Diabetology &
Metabolic Syndrome

REVIEW

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The role of myocardial fibrosis in the diabetic cardiomyopathy

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Abstract

Diabetic cardiomyopathy (DCM), a main cardiovascular complication of diabetes mellitus, can eventually develop into heart failure and seriously affect the prognosis of diabetic patients. Myocardial fibrosis (MF) is the main factor causing ventricular wall stiffness and heart failure in DCM. Early control of MF in DCM is of great significance to prevent or postpone the progression of DCM to heart failure. In this review, we systematically analyzed the relevant studies on diabetic MF in recent years, explored the formation mechanism of MF in the pathological process of DCM, and summarized and analyzed in detail the current studies with antifibrotic treatment for DCM, so as to provide guidance for the development of prevention and treatment strategies for MF in DCM.

Keywords Diabetic cardiomyopathy, Myocardial fibrosis, Heart failure, Diabetes mellitus, Cardiovascular complication

Diabetic cardiomyopathy

The global prevalence of diabetes mellitus (DM) has gradually improved in the past three decades and has turn into a major public health problem. Estimates of the global prevalence of diabetes in 2017 indicated that 451 million people aged 18–99 years worldwide have DM, and 693 million people are estimated to suffer from DM by 2045, the majority of whom have type 2 diabetes mellitus (T2DM) [1]. Long term uncontrolled DM will lead to many short-term and long-term complications, including cardiac disease, dyslipidemia, diabetes nephropathy, nerve injury. Among many complications of DM, diabetic cardiomyopathy (DCM) is the leading cause of heart failure (HF), cardiogenic shock and even death in diabetic patients [2]. DCM is a special cardiomyopathy, which was first described in 1972 in patients with diabetes and has a wide range of cardiac structural abnormalities [3]. DCM is defined as diffuse myocardial fibrosis (MF), myocardial hypertrophy and systolic dysfunction in patients with diabetes without valve disease, hypertension or ischemic heart disease [4].

DCM is the main cause of death in patients with DM (both T1DM and T2DM), although its prevalence varies from 20 to 60% in different studies [5]. Therefore, DCM is a harmful and common disease in DM, but it shows reticent development, especially in the early stage. The early stages of DCM include a latent subclinical phase characterized by structural and functional abnormalities, including left ventricular (LV) hypertrophy, MF, and cellular signaling abnormalities. The pathophysiologic changes of MF and the related subclinical diastolic dysfunction often develop into HF with preserved ejection fraction (HFpEF) and eventual progression to HF with reduced ejection fraction (HFrEF) [6]. The development of DCM may be multifactorial, and the main mechanisms include metabolic disorders, MF, microvascular disease, cardiac autonomic dysfunction, and insulin resistance [7].

At present, the number of patients with DCM is still continuously growing worldwide, so preventing and treating DCM is of vital importance for diabetic patients. However, no formal guidelines on DCM have been issued

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or specific therapeutic agents have been approved, and traditional hypoglycemic drugs generally have no effect on cardiovascular mortality in patients with DM, and sometimes even worsen HF [8]. Thus, it is very necessary to study the etiopathogenesis of DCM and seek effective therapeutic drugs.

The role of MF in DCM

Diffuse interstitial or replacement MF is a common feature of various types of cardiomyopathy. MF is associated with worsening ventricular systolic function, abnormal cardiac remodeling, and increased ventricular stiffness. Meanwhile, MF is also a major independent predictor of poor cardiac prognosis. Interstitial reactive fibrosis is diffusively distributed within the interstitium, but can also occur more specifically around blood vessels. This type of fibrosis has progressive episodes that occur with increased collagen synthesis in myofibroblasts under the influence of different stimuli. It is reversible with specific treatment. The replacement or scarring fibrosis is the formation of muscle cells replaced by plexiform fibrosis after cell damage or necrosis, mainly type I collagen. Once the integrity of the muscle cells is affected, replacement fibrosis occurs. Depending on the underlying etiology, there may be local distribution (ischemic cardiomyopathy, myocarditis, hypertrophic cardiomyopathy) or diffuse distribution (chronic renal insufficiency, toxic cardiomyopathy). Interstitial fibrosis eventually leads to replacement fibrosis with cell damage and cardiomyocyte necrosis/apoptosis in the later stages of the disease [9].

Myocardial interstitial and perivascular fibrosis is the major pathological mechanism of DCM, which is characterized by an imbalance in the extracellular matrix (ECM) resulting in excessive collagen accumulation, which alters the structure of the heart and impairs the systolic and diastolic functions, ultimately leading to HF and arrhythmia [10]. For instance, patients with T2DM lacking hypertension or coronary disease have been found to present with extensive MF [11]. Animal studies also support the above clinical findings that MF was dramatically increased in the myocardium of streptozocin (STZ)-induced diabetic rats [12]. MF is also strongly correlated with the high morbidity and mortality associated with DCM. However, there is a lack of specific clinical symptoms in the early stages of DCM, which makes it easy to misdiagnose or miss the diagnosis. Once MF progresses to an advanced stage, it will lead to rapid deterioration of heart function, ultimately leading to HF, at which point the patient's condition is difficult to reverse [13].

The decrease of ECM degrading enzyme matrix metalloproteinase (MMP) activity, accompanied by the increase of tissue metalloproteinase inhibitor (TIMP) activity, is considered to be the mechanism of ECM accumulation in STZ-induced DCM [14, 15]. The proportion of insoluble collagen had significantly increased in patients with non-insulin dependent DM [16]. In the experimental animal model of DM, the protein and gene expression of ECM (especially collagen) in the myocardium were markedly elevated, which was closely related to LV diastolic filling injury [17, 18]. Diabetes-induced MF is often accompanied by upregulation of transforming growth factor-β1 (TGF-β1), TGF-β receptor II, and its downstream mediator connective tissue growth factor (CTGF) [18, 19]. Sustained hyperglycemia stimulation can also result in overactivation of cardiac fibroblasts (CFs) and induce differentiation into myofibroblasts, resulting in myocardial ECM imbalance and MF [20].

CFs are the main effector cells of MF and can promote fibrosis in DCM through proliferation, collagen expression, and differentiation toward a myofibroblast phenotype. Myofibroblasts are the main contributors to ECM accumulation in fibrotic diseases and are mainly derived from resident fibroblasts, epithelial cells and bone marrow-derived cells [21]. In particular, endothelial cells (ECs) are the primary target of hyperglycemia during the pathology of DCM. Persistent endothelial damage during diabetes results in ECs undergoing a process of transdifferentiation from ECs to mesenchymal cells, called endothelial-mesenchymal transition (EndMT), which further transforms their phenotype into myofibroblasts [22, 23]. Notably, chronic hyperglycemia is a major promoter of EndMT, which is thought to be an essential mechanism of MF in DCM [24, 25]. The features of EndMT are loss of intercellular adhesion and alters in cell polarity, accompanied by decreased the expression of endothelial markers, such as vascular endothelial calreticulin and CD31, and increased the expression of mesenchymal markers, such as fibroblast-specific protein-1, α-SMA and vimentin [26]. Thus, early inhibition of MF progression in DM may be of great important in preventing or delaying the progression of DCM to HF.

Previously, the only method that could be used to assess MF was histopathological assessment of endocardial tissue biopsies or postmortem films. In recent years, noninvasive imaging has played a key role in the early identification and quantification of MF. For example, CMR has become a non-invasive imaging method that allows for a comprehensive assessment of myocardial anatomy and function with greater accuracy and reproducibility. The use of gadolinium extracellular contrast agents with CMR using late postgadolinium myocardial enhancement sequences (LGE) have further pushed our ability to accurately and precisely analyze myocardial tissue composition, especially MF content. The emergence of T1 mapping further improves our knowledge and the clinical

assessment of myocardial diffuse fibrosis and further refines the information provided by LGE-CMR [9, 27]. T1 mapping demonstrated a significant increase in myocardial interstitial fibrosis in diabetic patients [28]. In addition, T1 mapping could predict mortality as well as other composite endpoints (death/cardiac transplant/left ventricular assist device implantation) [29] and even ventricular arrhythmias [30].

Mechanism of MF induced by DM

Hyperglycemia is central to the pathogenesis of DCM and to trigger a series of maladaptive stimuli that result in MF and collagen deposition [31]. Therefore, MF is considered to be one of the important incentives for the occurrence and development of DCM, which can increase the incidence of HF and arrhythmia. A large amount of research data shows that many molecular proteins and signaling pathways play important roles in the development of MF in DCM (Fig. 1). These effects may be the result of direct or indirect actions of hyperglycemia [32]. Therefore, a deeper understanding of the molecular pathways involved in the pathogenesis of MF in DCM may provide direction for the development of prevention and treatment strategies for DCM.

Renin angiotensin aldosterone system

In the state of hyperglycemia, the renin angiotensin aldosterone system (RAAS) is significantly activated, and the myocardium and serum angiotensin (Ang) II secretion is increased [33]. Ang II is a multifunctional hormone that promotes the development of MF in diabetes by increasing the expression of several fibrogenic factors in the myocardial interstitium, including TGF-β1, CTGF and collagen, while decreasing collagen degradation [34]. Serum Ang II level is significantly correlated with insulin resistance and postprandial glucose concentration in patients with T2DM [35]. In conclusion, RAAS is activated in DM and promotes Ang II secretion to cause cardiac and vascular fibrosis, as well as increase TGF-β1 expression in cardiomyocytes and CFs to further enhance the pro-fibrotic effect [36]. Early use of angiotensin-converting enzyme inhibitors against MF may be an effective strategy for the treatment of DCM [37].

Ang-converting enzyme 2 (ACE2) is a homologous compound of ACE, which can catalyze the conversion of Ang II to vasodilator heptapeptide Ang-(1–7), which is then converted into an inactive nonpeptide Ang-(1–9), effectively acting as an endogenous ACE inhibitor. ACE2 overexpression reduced the generation of Ang II and the expression of collagen and TGF-β in HG-induced CFs, attenuated cardiomyocyte hypertrophy and myocardial

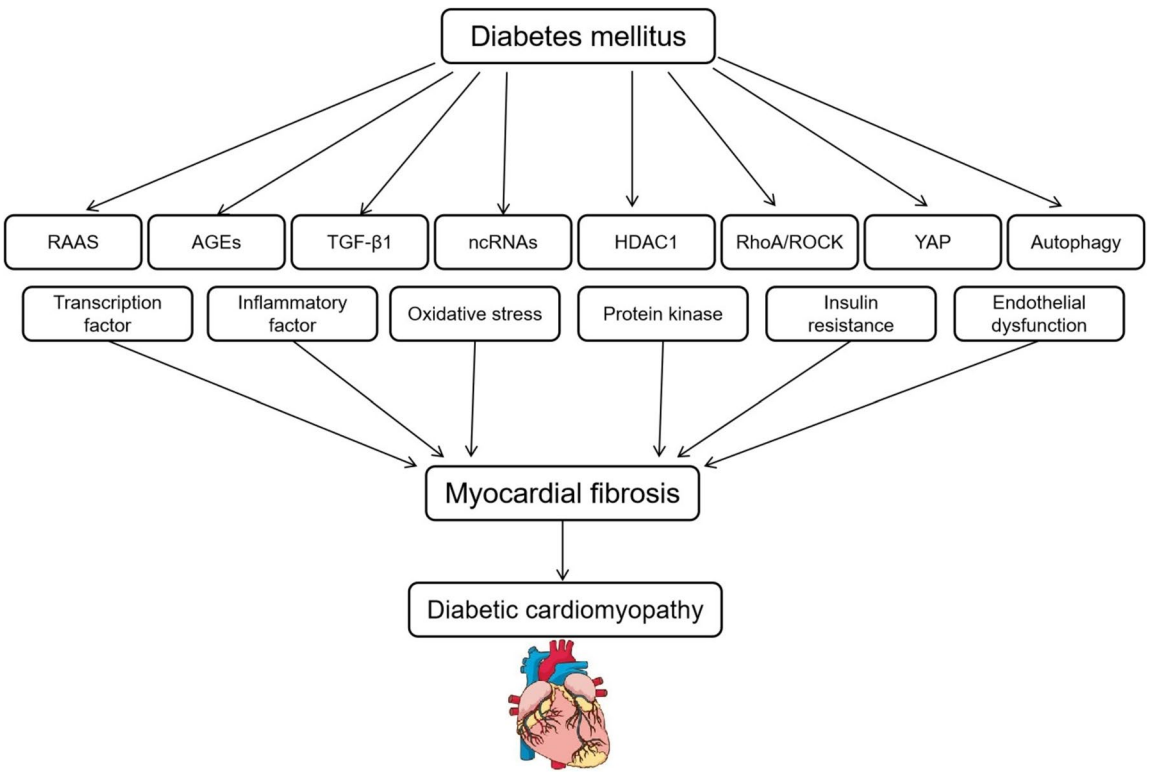

Fig. 1 The molecular mechanism of MF in DCM

collagen deposition, and improved cardiac systolic and diastolic function in DCM rats [38].

The pro(renin) receptor (PRR) is a specific receptor for renin, and binding to renin can increase the catalytic efficiency of converting Ang to Ang I by four times [39]. DM increased the expression of PRR and the nuclear translocation of prolymphocyte zinc finger protein (PLZF) in the myocardium, and PRR could activate PLZF, which exacerbated myocardial inflammation and oxidative stress [40]. In addition, PRR also ameliorated the pathological process of DCM by inhibiting myocardial inflammation and fibrosis through regulating the AMPK/yes-associated protein signaling pathway [41].

Advanced glycosylation end products

There is evidence that non-enzymatic glycosylation of collagen occurs in the myocardial mesenchyme and microvessel wall to forming advanced glycosylation end products (AGEs) in diabetic patients [42], which bind predominantly to the receptor for AGEs (RAGE) to induce CFs proliferation [43]. Long term hyperglycaemia induces this process continuously, which in turn promotes the secretion of several cytokines and growth factors, such as CTGF and TGF-β [44]. The excessive release of CTGF in long-term diabetes causes overexpression of ECM components and promotes interstitial fibrosis, leading to abnormal cardiac function [45]. AGEs combine with RAGE to further promote ventricular remodeling and impair myocardial energy metabolism [46]. For example, the binding of AGEs to RAGE on the surface of cardiomyocytes could induce myocardial inflammatory responses and increase the production of matrix proteins and connective tissue by activating Janus kinase (JAK) and MAPK pathways [46].

TGF-β1

TGF-β1 is currently considered to be one of the most important molecular mediators promoting the development of MF in DCM. Under continuous HG stimulation, the level of TGF-β1 in myocardial cells significantly increases, which can induce a large amount of collagen synthesis and promote the proliferation and transformation of CFs [47]. In addition, hyperinsulinemia and insulin resistance can also promote TGF-β1 secretion and activation of downstream Smad signaling, which increase MF [48].

Three types of TGF-β receptors (TβRs) are distributed in mammalian cells: TβR-I, TβR-II and TβR-III [49]. Upon binding of TGF-β1 to its receptor, intracellular Smad2 and Smad3 are phosphorylated, which then binds to Smad4 to form a complex and translocate to the nucleus to regulate the expression of many fibrosis-related downstream target genes, including collagen I/III and α-SMA, whereas Smad7 inhibits the phosphorylation of Smad2/3 [50]. Under the positive feedback mechanism, the protein complex acts on the promoter region of the TGF-β1 gene, promoting its expression and TGF-β1 autocrine signaling transduction. Moreover, TGF-β1 amplifies the TGF-β1/Smad2/3 signaling pathway via increasing the expression of the TβR-I and TβR-II genes and exerts a positive feedback effect [51, 52]. Furthermore, TGF-β1 can also enhance the pro-fibrotic effects of Ang II [53, 54]. Suppression of the TGF-β/Smad signaling pathway can attenuate collagen synthesis, CFs proliferation and transformation, ultimately inhibits MF [55]. Drugs commonly used in diabetes patients, such as pioglitazone [56] and aspirin [57], have good inhibitory effects on TGF-β1.

Transcription factor

NF-κB is a key transcription factors regulating pro-inflammatory cytokines, pro-fibrotic gene expression and cell survival involved in mitochondrial and cardiac dysfunction in the mice of T2DM [58]. In diabetes, AGEs, reactive oxygen species (ROS) and activated RAAS can directly induce NF-κB activation, which promotes abnormal immune responses and the secretion of pro-inflammatory cytokines, such as tumor necrosis factor α (TNF-α), monocyte chemotactic protein 1 (MCP-1), interleukins (IL) 6/8, thereby inducing the development of DCM [46]. Activated NF-κB in the heart of diabetic mice has been proved to be correlated with increased NADPH oxidase (NOX)-mediated production of ROS, peroxynitrite and superoxide. Inhibition of NF-κB can maintain the integrity of mitochondrial structure, reduce excessive oxidative stress, increase ATP synthesis and NO bioavailability, thereby restoring heart function in T2DM [59]. Toll-like receptors (TLRs) have IL-1 receptor-like intracellular signaling pathways leading to nuclear localization of NF-κB transcription factor [60]. TLR2 can interact with TLR6 to regulate inflammatory genes through ROS downstream signaling via IKKs and oxidative stress [61, 62]. TLR6 deficiency inhibited pro-inflammatory cytokine release and expression of α-SMA, TGF-β1, and collagen I/III in high fructose-fed mice by suppressing ROS production and NF-κB phosphorylation [63].

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated nuclear transcription factors that play significant roles in maintaining glucose and lipid homeostasis. Treatment with rosiglitazone, a PPARγ agonist, could consistently attenuate the expression of pro-inflammatory cytokines and collagen in T2DM rats [64]. Moreover, PPARγ agonist could attenuate MF, and improve cardiac function, as well as inhibit CFs proliferation and reduce cardiomyocyte apoptosis. The

mechanism of PPARγ inhibiting MF in DCM mice is achieved by regulating TGF-β/ERK pathway and decreasing EndMT [65].

Myocyte enhancer factor 2 (MEF2) is the second kind of transcriptional factors that control the expression of numerous muscle-specific, growth factor-induced and stress-induced genes [66]. MEF2A is a crucial nuclear mediator in hypertrophic cardiomyopathy, which may be involved in pathological remodeling and the formation of focal fibrosis [67]. The expression of MEF2A was markedly upregulated in T1DM mice, and inhibition of EC-derived MEF2A could suppress diabetes-induced MF and improve cardiac function by partially inhibiting EndMT. The mechanism was related to the translocation of MEF2A to the cytoplasm and its interaction with p38 MAPK and Smad2 [68].

Inflammatory factor

A large number of studies have shown that inflammation is also a major factor in inducing DCM and is notably increased in diabetic patients and animal models. Meanwhile, the myocardium of patients with DCM is rich in inflammatory cells and pro-inflammatory factors [6, 69, 70]. Low-grade inflammation of the heart in DM has been proven to be critical to the development of heart disease, and many inflammatory molecules are involved in the development of DCM, so inflammation is a causative factor in DCM [71]. Activation and expression of pro-inflammatory cytokines such as TNF-α, IL6/8, MCP-1, intercellular adhesion molecule 1 and vascular cell adhesion molecule 1 all involved in oxidative stress, ventricular remodeling and MF [46]. HG-induced inflammation and oxidative stress can cause a large number of transcriptional changes in cells, leading to increased expression of cytokines. In DCM, these cytokines induce inflammatory cell infiltration into the myocardium, where they promote the secretion of inflammatory cytokines through activation of the ERK2/3 pathway [72, 73]. Inflammasome activation can accelerate the process of myocardial inflammation, cardiomyocyte apoptosis and MF, leading to changes in the structure and function of the heart in DCM [74]. Myocardial inflammation caused by HG and metabolic stress molecules such as Ang II, AGEs and ROS can ultimately promote the progression of MF [75, 76].

As a major signal of the inflammatory response, NF-κB plays a crucial role in the regulation of MF, which increases TGF-β1 transcription and activates TGF-β1/Smad signaling [77]. IL-6 is one of the cytokines closely associated with MF. The expression of IL-6 was markedly elevated in both serum and myocardium of diabetic mice, whereas knockdown of IL-6 attenuated MF and improved cardiac function by regulating TGF-β1 and miR-29 pathways in STZ-induced diabetic mice [78]. IL-17 is also an important regulator of MF, which could stimulate the proliferation and migration of CFs by inhibiting the dual-specificity phosphatase MKP-1 [79]. Moreover, IL-17 promoted myofibroblast differentiation by increasing IL-6 expression in CFs [80]. Knockdown of IL-17 could improve cardiac function and significantly reduce collagen expression and deposition in STZ-induced diabetic mice and HG-induced CFs via suppressing the lncRNA-AK081284/TGFβ1 signaling pathway [81]. The NOD-like receptor 3 (NLRP3)/IL-1β pathway is upstream of the TGF-β/Smad pathway, and blockade of the NLRP3 pathway can attenuate MF [82, 83]. Fibrocytes are blood-derived monocyte lineage cells that differentiate fibroblasts into myofibroblasts by secreting increased ECM proteins in response to chronic injury/inflammation [84, 85]. T lymphocyte is widespread in STZ-induced DCM myocardium, which can activate profibrotic cells and participate in the pathological process of MF by secreting pro-inflammatory cytokines [86, 87]. Cardiac tissues include many resident macrophages. In HG conditions, macrophages can upregulate glucose uptake and utilization and enhance the production of inflammatory cytokines, such as TGF-β1 and TNF-α, which act on macrophages and promote the activation of inflammatory phenotype M1, and thereby stimulate MF [88].

High-mobility group box 1 (HMGB1), a nuclear protein widely present in almost all eukaryotic cells, is an essential mediator of the inflammatory response [89]. HMGB1 was significantly up-regulated in myocardium of T1DM mice, and knockdown of HMGB1 could ameliorate LV dysfunction and remodeling and reduce collagen accumulation. At the same time, HG induced translocation and secretion of HMGB1, and inhibition of HMGB1 decreased collagen expression, MMP activity and MAPKs signaling activation in HG-induced CFs [90]. RAGE was a major HMGB1 receptor mediating the inflammatory response of cardiomyocytes, and the HMGB-RAGE interaction activated MAPK signaling, which subsequently produced multiple inflammatory or pro-fibrotic factors [91]. Thus, the HG-HMGB1-MAPK pathway may be a vital mechanism of cardiac remodeling and MF in DCM, and silencing HMGB1 may be an effective means to ameliorate the pathological process of DCM.

Oxidative stress

Under normal physiological conditions, the heart exhibits significant metabolic substrate flexibility, utilizing energy from various substrates such as free fatty acids, glucose, ketone bodies, lactate, and some amino acids to produce ATP, which is the main source of energy for the heart [46]. Usually, mitochondrial oxidative phosphorylation

produces over 95% ATP [92]. However, in cases of hyperglycemia, insulin resistance, and hypertriglyceridemia, the ability of the myocardium to utilize glucose as an energy source decreases, and subsequently switches to using free fatty acids [93]. This energy substrate conversion is accompanied by oxidative phosphorylation damage and mitochondrial proton leakage, leading to an increase in ROS production. Due to the limited antioxidant capacity of the heart, the increase in mitochondrial ROS production leads to the destruction of NO and a decrease in bioavailable NO. Therefore, oxidative stress plays a crucial role in the pathological process of DCM.

In the pathological process of DCM, antioxidant factors such as superoxide dismutase (SOD) and glutathione peroxidase are significantly decreased, whereas ROS production is increased in myocardial tissues, leading to excessive oxidative stress in cardiomyocytes [94, 95]. Prolonged hyperglycaemic stimulation leads to impaired mitochondrial oxidative phosphorylation and excessive ROS production in the myocardium, thereby exacerbating oxidative stress, aggravating mitochondrial dysfunction, and accelerating the progression of MF and inflammation [95, 96]. ROS overproduction also can induce the activation and transfer of NF-κB into the nucleus, which in turn promotes TGF-β1 expression and significantly upregulates collagen and fibronectin expression, leading to excessive collagen deposition [97, 98]. AGEs not only damage cardiomyocytes directly, but also increase oxidative stress by promoting the production of ROS [6]. The NOX family is the main source of excessive ROS production in the cardiovascular system. Previous studies have shown that inhibition of NOX2 could attenuate hyperglycaemia-induced oxidative stress and attenuate the pathological process of DCM [99, 100]. In addition, knockdown of NOX4 could attenuate MF, oxidative stress, and improve ventricular remodeling by inhibiting Akt/mTOR and NF-κB pathways [101]. NOX1 induced MF and deterioration of cardiac function in DCM by activating the TLR2/NF-κB pathway and increasing ROS accumulation [102].

The Ras protein-specific guanine nucleotide releasing factor 1 (RasGRF1) is a family of Ras-selective guanyl exchange factors that can regulate the activation of oxidative stress and inflammation by regulating Ras family proteins [103]. RasGRF1 expression was upregulated in CFs, and knockdown of RasGRF1 reduced serum IL-6 levels, attenuated the fibronectin deposition and oxidative stress, and improved the diastolic function of heart in STZ-induced DCM in mice [104].

Aldose reductase (AR) was overexpressed in hyperglycemia, which decreased ATP production and elevated oxidative stress by increasing ROS in diabetic animals. The novel AR inhibitor AT-001 could inhibit the pathological process of DCM by improving cardiac diastolic function, increasing myocardial energy efficiency, and reducing MF and hypertrophy in animal models [105].

Autophagy

Autophagy is an overall degradation mechanism dependent on lysosomes, which is crucial for the degradation and recycling of misfolded or aggregated proteins and damaged organelles within cells to restore cellular homeostasis [106]. Increasing evidence suggested that defective autophagy significantly contributed to the progression of MF and HF, and exacerbated cardiac dysfunction in a variety of cardiomyopathies [107, 108]. Autophagy can reduce the excessive deposition of myocardial ECM, and activation of autophagy can suppress the TGF-β signaling pathway to attenuate MF [109, 110]. For example, mice lacking the autophagy protein Beclin1 could induce TGF-β1 expression in myofibroblasts and promote elevated collagen I levels [111].

Non-coding RNAs

In recent years, a large amount of evidence has shown that non-coding RNAs (ncRNAs) play a crucial role in the molecular mechanism of DCM. NcRNAs are a class of RNAs that have no function of coding proteins, mainly including microRNAs (miRNAs), long ncRNAs (lncRNAs), circular RNAs (circRNAs), etc.

Among them, miRNAs are a type of non-coding single stranded RNA with a length of approximately 19–22 nucleotides, which affect mRNA translation or degradation by binding to the 3′-UTR of the target mRNA [112]. Researches have shown that miRNAs can participate in various pathophysiological processes, including cell proliferation, differentiation and apoptosis, as well as glucolipid metabolism and insulin secretion [113, 114]. There is evidence that miRNAs can regulate pathological and physiological changes related to DCM, including MF, oxidative stress and apoptosis [115]. For example, the expression of miR-30d was significantly up-regulated in STZ-induced diabetic rat models [116]. In the myocardium of STZ-induced diabetic mice, the level of miR-133a was down-regulated, the expression of fibrosis markers (TGF-β1, CTGF, fibronectin and collagen4A1) and focal MF were increased, while overexpression of miR-133a could significantly alleviate MF by blocking ERK1/2 and Smad2 phosphorylation [117]. miR-21 expression was significantly upregulated in HG-induced CFs. Overexpression of miR-21 was able to promote proliferation and collagen synthesis in HG-induced CFs through the JNK/stress-activated kinase and p38 MAPK signaling by inhibiting the expression of dual specific phosphatase 8 [118]. Downregulation of miR-15a/b in T2DM patients

and mice myocardium could activate fibrotic signaling by TβR-I and CTGF [119]. miR-200b could mediate EndMT in diabetic mice and lead to increased MF in DCM [25]. Overexpression of miR-203 targeting PIK3CA repressed the PI3K/Akt pathway and decreased oxidative stress and cardiomyocyte apoptosis, thereby attenuating MF in DCM mice [120]. Downregulation of miR-223 could inactivate NLRP3 inflammasome and attenuate MF and apoptosis in DCM rats [121]. miR-142-3p was significantly down-regulated in human aortic ECs (HAECs) in a dose- and time-dependent manner in response to HG stimulation. Overexpression of miR-142-3p was able to diminish HG-induced EndMT in HAECs by blocking the TGF-β1 pathway [122]. The expression of miR-195-5p was increased in the myocardium of DCM rats, and down-regulation of miR-195-5p could improve cardiac dysfunction and suppress the expression of fibrosis markers, collagen deposition and EndMT by targeting Smad7 [123]. miR-18a-5p was decreased in HG-induced HAVECs, and overexpression of miR-18a-5p could suppresse EndMT of HAVECs by down-regulating Notch2, thereby reducing HG-induced MF [124]. The level of miR-34a was significantly reduced in ventricular tissues of DCM mice and HG-induced CFs. Overexpression of miR-34a could decrease MF in DCM by inhibiting collagen I production, cell viability and migration, and increasing apoptosis in CFs via targeting the Pin-1 pathway [125].

LncRNAs are a type of transcript with a length of over 200 nucleotides but no protein-coding ability, participated in many biological processes, including genomic imprinting, transcriptional regulation, RNA splicing and nuclear-cytoplasmic trafficking [126–128]. There has been increasing evidence that lncRNAs are involved in the pathogenesis of a variety of cardiovascular diseases, including DCM [129]. For example, the level of lncRNA AK081284 was obviously elevated in HG-treated CFs, and overexpression of AK081284 promoted the production of collagen and TGF-β1 [81]. LncRNA ANRIL was able to modulate structural and functional abnormalities in the heart of STZ-induced DM by controlling the expression of ECM proteins and VEGF [130]. LncRNA GAS5 was markedly upregulated in DCM, whereas knockdown of lncRNA GAS5 effectively improved cardiac function, attenuated MF and HG-induced cardiomyocyte apoptosis by negatively modulating miR-26a/b-5p [131]. The expression of lncRNA Kcnqot1 was markedly upregulated both in the serum of diabetic patients and HG-induced CFs. Silencing Kcnq1ot1 could alleviate cardiac dysfunction and attenuate MF in STZ-induced C57BL/6 mice, and suppress inflammation and pyroptosis in HG-treated CFs via regulating miR-214-3p/caspase-1/TGF β1 pathway [132]. In DCM mice model, the expression of lncRNA TUG1 and Cfl2 significantly increased, while the expression of miR-145a-5p decreased. Silencing lncRNA TUG1 could improve cardiac function and MF by regulating the miR-145a-5p/Cfl2 pathway in DCM mice [133].

CircRNAs can control target genes by adsorption of miRNAs as sponges and modulate the splicing and stability of mRNAs through interactions with RNA-binding proteins [134]. The level of circRNA_000203 was increased in the myocardium of diabetic db/db mice and Ang II-treated CFs. Overexpression of circRNA_000203 could increase the expression of Col1a2, Col3a1 and α-SMA in CFs. Mechanistically, circRNA_000203 was able to specifically sponge miR-26b-5p that post-transcriptionally inhibited expressions of Col1a2, CTGF, Col3a1 and α-SMA in CFs. Thus, upregulation of circRNA_000203 was able to antagonize the antifibrotic effect of miR-26b-5p in CFs [135]. Similarly, circRNA_010567 was obviously upregulated in diabetic db/db mice myocardium and Ang II-induced CFs. CircRNA_010567 could promote MF via inhibiting miR-141 by targeting TGF-β1 in diabetic mice [136]. The level of the circRNA HIPK3 was markedly upregulated in the DCM mice model. Knockdown of circHIPK3 could attenuate MF and improve cardiac function in DCM mice and inhibit proliferation of Ang II-treated CFs by functioning as a competing endogenous RNA of miR-29b-3p to inhibit the expression of Col1a1 and Col3a1 [137].

Protein kinase

Persistent hyperglycemia can induce activation of mitogen-activated protein kinases (MAPKs), which are involved in the pathological process of DCM [138]. Extracellular signal regulated protein kinase 1/2 (ERK1/2), p38 MAPK and JNK are three major MAPKs subfamilies that regulate ventricular hypertrophy and remodeling [46]. Both ERK1/2 and p38 MAPK could mediate intracellular signaling and regulate the expression of procollagen in CFs, which participated in the occurrence of MF [139]. Oxidative stress and inflammatory cytokines can activate JNK that contributes to oxidative stress, ERS and MF in the heart of DM. In contrast, inhibition of JNK phosphorylation by the curcumin analogue C66 could suppress the pathological process of DCM [140]. More importantly, inhibition of JNK and p38 MAPK signaling could alleviate the pathological process of DM-related MF in rats [141].

Hyperglycemia can activate protein kinase C (PKC), which induces changes in several downstream factors associated with DCM, such as TGF-β, CTGF [142, 143], MAPKs [144], TNF-α and NF-κB [145, 146] and NOX [147]. Overexpression of PKCβ2 in cardiomyocytes could lead to significant myocardial hypertrophy, myocardial necrosis, MF, and cardiac dysfunction, accompanied by

upregulation of TGF-β1, β-myosin heavy chain and collagen gene expression [148]. However, PKCβ inhibitors could maintain LV diastolic function, alleviate cardiomyocyte hypertrophy and LV collagen deposition in DCM rats [149].

Insulin resistance

Insulin resistance is closely related to the pathological process of MF in DCM, in which many molecules play important roles. Prostaglandin F2α-F-prostanoid (FP)-receptors are strongly related to insulin resistance, which play a vital role in the pathogenesis of DCM. Silencing of FP-receptors could reduce cholesterol, triglyceride and glucose levels, improve insulin resistance, and significantly decrease collagen expression in DCM rats. Furthermore, the activated PKC and Rho kinase were obviously reduced, and the blunted Akt phosphorylation was restored by FP-receptor gene silencing. Thus, knockdown of the FP receptor might exert a protective effect against DCM by modulating the activity of the PKC/Rho and Akt pathways and ameliorating the MF and insulin resistance states [150].

Six transmembrane protein of prostate 2 (STAMP2) could dramatically ameliorate insulin resistance in many cellular and animal models. For example, STAMP2 silencing exhibited marked inflammation, spontaneous insulin resistance, glucose intolerance, mild hyperglycaemia and dyslipidaemia in mice [151], whereas overexpression of STAMP2 in diabetic mice decreased pro-inflammatory cytokine levels and ameliorated insulin resistance via suppressing JNK phosphorylation [152]. What is more, the level of STAMP2 was decreased in the myocardium of T2DM rats, and STAMP2 overexpression improved glucose tolerance and insulin sensitivity and attenuated cardiac dysfunction and MF. Mechanistically, STAMP2 attenuated cardiac dysfunction and MF in DCM by promoting the translocation of NMRAL1 from cytoplasm to nucleus and inhibiting the phosphorylation of NF-κB p65 [153].

Soluble Klotho (sKL) is closely associated with insulin resistance, and sKL levels are reduced in plasma of insulin resistant patients [154]. Similarly, sKL expression and collagen deposition were significantly reduced in HG-treated CFs and STZ-induced diabetic mice. sKL overexpression could attenuate insulin resistance and metabolic disorders, decrease myocardial hypertrophy, MF and inflammation, and improve cardiac dysfunction. In addition, decreased sKL combining integrin β1 suppressed the Akt pathway and activated the ERK1/2 pathway, which induced selective insulin resistance, and resulted in MF in an insulin-resistant state. Thus, sKL is a potential target for improving DCM primarily via the ERK1/2 pathway through attaching to integrin β1 [155].

Endothelial dysfunction

ECs are the main target of hyperglycemia, and endothelial dysfunction is an important cause of MF in DCM. Dimethylarginine dimethylaminohydrolase 2 (DDAH2) is an enzyme which can metabolize competitive endogenous inhibitors of nitric oxide synthase (NOS) [156]. The level of DDAH2 was related to endothelial dysfunction in diabetic rats and cellular injury in the HG environment [157, 158]. Overexpression of DDAH2 could inhibit MF and improve cardiac function in DCM rats via activating the DDAH/ADMA/NOS/NO pathway [159].

Studies have shown that persistently high plasma endothelin-1 level is related to the progression of MF and diastolic dysfunction in diabetic patients. Specific knockdown of endothelin-1 in ECs could attenuate DM-induced MF and prevent the progression of DCM via inhibiting EndMT [24]. In addition, the overexpression of endothelin-1 was associated with the increase of myocardial focal fibrous scar in diabetes rats, and bosentan (an endothelin-1 inhibitor) was able to completely block the fibrotic process. This suggests that hyperglycaemia-induced activation of the endothelin system plays a vital role in the pathological process of MF in DCM [160].

The tissue kallikrein-related peptidase (KLK) family is a group of secreted serine proteases. The level of KLK8 was obviously upregulated in the myocardium of STZ-induced diabetic mice. Overexpression of KLK8 lead to myocardial interstitial and perivascular fibrosis, endothelial damage and EndMT in diabetic mice. However, KLK8 knockdown attenuated MF, improved impaired cardiac function, and inhibited HG-induced endothelial damage and EndMT. Mechanistically, HG might promote plakoglobin-dependent cooperation of p53 with HIF-1α and Smad3, which in turn increase the expression of pro-EndMT target genes in a KLK8-dependent manner [161].

Histone deacetylase 1

The histone deacetylases (HDACs) are a family of enzymes that catalyse lysine deacetylation of both histone and non-histone proteins. HDAC1 expression was up-regulated and bone morphogenetic protein 7 (BMP-7) expression was down-regulated in DCM mice and HG-treated CFs. HDAC1 could inhibit BMP-7 transcription by deacetylation. Knockdown of HDAC1 could inhibit the proliferation of CFs and reduce the levels of collagen, α-SMA and vimentin. However, inhibition of histone acetylation levels or downregulation of BMP-7 reversed the effects of HDAC1 silencing on the fibrotic response of CFs. Thus, HDAC1 suppressed BMP-7 transcription via enhancing histone deacetylation, thereby promoting the pathological process of MF in DCM [162].

RhoA/Rho-kinases

RhoA is a member of the Ras superfamily of GTP conjugated proteins. Its downstream effector, Rho-kinases (ROCK), regulates multiple biological functions within cells, such as cell adhesion, migration, proliferation, and apoptosis [163]. Inhibition of ROCK could attenuate Ang II-induced MF in ApoE$^{-/-}$ mice [164]. More importantly, HG could promote the proliferation of CFs and the expression of type I procollagen and ROCK1 in CFs. Y27632 is a depressant of the RhoA/ROCK pathway, which could significantly repress the expression of HG-induced ROCK1 and type I procollagen. This suggests that HG activated the RhoA/ROCK pathway, which in turn promoted the secretion of type I procollagen in CFs [165].

Yes-associated protein

Yes-associated protein (YAP) is a major effector molecule of the Hippo pathway. The expression of YAP was obviously upregulated in HG-induced CFs and DCM rats. Inhibition of YAP could improve cardiac function and decrease the expression of CTGF, fibronectin, profilin-1, and plasminogen activator inhibitor-1 in DCM rats. In addition, YAP activated CTGF by interacting with TEADs in CFs. These results suggest that YAP played a crucial role in the pathological process of DCM, possibly by regulating the TEAD/CTGF pathway [166].

Treatment of MF in DCM

Although DCM has a severely adverse prognosis, no formal guidelines have been issued and there are no specific treatments [167]. Numerous studies have shown that MF is a significant pathological process of DCM, and inhibition of MF is regarded as an effective means to prevent and treat DCM (Figs. 2, 3, 4).

1-Deoxynojirimycin

1-Deoxynojirimycin (1-DNJ), a piperine alkaloid extracted from Bombyx Batryticatus, significantly downregulated myocardium protein N-glycosylation in db/db mice. It also reduced the expression of serum indicators and fibrosis-associated cytokines in a dose-dependent manner. The alleviation of DCM-associated fibrosis by 1-DNJ was associated with the suppression of N-acetylglucosamine formation and the reduction of substrate concentration [168].

Adiponectin

The adiponectin (APN) secreted by adipocytes possesses anti-insulin resistance and anti-inflammatory properties [169]. Bone marrow mesenchymal stem cells (BMSCs) are a type of multipotential stem cells that exert protective effects through paracrine-associated factors and immunomodulation of host cells [170]. BMSCs could improve cardiac function in patients with DCM [171].

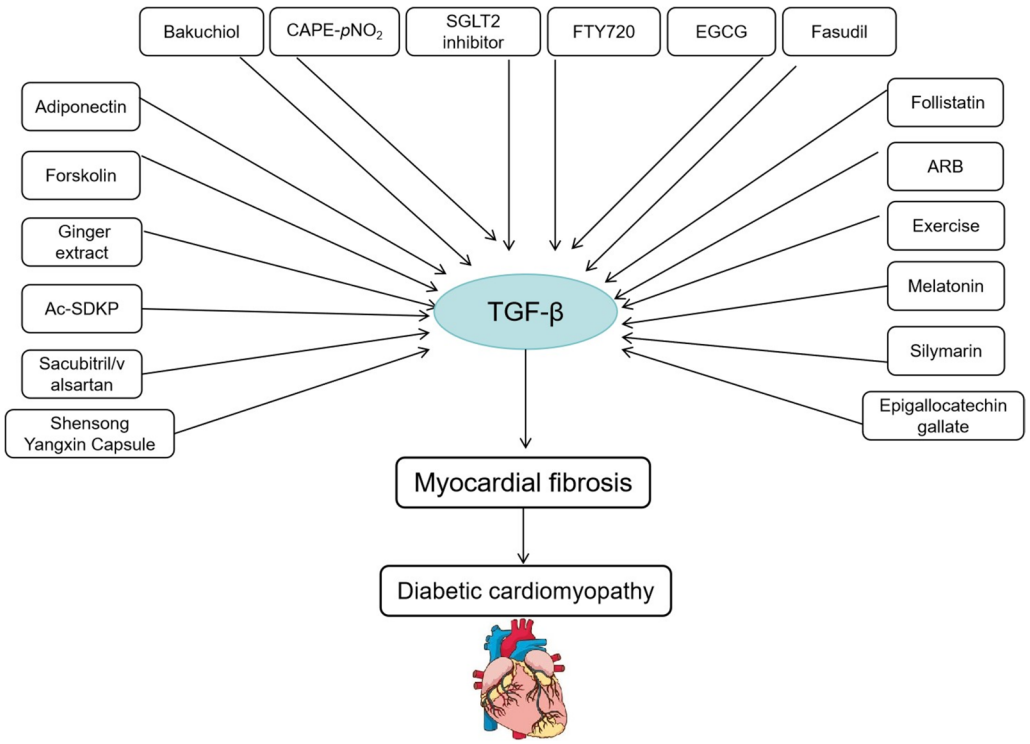

Fig. 2 Drugs for the prevention and treatment of DCM by regulating TGF-β signaling pathway to inhibit MF

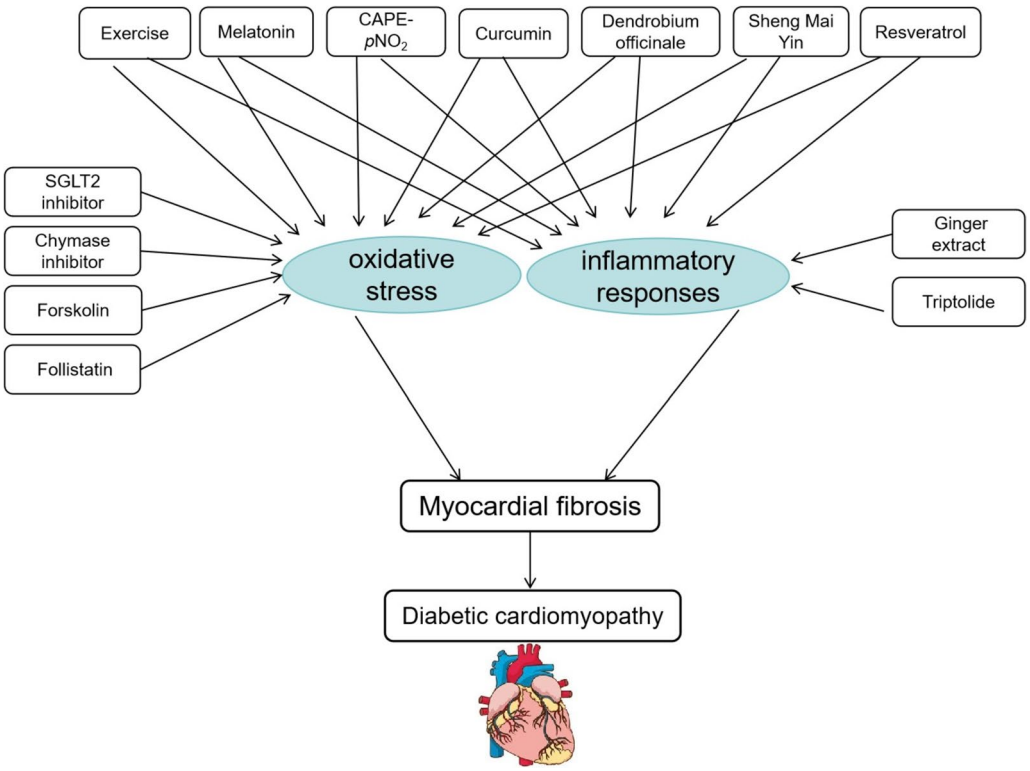

Fig. 3 Drugs for the prevention and treatment of DCM by regulating oxidative stress and inflammatory responses to inhibit MF

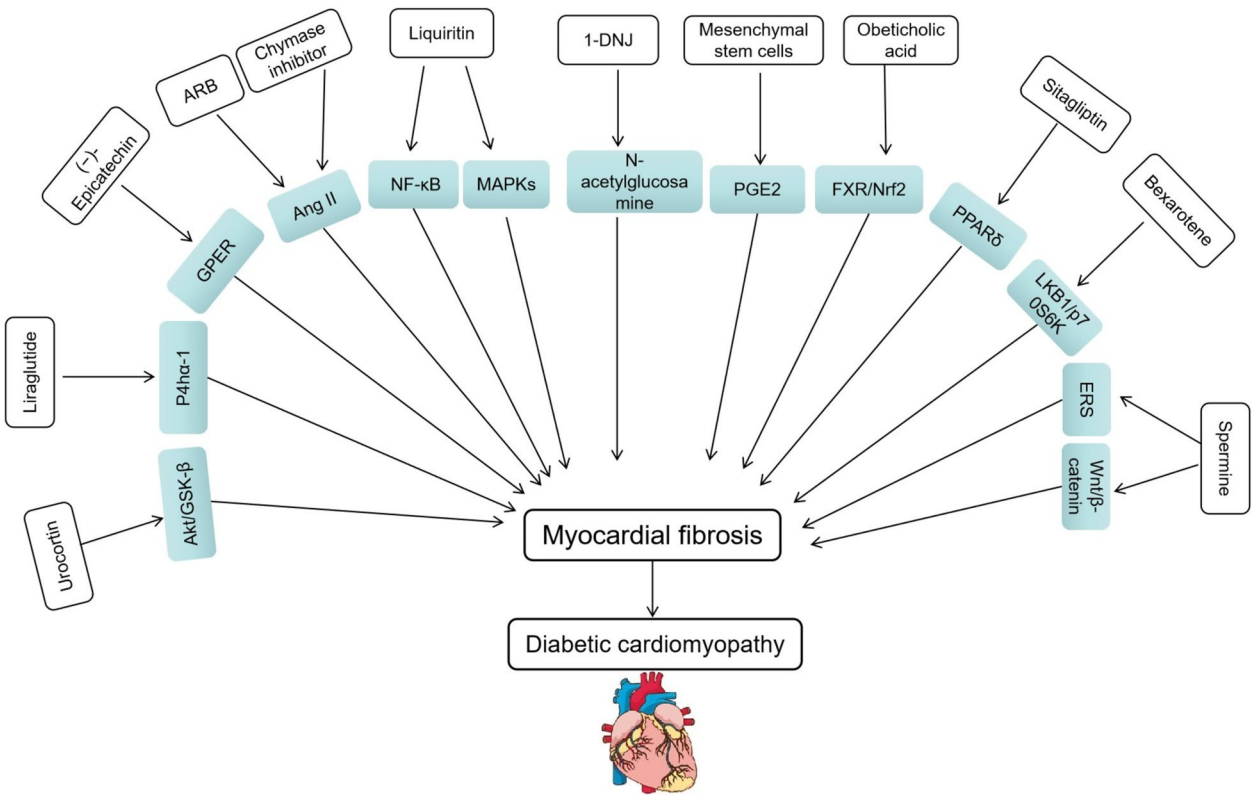

Fig. 4 Drugs for the prevention and treatment of DCM by regulating other mechanisms to inhibit MF

APN-modified BMSCs in diabetic rats induced by HFD combined with STZ could decrease myofibrillar disorder, inhibit proliferation and transformation of CFs via regulating the TGF-β1/Smad signaling pathway [172].

Bakuchiol

Bakuchiol (BAK) is a biologically active natural meroterpene extracted from the seeds of *Psoralea corylifolia*. BAK could significantly decrease blood glucose levels, improve glucose tolerance and elevate serum insulin levels in STZ-induced diabetic mice [173]. In addition, BAK significantly attenuated DCM by attenuating cardiac dysfunction, ameliorating MF and myocardial hypertrophy, and reducing cardiomyocyte apoptosis. The antifibrotic effect of BAK was achieved by inhibiting the TGF-β1/Smad3 pathway [174].

Caffeic acid para-nitro phenethyl ester

Caffeic acid para-nitro phenethyl ester (CAPE-*p*NO_2) has multiple pharmacological actions, such as anti-oxidation, anti-inflammation and anti-fibrosis, and is able to ameliorate acute myocardial ischaemia–reperfusion injury in rats [175]. In STZ-induced DCM mice, CAPE-*p*NO2 could inhibit ROS activity and decrease serum levels of CK, LDH, TC and TG via decreasing the expression of NOX4 and increasing SOD activity. Meantime, CAPE-*p*NO2 was able to reduce the level of TNF-α, IL-1β and IL-6 by regulating the NOX4/NF-κB pathway to ameliorate inflammation in DCM mice. In addition, CAPE-*p*NO2 repressed the expression of collagen and fibronectin, and attenuated ECM deposition by regulating the TGF-β1/Smad pathway in DCM mice. In conclusion, CAPE-*p*NO2 was able to inhibit myocardial injury through anti-fibrotic, anti-oxidant and anti-inflammatory effects in DCM mice [176].

Curcumin

Curcumin, a yellow pigment extracted from the dried root of turmeric, has significant economic value and various pharmacological actions, such as anti-oxidative stress, anti-inflammatory, anti-tumour effects [177]. In STZ-induced diabetic rats, curcumin could significantly lower blood glucose, reduce superoxide production in ventricular tissues, and inhibit ECM protein accumulation, myocardial hypertrophy, and cardiac dysfunction by inhibiting PKC-MAPK signaling pathway [178].

C66, a curcumin analogue, possesses anti-inflammatory, anti-fibrotic, anti-oxidant and anti-apoptotic effects in diabetic mice [140, 179]. C66 protected against DCM by suppressing JNK2 activation, leading to reduced cardiac inflammation, MF, oxidative stress and apoptosis [180]. At the same time, research shows that JNK inactivation could obviously activate nuclear factor (erythroid-derived 2)-like 2 (Nrf2), thereby reducing inflammation, fibrosis and oxidative stress induced by DM [181].

As one of the curcumin analogues, A13 has the general properties of curcumin and is superior to curcumin in metabolism and bioavailability [182]. A13 was able to increase MDA level and SOD activity, activate Nrf2/ARE pathway, and inhibit collagen deposition in myocardium of diabetes rats induced by HFD/STZ. The protective effect of A13 in DCM is achieved by activating the Nrf2/ARE pathway, promoting Nrf2 nuclear translocation, and thereby inhibiting oxidative stress [183].

Tetrahydrocurcumin (THC), a main bioactive metabolite of the curcumin, has stronger antioxidant and antifibrotic effects, and anti-inflammatory and anti-diabetic abilities [184, 185]. In STZ-induced diabetic mice, THC dramatically improved heart dysfunction and ameliorated MF and cardiac hypertrophy while reducing the production of ROS. Mechanistically, THC achieved its antifibrotic effects via inhibiting the ROS-stimulated TGF-β1/Smad3 pathway and decreasing the level of markers of MF (α-SMA, collagen I/III). In summary, THC treatment could attenuate DCM primarily via inhibiting HG-induced oxidative stress and fibrosis [186].

Chymase inhibitor

Chymase is a serine proteinase that specifically hydrolyses the Phe8-His9 bond in Ang I to produce Ang II in local tissues of multiple species [187]. Human and hamster cardiac chymases possess a common biochemical role in the production of Ang II from Ang I and are major sources of tissue Ang II [188]. Myocardial chymase level was significantly increased in a glucose-dependent manner in STZ-induced diabetic hamsters. Chymase-specific inhibitor could suppress Ang II elevation and completely reverse NOX4-induced oxidative stress and MF in STZ-treated diabetic hamster myocardium [189].

Sodium-glucose cotransporter-2 inhibitor

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a new type of FDA approved anti-diabetic drugs that act on SGLT2 receptors in the proximal tubules of the kidney to reduce renal glucose reabsorption [190]. In many clinical trials and guidelines, SGLT2 inhibitors have been prioritised for the treatment of patients with DM combined with cardiovascular disease [191, 192]. Empagliflozin mitigated interstitial MF in a nondiabetic HF porcine model [193] and in nondiabetic patients with HFrEF [194]. Dapagliflozin (DAPA), a SGLT2 inhibitor, could reduce fibrosis, inflammation, oxidative stress and improve cardiac function in DCM [195]. DAPA suppressed MF to improve DCM by regulating AMPKα to inhibit TGF-β/Smad pathway, which in turn inhibited

CFs proliferation, activation, collagen production and EndMT [196]. DAPA also significantly inhibited NOX4 expression in myocardium of T2DM rat and HG-treated HUVECs in an AMPKα-dependent manner, thereby inhibiting oxidative stress and improving DCM [196]. In mice model of T2DM, Empagliflozin also could improve heart function by regulating the TGF-β/Smad pathway to reduce the deposition of ECM proteins, and decreasing oxidative stress by facilitating the translocation of Nrf2 to the nucleus and activating the Nrf2/ARE signaling pathway [197]. Although SGLT2 inhibitors has shown good effects in animal experiments, its efficacy remains to be clarified through clinical studies.

Dendrobium officinale

Dendrobium officinale Kimura et Migo is a functional food and medicinal herb with great pharmacological effects on DM and hypertension [198]. Studies have shown that the water-soluble extract of Dendrobium officinale (DOE) could obviously decrease blood glucose and prevent DCM by inhibiting oxidative stress, inflammatory responses and fibrosis in STZ-treated diabetic mice [199]. In addition, DOE ameliorated insulin resistance, fatty acid metabolism and collagen deposition, while increased PPAR-α expression, phosphorylation of insulin receptor substrate 1 and E-cadherin and inhibited the expression of TGF-β1, p-JNK, Twist, Snail1 and Vimentin in HFD/STZ-treated DCM mice. Thus, DOE improved HFD/STZ-induced DCM through accelerating lipid transport, ameliorating insulin resistant and epithelial mesenchymal transition [200].

Fingolimod

Fingolimod (FTY720) is a synthetic structural analogue of sphingosine that is activated by phosphorylation of sphingosine kinase 2 and acts on all five S1P receptors [201, 202]. FTY720 could decrease interstitial fibrosis and cardiomyocyte hypertrophy in non-infarcted distal myocardium of porcine ischemia–reperfusion model [203]. In hyperglycaemic states, FTY720 treatment induced sustained decrease of circulating T lymphocytes and decreased infiltration of CD3 T cells into heart tissue. In addition, FTY720 treatment markedly decreased interstitial and perivascular fibrosis in STZ-induced DCM. The mechanism of action was associated with reduced expression of $S1P_1$ and TGF-β1 in myocardial tissue [204].

Epigallocatechin-3-gallate

Epigallocatechin-3-gallate (EGCG) is one of the most abundant catechins in green tea and possesses antifibrotic effects in a variety of tissues. EGCG could improve cardiac contractile function and inhibit MF in T2DM rats. The mechanism can be mainly through the activation of autophagy by modulating the AMPK/mammalian target of rapamycin pathway, which in turn down-regulates the TGF-β/MMPs signaling pathway [205].

Spermine

Spermine (SPM) is a product of polyamine metabolism, which plays significance roles in a variety of cardiovascular diseases, such as myocardial hypertrophy, ischemia and infarction. Exogenous SPM increased body weight, blood insulin levels and heart function, and reduced blood glucose, heart weight/body weight ratio, and ERS-related protein expression in STZ-induced diabetic rats. Moreover, exogenous SPM reduced collagen deposition in the myocardial interstitium and perivascular regions of diabetic rats and attenuated the abnormal proliferation of HG-stimulated CFs. The mechanism of SPM alleviating MF in DCM rats is realized by inhibiting ERS and Wnt/β-catenin pathway [206].

Follistatin

The level of follistatin (FST), an endogenous antagonist of the TGF-β pathway, was downregulated in the hearts of db/db mice. Overexpression of FST decreased myocardial interstitial fibrosis and ROS production, enhanced MMP9 activity, and improved cardiac function in db/db mice. Mechanistically, FST may improve the pathological process of DCM via inhibiting the TGF-β/Smad3 pathway and reducing ROS production [207].

Forskolin

Forskolin (FSK) is a natural product extracted from the root of Coleus forskohlii [208]. FSK treatment markedly improved the diastolic function of diabetes heart and alleviated the abnormal morphological change and MF in diabetic hearts. Moreover, FSK treatment significantly reduced the level of fibronectin, collagen I, TGF-β and α-SMA, as well as inhibited MDA content, increased SOD activity and the GSH/GSSG ratio in diabetic hearts. Thus, FSK can prevent the development of DCM by repressing oxidative stress and MF in STZ-treated diabetic mice [209].

Neuregulin-1

Neuregulin-1 (NRG-1) is a cardiac-active growth factor released by ECs, which is essential for cardiac development, maintenance of cardiac structure and functional integrity [210, 211]. Gene transfer of human NRG-1 (hNRG-1) to the myocardium could decrease the expression of bax, type I/III procollagen, increase the level of bcl-2, and improve the cardiac function in DCM rats. Moreover, hNRG-1 gene transfer could activate Akt and eNOS pathways through phosphorylation in the

myocardium. Thus, gene transfer of hNRG-1 alleviated cardiac remodeling by modulating cardiomyocyte apoptosis and MF in DCM rat model [212].

Ginger extract

Ginger (Zingiber officinale Roscoe) belongs to the Zingiberaceae family and is a medicinal plant, which is used to treat rheumatism, asthma, liver fibrosis and diabetes [213, 214]. Up to 12 weeks of ginger consumption or administration of the active compound, zingerone, obviously decreased fasting blood glucose, glycated haemoglobin, and associated fibrotic and inflammatory factors, and improved insulin sensitivity. This suggests that ginger may be an effective drug to prevent diabetes and its complications [213, 215, 216]. Moreover, ginger extract could reduce MF and inflammatory cell infiltration in diabetic rats by regulating the expression of genes related to the TGF-β/Smad pathway [217].

Fasudil

Fasudil treatment significantly decreased myocardial collagen deposition and improved cardiac dysfunction in a rat model of T2DM. Fasudil is the only ROCK inhibitor that can be used in vivo for long periods of time. Fasudil not only suppressed ROCK activity, but also inhibited JNK overactivation in the diabetic heart, resulting in reduced collagen production in the myocardium and improved cardiac function. However, fasudil had no effect on glycolipid metabolism and insulin resistance. Mechanistically, fasudil suppressed MF in diabetic rats at least in part by repressing activation of JNK and TGF-β1/Smad2/3 pathway, and these beneficial effects of fasudil were independent of glycaemic control [218].

Ang II receptor blocker

Irbesartan is an Ang II receptor blocker (ARB) that effectively blocks the combination of Ang II to its receptor and prevents its downstream biological functions. Irbesartan could significantly inhibit the proliferation of CFs induced by HG and the synthesis of PICP and PIIINP. Moreover, irbesartan significantly attenuated the degree of MF and reduced the expression of TGF-β1 and p-Smad2/3 in the myocardium of DCM rats, suggesting that irbesartan may attenuate MF in DCM rats via suppressing the activation of TGF-β1/Smad pathway [219].

Losartan was able to inhibit interstitial fibrosis of DCM and improve heart function through inhibiting the JAK/STAT pathway and decreasing TGF-β1 expression [220]. The JAK/STAT pathway is an essential cytokine signal transduction pathway that regulates a variety of pathophysiological processes, such as cellular proliferation, differentiation, apoptosis and inflammation. Ang II is one of the factors that activate the JAK/STAT pathway. HG or AGEs could stimulate RASS to produce Ang II, which in turn activated the JAK/STAT pathway, whereas suppression of the JAK/STAT pathway reduced TGF-β1 synthesis in HG-cultured mesangial cells [221].

Minelarocorticoid receptor antagonist

RAAS are activated in DCM, resulting in increased aldosterone levels. Aldosterone is the main mineralocorticoid, which binds to the mineralocorticoid receptor (MR) to induce HF, and also directly causes MF [222]. The MR in DCM is excessive activated, which leads to myocardial damage. Spironolactone (SPR) is the first-generation minelarocorticoid receptor antagonist (MRA). Short-term SPR treatment reversed MF and attenuated the increased diastolic stiffness in STZ-induced diabetic rats [223]. Moreover, SPR could ameliorate mitochondrial dysfunction and inhibit cardiac oxidative stress, MF, inflammation in STZ-induced diabetic rats [224].

The second-generation MRA eplerenone, a specific MR blocker, has demonstrated anti-fibrotic and anti-apoptotic properties in left ventricular hypertrophy, hypertension, and MI [225, 226]. In DCM rats, eplerenone can improve left ventricular diastolic function, inhibit cardiomyocyte apoptosis and oxidative stress [227]. Moreover, eplerenone may attenuate cardiac steatosis and apoptosis, and subsequent remodelling fibrosis, hypertrophy and diastolic dysfunction in obese/type-II diabetic rats [228].

Finerenone is a third-generation MRA with stronger specificity for mineralocorticoid receptor. In large-scale clinical trials, finerenone has demonstrated strong cardiac benefits, including reduced cardiovascular mortality and reduced MF in patients with T2DM [229, 230]. Moreover, finerenone could attenuate myocardial lipid uptake, myocardial apoptosis and MF in DCM rats [231]. Finerenone can improve DCM through a variety of mechanisms. For example, it can effectively block programmed cell death in the heart, including inhibiting cardiomyocyte apoptosis and restoring autophagy in cardiomyocytes. Moreover, finerenone can inhibit oxidative stress by reducing the production of ROS and suppressing the activation of NADPH oxidase. At the same time, finerenone can effectively anti-inflammatory [232].

Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 (GLP-1) is mainly secreted by intestinal enteroendocrine L-cells. The physiological function of GLP-1 is to decreased blood glucose levels in a glucose-dependent manner by promoting insulin secretion [233]. Several studies have shown that GLP-1 receptor agonists (GLP-1RA) or GLP-1 analogues suppressed the expression of collagen and MMPs and improved cardiac diastolic dysfunction in diabetic rats [234, 235].

Liraglutide, a GLP-1 analogue, could attenuate obesity, hypertension and age-induced inflammation, oxidative stress and MF in C57BL/6J mice [236]. Furthermore, liraglutide significantly alleviated cardiac dysfunction and MF in STZ-treated diabetic rats by repressing the expression of collagen hydroxylase (P4hα-1), collagens (collagen I/III), and collagen degrading enzymes (MMP-1/9) [237]. P4hα-1 was a crucial enzyme responsible for collagen synthesis, and up-regulation of P4hα-1 could promote MMP expression [238]. Therefore, liraglutide decreased cardiac dysfunction and MF in STZ-treated diabetic rats by suppressing the expression of collagen I/III and MMP-1/9, which may be related to the downregulation of P4hα-1 expression. Exenatide, a long-acting GLP-1RA, obviously improved serum BNP, MF, lipid deposition of the myocardium and echocardiography parameters in DCM mice. The effect of exenatide is achieved by binding to GLP-1 receptor in cardiomyocytes and further regulating miR-29b-3p/SLMAP expression [239]. Semaglutide, as a long-acting analog with high homology with GLP-1, can reduce MF, apoptosis, and oxidative stress in myocardial tissue of DCM rats by activating PI3K/Akt/Nrf2 signaling pathway, thereby improving diabetic myocardial injury [240].

Sitagliptin

Sitagliptin, a GLP-1 enhancer, is a new class of anti-diabetic drug that prevents the degradation of insulinotropic incretins [241]. Sitagliptin attenuated cardiomyocyte hypertrophy and apoptosis/necrosis in T2DM rats. In addition, sitagliptin decreased the expression of profibrotic factors and MF, and increased the secretion of GLP-1 under fasting and glucose overloaded conditions in GK rats. Mechanistically, sitagliptin could inhibit myocardial apoptosis, hypertrophy and fibrosis via the GLP-1/PPARδ pathway, thereby improving cardiac function in diabetic rats [242].

Exercise and metformin

During aerobic exercise, more glucose transporter protein 4 was transferred to the cell membrane, which facilitated the metabolism of glucose molecules into the cell, thereby lowering blood glucose levels [243]. Exercise reduced the degree of MF, which might be associated with inhibiting oxidative stress, RAS activity and the production of AGEs in diabetic myocardium [244, 245]. Furthermore, moderate exercise improved mitochondrial adaptations that inhibited fibrosis-associated oxidative stress, thereby improving cardiac function in diabetic rats [246–248]. It was found that prolonged exercise reduced the expression of collagen I/III in STZ-induced DCM by down-regulating MMP-2/9 expression, which was related to mediation by tissue inhibitors of MMPs. Another study showed that 8 weeks of treadmill exercise lowered blood glucose, inhibited MF, and reduced myocardial TGF-β1 expression and Smad2/3 phosphorylation in T2DM rats [249]. In addition, exercise and metformin alone or their combination intervention suppressed the TGF-β1/Smad pathway to alleviate MF via decreasing NF-κB-mediated inflammatory response. The anti-fibrotic effect was modulated by exercise-induced elevation of IL-6 or metformin-activated AMPK, whereas there was no synergistic effect of the combination of the two interventions [250]. Therefore, exercise can inhibit diabetes-induced MF through multiple pathways, such as oxidative stress, inflammation, TGF-β1/Smad pathway, and MMP expression.

Metformin is a widely used hypoglycemic drug that has been proven to reduce the risk of cardiovascular rehospitalization in patients with diabetes complicated with HF and lower the high risk of aggravating DCM in patients with prediabetes [251, 252]. Animal experiments have confirmed that metformin can exert a cardiac protective effect by improving the cardiac morphology and structure of db/db mice [253]. Metformin could alleviate myocardial interstitial fibrosis and perivascular fibrosis in type 2 diabetic rats, and its effect is related to the activation of AMPK [196]. In addition, metformin could inhibit MF in db/db mice by increasing the expression of M2 macrophages in the myocardium [254].

Melatonin

Melatonin, a major product secreted by the pineal gland, plays an essential role in the pathological process of DM. Melatonin was proved to be a strong antioxidant in STZ-induced diabetic rats. Intraperitoneal injection of melatonin increased antioxidant enzyme activity and repressed the release of superoxide radicals in mice [255]. Another experiment also demonstrated that melatonin was able to effectively reduce inflammation and oxidative stress in T2DM mice [256]. Moreover, melatonin was able to modulate a variety of DCM pathological processes, such as improving cardiomyocyte metabolism, reducing vascular endothelial cell death, reversing microcirculatory disturbances, decreasing MF, oxidative and ERS, modulating cellular autophagy and apoptosis, and improving mitochondrial function [257]. What's more, melatonin could ameliorate the pathological process of MF via promoting the expression of miR-141 to inhibit the expression of TGF-β1, p-Smad2/3, and NLRP3 inflammasome complex and the NLRP3 downstream factors IL-1β, IL-18 and cleaved caspase-1 in the myocardium of DCM [258].

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) possess significant secretory, immunomodulatory and anti-inflammatory properties, with therapeutic potential for DM and certain cardiac diseases [259, 260]. Several studies have evidenced the beneficial effects of MSCs on DCM. After MSCs infusion in DCM rats, the abnormal glucose and lipid metabolism, MF and cardiac dysfunction were significantly improved, and the expression of TGF-β and collagen I/III were obviously reduced. The concentration of PGE2 was increased, while the proliferation and collagen secretion of CFs were decreased in MSC-treated DCM rats. However, PGE2-deficient MSCs had reduced ability to attenuate MF and cardiac dysfunction. Thus, MSC infusion can improve cardiac dysfunction and fibrosis in DCM rats via secreting PGE2 [261].

Endothelial progenitor cells

Endothelial progenitor cells (EPCs) are a subset of bone marrow-derived stem cells that exist in the peripheral circulation with the potential to differentiate into functional and mature ECs. In a STZ-induced diabetic rat model, EPCs transplantation could attenuate diabetes-associated cardiac function impairment and myocardial interstitial fibrosis, as well as down-regulated the level of collagen, Bax, and caspase-3, and up-regulated the expression of Bcl-2 and manganese superoxide dismutase. Therefore, transplantation of bone marrow EPCs could improve heart function, inhibit cardiomyocyte apoptosis and oxidative stress, and decrease MF in the STZ-induced diabetic rat model [262].

Obeticholic acid

Obeticholic acid (OCA) is a semi-synthetic bile acid analogue that improves metabolic abnormalities, including lowering blood glucose and insulin levels, decreasing content of TG, TC and FFAs, and improving glucose tolerant impairment. In addition, OCA was able to reduce mRNA expression of fibrosis biomarkers including CTGF, osteopontin, TGF-β1, and collagen I/III in myocardial tissues of db/db mice. FXR is a major target mediating the beneficial effects of OCA. OCA could inhibit pathological changes such as metabolic disorders, oxidative stress, inflammation, fibrosis, and amelioration of heart dysfunction in DCM mice via modulating the FXR/Nrf2 pathway [263].

Ac-SDKP

Ac-SDKP (*N*-acetyl-seryl-aspartyl-lysine-proline), a physiological tetrapeptide hydrolysed by ACE, has anti-fibrotic effects on LV treated by Ang II in rats [264] and aldosterone-salt hypertensive rats [265]. More importantly, Ac-SDKP was able to significantly decrease LV interstitial and perivascular fibrosis and improve diastolic function in STZ-induced diabetic rats by repressing the TGF-β1/Smad2/3 signaling pathway [266].

Triptolide

Triptolide is an essential active ingredient extracted from Tripterygium, which has been widespread used in the treatment of immune system disorders because of its immunosuppressive, anti-proliferative and anti-inflammatory actions. Triptolide was effective in protecting against DCM immunomodulatory imbalance, myocardial inflammation and MF in diabetic rats, thereby improving cardiac function. In addition, the protective effect of triptolide on cardiac tissues can be achieved by inhibiting TLR4-induced NF-κB pathway to modulate the innate immune system, leading to suppressing the inflammatory response by the NF-κB/TNF-α/VCAM-1 pathway, which in turn improves MF through the TGF-β1 pathway [267].

Resveratrol

Resveratrol, a polyphenolic compound and naturally occurring phytoalexin exist in red wine and vegetable foods, has been proven to slow the progression of DCM [268, 269]. The level of high-mobility group box 1 (HMGB 1) was significant elevated in serum, monocytes and heart tissues, whereas resveratrol could significantly suppress the up-regulation of HMGB 1 levels in T1DM rats [270]. HMGB 1 was a pro-inflammatory cytokine that regulated fibrosis and inflammation in multiple organs, and inhibition of HMGB 1 could attenuate MF and cardiac remodeling in DCM [90]. HMGB 1 could lead to NF-κB activation through binding to RAGE or TLRs, thereby causing inflammatory response [271]. Several studies have shown that CFs were the source of HMGB 1 [90, 272], which could stimulate fibroblast activation and trigger MF [90], suggesting that crosstalk between HMGB 1 and CFs may play an essential role in MF of DCM. Further studies confirmed that resveratrol prevented oxidative damage, MF and inflammation via repressing the HMGB1/RAGE/TLR4/NF-κB pathway in diabetic mice [273]. In addition, resveratrol also significantly attenuated myocardial oxidative stress and interstitial fibrosis in STZ-induced DM and improved the proliferation and differentiation of CFs via inhibiting the ROS/ERK/TGF-β/periostin pathway [274].

Sacubitril/valsartan

Sacubitril/valsartan (Sac/Val), the first angiotensin receptor-neprilysin inhibitor, could attenuate MF and cardiac remodeling, which was correlated with an improved prognosis in patients with HFrEF [275, 276]. In addition, Sac/Val was able to suppress the pathological process of

MF in DCM rats via inhibiting the TGF-β1/Smad3 pathway [277].

Silymarin

Silymarin is extracted from the Silybum marianum plant and is used to treat liver disorders, which has antioxidant, anti-inflammatory, and hypoglycemic properties. Silymarin could decrease blood glucose levels and improve cardiac function in diabetic rats induced by STZ. Meanwhile, silymarin attenuated collagen deposition by decreasing the expression of TGF-β1 and p-Smad2/3 and increasing the level of Smad7 in the heart of DM rats. Therefore, silymarin was able to ameliorate the pathological process of MF in DCM via inhibiting the TGF-β1/Smad pathway [278].

Sheng Mai Yin

Sheng Mai Yin (SMY) is made up of three herbs, ginseng, radix ophiopogonis and Schisandra chinensis, and has been used in the treatment of cardiac diseases, including myocardial ischaemia–reperfusion, coronary heart disease and HF [279–281]. SMY could decrease blood glucose and lipid levels, improved cardiac dysfunction and myocardial histopathological changes, down-regulated myocardial enzymes levels, and attenuated cardiomyocyte apoptosis and MF in DCM rats. Meantime, SMY could suppress the expressions of NLRP3, ASC, Caspase-1, GSDMD and IL-1β. Thus, these cardioprotective effects of SMY on DCM may be mediated by modulation of the NLRP3/caspase-1/GSDMD signaling pathway [282].

Shensong Yangxin Capsule

Shensong Yangxin Capsule (SSYX) markedly decreased heart weight/body weight ratio and improved the impaired heart function of T2DM rats. Moreover, SSYX obviously attenuated MF through suppressing collagen production, CFs proliferation, and myofibroblast formation. Mechanistically, SSYX decreased the expression of TGF-β1, collagen, MMP-2/9 and p-Smad2/3, whereas increased Smad7 level. Thus, SSYX could attenuate MF via repressing TGF-β1/Smad pathway in diabetic rats induced by STZ/HFD [283].

Liquiritin

Liquiritin, the main component of Glycyrrhiza Radix, has a variety of pharmacological activities, which can significantly down-regulate the expression of inflammatory factors and block the activation of NF-κB for the treatment of diabetic vasculopathy [284, 285]. Liquiritin ameliorated high fructose-induced abnormalities of lipid metabolism, insulin resistance and cardiac dysfunction, and reduced the overexpression of collagen, α-SMA and MMP-9. In addition, liquiritin significantly decreased the release of high fructose-induced inflammatory cytokines and the phosphorylation of NF-κB, and inhibited the activation of MAPKs. Thus, liquiritin has a protective effect against high fructose-induced MF by inhibiting NF-κB and MAPKs pathways [286].

Urocortin

Urocortin, a peptide belonging to the adrenocorticotropin-releasing hormone family, is a novel inotropic drug with significant effects on the cardiovascular disease [287]. Endothelial urocortin repressed Ang II-induced ROS production in ECs [288]. Urocortin could inhibit cardiac dysfunction, MF, and inflammation in the myocardium of diabetic rats induced by STZ, as well as promote the phosphorylation of Akt and GSK-3β, and repress the expression of TGF-β1 and CTGF. Thus, urocortin could downregulate the expression of TGF-β1 and CTGF through activation of the Akt/GSK-β signaling pathway, which attenuated fibrosis and inflammation and improved DCM [289].

Bexarotene

Bexarotene, a retinoic acid X receptor (RXR) agonist, could ameliorate cardiac dysfunction via inhibiting cardiomyocyte apoptosis and MF. HG-induced CFs significantly decreased the activity of liver kinase B1 (LKB1) and increased the activity of p70 ribosomal protein S6 kinase (p70S6K), while bexarotene could inhibit this trend. Thus, bexarotene ameliorated STZ-induced DCM by suppressing MF through modulation of the LKB1/p70S6K signaling pathway [290].

(−)-Epicatechin

(−)-Epicatechin (Epi) treatment could dramatically inhibit the HG-induced elevation of TGF-β1, Smad, fibronectin and total collagen levels in CFs. Meanwhile, the level of G-protein coupled estrogen receptor (GPER) was obviously downregulated in HG-induced CFs, and Epi treatment could restore this trend. Moreover, Epi bound the GPER and activated the downstream TGF-β1/Smad pathway. Thus, Epi was able to inhibit HG-induced activation of CFs via inhibiting the TGF-β1/Smad pathway through upregulation of GPER [291].

Epigallocatechin gallate

Epigallocatechin gallate (EGCG), a major component of rhubarb tannins, has antioxidant, antiangiogenic, anticancer and antiviral activities. EGCG improved glucose-lipid metabolism and heart function, inhibited the deposition of collagen and the expression of TGF-β1, JNK and TIMP-1 tissue inhibitor, and promoted the expression of MMP-9 in STZ-induced diabetic rats. The

results indicated that EGCG improved cardiac function and MF through inhibition of the TGF-β1/JNK pathway in STZ-induced diabetic rats [292].

Conclusions

MF is one of the most important causes of morbidity and mortality in DCM, which can increase the incidence of HF and arrhythmia. DCM has been studied for more than 50 years, but effective preventive and therapeutic strategies are still lacking. Increased proliferation and differentiation of CFs, promoted collagen deposition, and disrupted MMPs synthesis are the results of long-term abnormalities in glycolipid metabolism, which break the balance between ECM synthesis and degradation in DCM, and activate various molecular signaling pathways, and ultimately lead to ventricular remodeling and increased MF. Therefore, the in-depth study of the pathological mechanism and related molecular pathways of MF in DCM, as well as the summary of the relevant achievements in the treatment of current research are expected to provide ideas for the prevention and therapy of MF in DCM. However, the current research mostly focuses on the basic experimental stage and lacks large-scale clinical data. Therefore, in the future, it is necessary to explore potential drugs and conduct relevant clinical studies in order to apply them in clinical practice at an early stage.

Advanced MF is irreversible. Future research may focus on the prevention of the subclinical stage before the diagnosis of DM. The pathogenesis of DCM is very complex, and a single treatment plan is difficult to achieve a good therapeutic effect. Future treatments may tend towards a multi-dimensional strategy of "metabolic repair + anti-fibrosis + immune regulation", combining gene editing and intelligent drug delivery systems to provide more efficient treatment options for DCM.

Acknowledgements
Not applicable.

Author contributions
S.J. was a major contributor in writing the manuscript. Z.R. and L.M. were responsible for reviewing the relevant literature. S.J. and Z.D. were responsible for the conception and proofreading of the article. All authors read and approved the final manuscript.

Funding
This work was supported by the National Natural Science Foundation of China (grant number 82305028) and the Fundamental Research Funds for the Central public welfare research institutes (grant number ZZ16-YQ-005).

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All the authors agreed to publish the paper.

Competing interests
The authors declare no competing interests.

Received: 7 March 2025 Accepted: 31 May 2025
Published online: 24 June 2025

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