metabolic waste, thereby closing the vicious cycle between impaired vasculature and pathological structure [53]. Essentially, Tongluo Pohuai transforms the ischemic microdomains that once sustained Zhēngjiǎ persistence into renewed tissue units. This transformation reinstates both quantitative and qualitative perfusion, as well as metabolic flux.

In summary, the Tongluo Pohuai paradigm is an integrated antifibrotic strategy that concurrently employs cellular reprogramming, ECM decrosslinking and defibrillation, and microvascular reconnection to dismantle the physical, biochemical, and vascular architecture of the Zhēngjiǎ lesion. It bridges ancient concepts of collateral unblocking and contemporary molecular cardiology by converting the fibrotic lesion

core into a dynamically remodeling matrix. Within the DMF paradigm, therapeutic success is redefined not as the mere suppression of fibrosis, but as the restoration of structural reversibility - shifting from a state of pathological stasis to one of adaptive remodeling. Consequently, Tongluo Pohuai represents a mechanistically convergent strategy that dismantles the microstructural hierarchy of the "Zhēngjiǎ" lesion, thereby reinstating metabolic fluidity and mechanical coherence within the diabetic heart.

"Tiaoqi Huanjie" - rebuilding intercellular and microvascular communication

Restoring homeostatic crosstalk between cardiac cells and the microvasculature constitutes the top-tier therapeutic objective of the Huoxue-Tongluo model. The principle of Tiaoqi Huanjie (harmonizing Qi and reconnecting interfaces) transcends mere symptomatic antifibrosis; it aims to re-establish integrated multicellular communication across mechanical, metabolic, and vascular signaling axes in the diabetic heart. This process directly aligns with the Micro Zhēngjiǎ paradigm by rewiring disrupted communication loops within cardiomyocyte-endothelial-fibroblast networks and reintegrating capillary-interstitial coupling. Ultimately, it transforms a compartmentalized, fibrotic myocardium into a coordinated and efficiently perfused tissue.

When DCM first appears, the cardiomyocyte-endothelial interface develops decoupling. This manifests as a loss of paracrine coherence, endothelial glycocalyx degradation, and impaired nitric oxide signaling. Tiaoqi Huanjie addresses this loss of contact by enhancing the activity of eNOS and stabilizing vascular endothelial cadherins. This normalizes endothelial permeability and restores the two-way communication of metabolic and mechanical signals [54]. Tanshinone IIA and ferulic acid are bioactive compounds that trigger the PI3K-Akt-eNOS and SIRT1 signaling pathways to enhance endothelial nitric oxide bioavailability and counteract oxidative stress [55]. This subsequent enhancement in endothelial-myocyte crosstalk restores symmetrical oxygen supply and synchronized contractile activity, thereby re-establishing the physiological basis for a functional myocardial syncytium.

The second axis of Tiaoqi Huanjie targets the fibroblast-endothelial- immune triad, a key junction integrating inflammatory, angiogenic, and fibrotic signaling. Chronic inflammation and hypoxia within the diabetic microenvironment drive the polarization of fibroblasts toward a pro-fibrotic, immunostimulatory phenotype. Active ingredients from *Astragalus membranaceus* (Huangqi) and *Paeonia lactiflori* (Baishao) inhibit NF-κB activation and suppress NLRP3 inflammasomes, thereby reducing macrophage secretion of IL-1β and TNF-α [56]. At the same time, they promote macrophage polarization toward an M2 reparative phenotype, which increases the expression of VEGF-A and HGF. These molecular changes are involved in angiogenic remodeling and the recruitment of endothelial progenitor cells, which promotes the repopulation of injured microvessels and the reduces interstitial inflammation [57]. In that way, Tiaoqi Huanjie transforms the pro-inflammatory, fibrotic niche into an immuno-angiogenic regenerative interface.

In addition to vascular repair, Tiaoqi Huanjie restores the electromechanical and metabolic communication between cardiomyocytes - a function often compromised by ECM expansion and gap junction remodeling. Huoxue-Tongluo components preserve connexin-43 phosphorylation and sarcolemmal localization by softening and reducing oxidation of the matrix, thereby restoring intercellular electrical conduction. At the same time, activation of the AMPK-PGC-1α pathway within mitochondrial networks restores metabolic coupling associated with shared energy substrates and redox buffers [58]. These effects reestablish the bioelectrical coherence of the myocardial syncytium, contributing to reduced arrhythmogenicity and enhanced diastolic relaxation.

Tiaoqi Huanjie is a phase of myocardial repair which integrates cellular, structural, and hemodynamic restoration - a true systems-level integration. It essentially restores the myocardial communication network damaged by diabetes through the coordinated modulation of endothelial activity, fibroblast plasticity, immune homeostasis, and metabolic synchrony (**Figure 4**).

From evidence to practice: in-depth analysis of representative Huoxue-Tongluo therapy

Huoxue-Tongluo therapy, rooted in TCM, is becoming popular in the treatment of DMF due to its multifactorial therapeutic approach. The

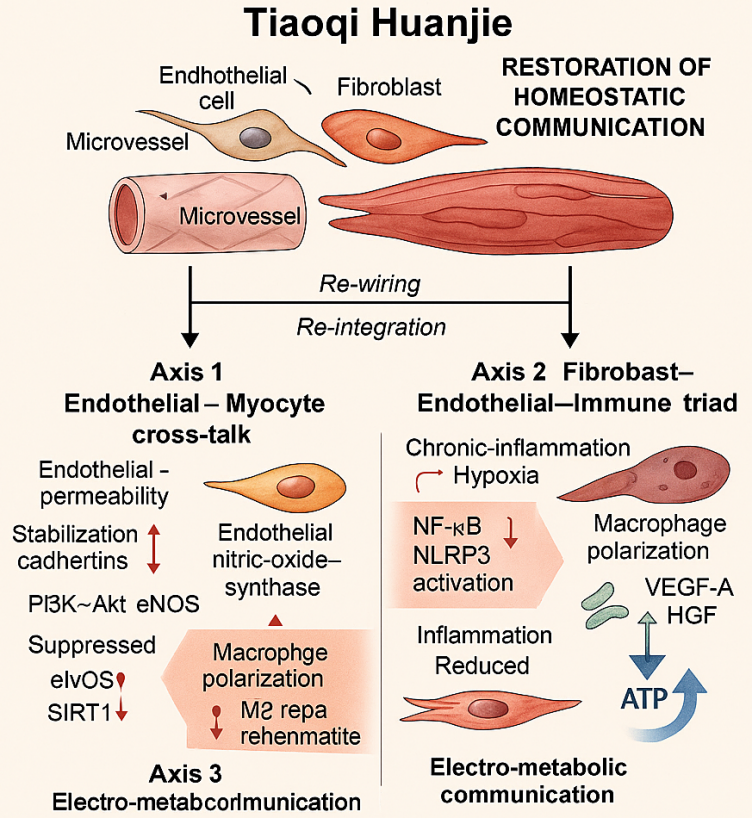

Figure 4. Mechanistic schema of the Tiaoqi Huanjie process within the "micro Zhēngjiǎ" lesion paradigm. This figure illustrates the multi-axis restoration of myocardial homeostasis mediated by Tiaoqi Huanjie therapy in diabetic myocardial fibrosis. The therapeutic process re-establishes communication between endothelial cells, cardiomyocytes, fibroblasts, and immune cells through three integrated axes: (1) Endothelial-myocyte cross-talk, characterized by PI3K-Akt-eNOS and SIRT1 activation, stabilization of vascular cadherins, and normalization of nitric oxide signaling; (2) Fibroblast-endothelial-immune triad, involving NF-κB and NLRP3 suppression, M2 macrophage polarization, and angiogenic remodeling via VEGF-A and HGF; and (3) Electro-metabolic communication, defined by restoration of connexin-43-mediated electrical coupling and AMPK-PGC-1α-driven mitochondrial rejuvenation. Together, these axes converge to rewire intercellular communication circuits, reintegrate microvascular-interstitial coupling, and reconstruct a synchronized, perfused myocardial network - representing the upper echelon of the Huoxue-Tongluo therapeutic framework. Note: PI3K-Akt-eNOS, Phosphoinositide 3-kinase - Protein kinase B - Endothelial nitric oxide synthase; SIRT1, Sirtuin 1; NF-κB, Nuclear Factor Kappa-light-chain-enhancer of Activated B cells; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; VEGF-A, Vascular Endothelial Growth Factor A; HGF, Hepatocyte Growth Factor; AMPK-PGC-1α, AMP-activated Protein Kinase - Peroxisome Proliferator-activated Receptor Gamma Coactivator 1-alpha; ATP, Adenosine Triphosphate.

secret of its success lies in the use of pharmacologically active herbs that target not only fibrotic processes but also the underlying metabolic and vascular dysfunctions inherent to diabetes. *Salvia miltiorrhiza* (Danshen), *Ligusticum chuanxiong* (Chuanxiong), *Paeonia lactiflora* (Baishao), and *Astragalus membranaceus* (Huangqi) are essential medicines for targeting the core pathophysiological characteristics of the disease. The combination of these herbs re-establishes tissue homeostasis, reduces oxidative and inflammatory stress, and promotes microvascular perfusion - collectively reversing the structural and functional decline observed in DCM. Their individual and combined activities should be progressively analyzed, which will give a better picture of their therapeutic potential and mechanisms of action in DMF.

One of the most famous TCM herbs, *Salvia miltiorrhiza* (Danshen), has strong antioxidative and anti-inflammatory activities that effectively counteract the oxidative stress and chronic inflammation in the diabetic myocardium. Tanshinone IIA, an active ingredient of Danshen, activates the NRF2 antioxidant pathway, reducing ROS levels and mitigating oxidative damage to cardiomyocytes and endothelial cells [59]. Moreover, it suppresses the NF-κB pathway and the development of proinflammatory cytokines like TNF-α and IL-1β, which are critical in driving fibrosis. All these measures effectively reduce collagen deposition and regain cardiac metabolic activity, thereby inhibiting the onset and spread of fibrosis [60]. Another herb that is essential in Huoxue-Tongluo therapy is *Ligusticum chuanxiong* (Chuanxiong), whose primary effects include enhancing the perfusion and endothelial activity of microvessels. Ligustilides and other active ingredients enhance the production of nitric oxide, thereby improving endothelial-dependent vasodilation. This is especially helpful in the diabetic heart, where it counter-

acts the microvascular dysfunction that would otherwise promote fibrosis. Chuanxiong preserves capillary integrity and mitigates local hypoxia by enhancing blood flow and reducing endothelial apoptosis, thereby suppressing the hypoxia-initiated fibrotic pathways.

Beyond its vascular effects, *Paeonia lactiflora* (Baishao) appears to play a key role in modulating fibroblast activity and regulating the immune response. Its active constituent, paeoniflorin, has been reported to inhibit TGF-β1 signaling - a key mediator in fibroblast activation and their differentiation into myofibroblasts [61]. By reducing α-SMA production and suppressing collagen synthesis, Baishao inhibits excessive ECM deposition, which would prevent stiffening of the myocardium [62]. Furthermore, Baishao has anti-inflammatory properties by promoting the polarization of macrophages from the pro-inflammatory M1 phenotype to the healing M2 phenotype. This change reduces the chronic inflammatory load which maintains fibrosis, promoting regulated tissue repair instead of uncontrolled scarring. The adaptogenic herb *Astragalus membranaceus* (Huangqi) is useful in mitochondrial activity and cellular energetics, both of which are impaired in the diabetic myocardium. Huangqi promotes the biogenesis of mitochondria, resumes the activities of ATP production, and decreases oxidative stress by activating AMPK and PGC-1α signaling [63]. Also, Huangqi enhances endothelial repair, angiogenesis, and microvascular regeneration, which guarantees that nutrient and oxygen delivery to the heart is in place once again. Such activities not only alleviate ischemic damage but also help reverse the fibrotic changes triggered by cellular maladaptation to metabolic stress.

These four herbs are used as a synergistic approach, targeting various relevant pathways in DMF. The holistic nature of Huoxue-Tongluo therapy is unique in its ability to deal with the metabolic, inflammatory, fibrotic, and vascular aspects of the disease through a coherent therapeutic strategy. Through modulation of the redox environment, enhancement of microvascular perfusion, reprogramming of fibroblast activity, and restoration of mitochondrial function, these herbs can stop or even reverse the pathological fibrosis in DCM. The capability of Huoxue-Tongluo therapy to target multiple disease mechanisms underscores its efficacy as a comprehensive strategy for treating complex cardiovascular diseases especially those associated with diabetes. In addition, these herbs act synergistically, a system-based approach to medicine; this pharmacological synergy has been observed to have a more effective and lasting therapeutic outcomes compared to single-agent modalities. Therefore, Huoxue-Tongluo is a promising integrative strategy for managing DMF, with the potential for broad clinical use.

Challenges and future perspectives: the next step in advancing the paradigm shift

The creation of the Micro Zhēngjiǎ lesion paradigm and the mechanistic explanation of Huoxue-Tongluo treatment should be considered as a significant conceptual shift, as it shifts DMF from a diffuse and irreversible nature into a dynamic and microdomain-oriented pathology. However, a number of scientific and translational issues need to be resolved before this paradigm can be widely introduced into the clinical practice. Currently, the evidence in the field is not spatially resolved and multi-scaled to offer any direct connection between microarchitectural lesions and molecular disturbances in vivo. Although emerging technologies, including high-resolution cardiac imaging, single-cell sequencing, and spatial transcriptomics, have started casting new light on the microstructural grounds of diabetic myocardial injury, their systematic synthesis with longitudinal and interventional studies will be crucial. This integration is necessary to confirm the causal role of Micro Zhēngjiǎ lesions and define their reversible therapeutic characteristics under Huoxue-Tongluo regimes.

The standardization and mechanistic dissection of Huoxue-Tongluo herbal preparations is another important area for future research. Given their multi-component properties, the pharmacokinetics of active constituents, molecular targets, and synergetic interactions still require analysis through systems biology and network pharmacology methods. These will be effective in promoting uniformity of formulation and inter-study reproducibility. Besides, mechanistic studies should extend beyond fibrosis inhibition to include microvascular regeneration, intercellular communication reprogram-

ming, and metabolic rewiring. This synthesis will better align classic herbal ideas with contemporary molecular cardiology across a synthesized spatiotemporal spectrum. Clinically, the next step is to translate this paradigm into precise and evidence-based therapeutic interventions. It will necessitate the creation of quantitative biomarkers - including spatial imaging signatures, microvascular functional indices, and circulating molecular markers - capable of tracking lesion dynamics and therapeutic responses at the microdomain scale. Large-scale, multicenter clinical trials are necessary to test the hypothesis that modulation of Micro Zhēngjiǎ lesions leads to superior improvements in cardiac structure and clinical outcomes compared to traditional global functional measures. Simultaneously, regulatory and quality control procedures should be put in place to ensure the purity, steadiness and standardization of complex herbal preparations before they can be integrated into standard cardiovascular therapeutics.

Lastly, there is potential for synergy between Huoxue-Tongluo therapy and other emerging cardiometabolic approaches like metabolic modulators, mitochondrial protectants, anti-fibrotic agents, or endothelial rejuvenation therapies. Such combinations could concurrently address both systemic metabolic dysregulation and local fibrotic microenvironments. The future evolution of the Micro Zhēngjiǎ paradigm is ultimately dependent on integrating ancient pathophysiological knowledge with the rigor of modern precision medicine. This synthesis is likely to develop a new system with microdomains oriented to prevent and cure DCM.

Limitations and flaws of this study

Although this review provides a new conceptual framework and a comprehensive mechanistic synthesis, several important limitations must be considered. First, the paradigm of the Micro Zhēngjiǎ suggested above is mostly based on indirect evidence - including histopathological observations, spatial omics analyses, and mechanistic suppositions; direct experimental confirmation of microdomain lesion reversibility in the diabetic myocardium remains a significant challenge. Second, despite Huoxue-Tongluo therapy being presented as a mechanistically aligned intervention, the majority of this supporting information stems from preclinical or earlier translation studies. Critical knowledge gaps remain regarding the pharmacokinetic properties, dose-response relationships, and interaction of active compounds in these multi-component formulations. Third, the non-standard form of the herbal preparation, changes in the extraction systems and absence of standardized quality control systems create uncertainties that limit cross-study comparability and may confound the assessment of therapeutic efficacy. Fourth, while the review is based on multi-scale evidence, its scope and conclusions are inherently constrained by the quality and breadth of the available literature. Furthermore, potential publication bias (e.g., unpublished negative results) and inconsistencies across studies may remain undetected. Lastly, as a narrative synthesis rather than a systematic review or meta-analysis, potential selection bias cannot be entirely ruled out. Future experiments employing longitudinal imaging, spatially resolved molecular profiling, and properly designed clinical trials will be necessary to support the microdomain-targeted mechanisms put forward by the paradigm and to establish the therapeutic value of Huoxue-Tongluo in DMF.

Conclusion

In summary, this analysis elucidates the interaction between systems within the Micro Zhēngjiǎ lesion paradigm, revealing a new microstructural and mechanistic model of DMF. Every paradigm mentions the pathological overlap of microvascular rarefaction, ECM remodeling, and microinflammatory niche formation - major factors of fibrotic development during chronic metabolic distress. Integrating cellular, ultrastructural, and imaging evidence, our results define the multifaceted cardioprotective mechanisms of Huoxue-Tongluo therapy: it restores microcirculatory integrity, reprograms fibroblast-endothelial crosstalk, and rebalances the fibrotic microenvironment. These findings not only support the micro-targeting concept underlying the TCM, but also connect it with modern molecular cardiology, providing a therapeutic opportunity for DCM and establishing a robust translational platform. Future research will focus on enhancing this paradigm by means of multimodal omics and advanced

imaging to further identify the spatial and temporal dynamics of Micro Zhēngjiǎ lesion, while confirming the therapeutic impact of Huoxue-Tongluo in large-scale clinical studies.

Disclosure of conflict of interest

None.

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