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REVIEW

Traditional Chinese Medicine Treating Dilated Cardiomyopathy: A Literature Review

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Abstract: Dilated cardiomyopathy (DCM), as a difficult problem in modern medical treatment, has become an important cardiovascular disease threatening human beings all over the world with an increasing incidence rate and mortality. Conservative drug therapy is mainly used in clinical practice, but due to unavoidable adverse reactions such as low blood pressure, it is often difficult to achieve satisfactory prognosis. Traditional Chinese medicine has the characteristics of syndrome differentiation and multi-target treatment for DCM, with few adverse reactions and certain advantages. It has achieved good therapeutic effects in clinical practice. Therefore, we summarized and analyzed the clinical evidence and mechanism of traditional Chinese medicine in the treatment of DCM, and combined with the current research status of this disease to analyze the problems and shortcomings, in order to provide more ideas and methods for the treatment of DCM with traditional Chinese medicine.

Keywords: dilated cardiomyopathy, traditional Chinese medicine, clinical evidence, potential mechanisms, research progress

Introduction

Dilated cardiomyopathy (DCM) is a type of primary mixed cardiomyopathy.[1] Its main character is enlargement of the left, right, or biventricles, accompanied by myocardial hypertrophy, decreased myocardial contractile function.[2] It has a high incidence rate in cardiomyopathy and poor prognosis. In global, the prevalence of DCM is 36 per 100,000 population per year.[3] And the 5-year mortality rate of DCM is 80% in China.[4] With the development of scientific research, people allowed establishment of DCM as mostly cytoskeleton, force transmission disease.[2] Its main clinical features include low ejection fraction, progressive heart failure, malignant arrhythmia, thromboembolism, cardiogenic shock, or sudden death, which can occur at any stage of the disease development process. What's more, DCM is one of the main causes of heart failure.[5] The etiology of DCM is not yet clear. Several possible causes include gene mutation (for example, genes encoding structural metabolites of the sarcomere and desmosome); inflammation of the myocardium due to an infection (mostly viral); exposure to drugs, toxins or allergens; and systemic endocrine or autoimmune diseases[6] (Figure 1).

DCM is treated only with palliative pharmacological (prevent or treat heart failure) or invasive therapy (eg cardiac resynchronization therapy and implantable cardioverter defibrillators).[6] Western drugs used to treat DCM include: diuretics, digitalis, sacubitril valsartan, angiotensin converting enzyme receptor inhibitors/angiotensin II receptor antagonists, and beta receptors blockers, etc., mainly improve the symptoms of heart failure in the later stage of DCM. Above strategies either lack targeted treatment or incur significant costs and cannot be promoted.

Unlike modern medicine, traditional Chinese medicine (TCM) has its own unique diagnostic and treatment system, which has undergone thousands of years of clinical practice and inheritance. In the past, due to the lack of quantitative and objective evaluation standards, the application of TCM in other countries around the world was relatively limited. With the increasing research achievements in TCM, it is becoming increasingly popular in many developed countries, such as the United States, Australia and so on.

Many studies shown that TCM has advantages in improving heart function and clinical symptoms, and increasing survival rates in DCM. As early as 1997, Ferguson et al had published an article on the use of Chinese herbal to treat DCM.[7] Due to the limitations of Western medicine treatment, researchers gradually focus on TCM. Since 2016, research

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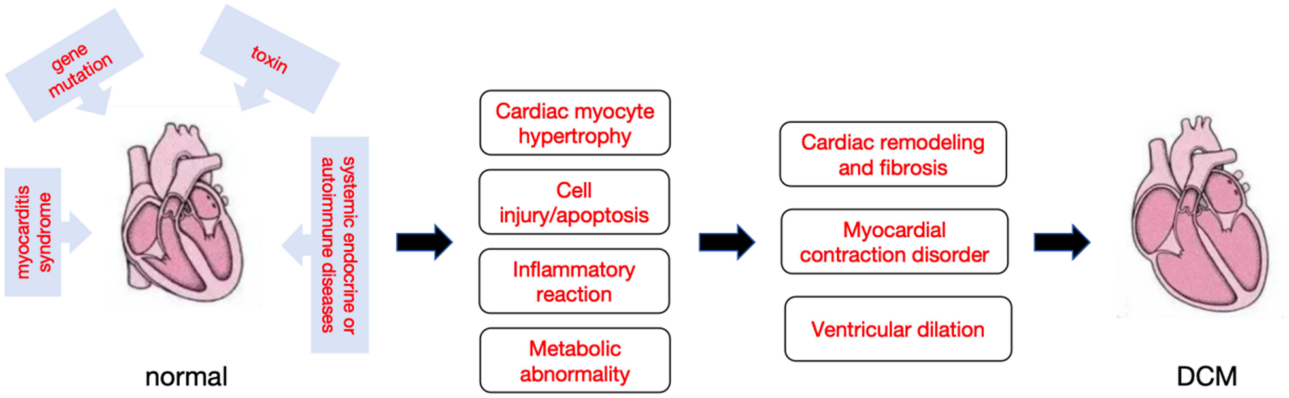

Figure 1 Etiology and pathological changes of DCM.

on the treatment of DCM with TCM has increased significantly. Although TCM can improve the heart function of DCM, its mechanisms are still in the early stages, and its target areas are still largely unclear. TCM's potential to regulate heart function deserves further study.

In this review, we searched for relevant studies from PubMed, CNKI, and Wanfang databases using keywords including "dilated cardiomyopathy" "traditional Chinese medicine" and "herbal decoction." Articles published between 1997 and 2024 were included, with a focus on randomized controlled trials and mechanistic studies. We aim to summarize and provide the latest advances in the regulation of DCM by TCM.

Traditional Chinese Medicine in the Treatment of DCM

The clinical manifestations of DCM are similar to the descriptions of diseases such as "heart fluid retention" and "heart distension" in ancient Chinese medicine books. TCM believes that DCM is often caused by insufficient endowment or deficiency of vital energy. Then, external evil take advantage of the deficiency and transmit to the heart. Over time, the heart qi dissipates, the heart volume swell, and blood stasis and water stop, leading to the onset of the disease. DCM is located in the heart and involves the lung, spleen, and kidney. In terms of treatment, the cornerstone is to nourish yang and qi, supplemented with promoting diuresis and removing blood stasis. The purpose of treatment is to harmonize yin and yang, so that the heart yang can be filled and the turbid yin can be eliminated.[8] Clinical practice shows that many Chinese herbal decoction, patent medicines and single medicinal herb can significantly improve DCM.

Chinese Herbal Decoction for the Treatment of DCM

After taking Chinese herbal decoction such as Sijunzi decoction,[9] Linggui Zhugan Tang,[10] Shengmaisan,[11] Xuanxin recipe,[12] Yiqi Xiefei prescription,[13] Qishen Yiqi Huoxue Formula,[14] Renshen Yangrong Decoction,[15] Yixin Xiaozhang Decoction,[16] Huangqi Baoxin Decoction,[17] etc., DCM patients' clinical symptoms and activity endurance can be significantly improved. Laboratory tests such as left ventricular end diastolic diameter (LVEDD), left ventricular ejection fraction (EF), NYHA heart function grading, serum BNP, serum NT-proBNP, cTnT, IGF-1 and so on showed significant improvement. Kangxian Yixin Formula[18] can treat ventricular remodeling in dilated cardiomyopathy. After treatment, there were significant improvements in indicators such as LVEDD, left ventricular end systolic diameter (LVESD), left ventricular short axis shortening rate (FS), left ventricular mass fraction (LVMI), right ventricular end diastolic diameter (RVEDD), interventricular septal thickness (IVSD), left ventricular posterior wall thickness (LVPWD), EF, ST2, and myocardial collagen volume fraction (CVF). What's more, Kangxian Yixin Formula can better stabilize the blood pressure of DCM patients.[19] Zhigancao Decoction[20] can regulate the levels of IL-8, TNF-α, and high-sensitivity C-reactive protein (hs-CRP) in DCM patients. Combined with amiodarone treatment, it can effectively reduce the inflammatory response and improve cardiac function in DCM with ventricular arrhythmia patients (the specific contents of traditional decoction are shown in Table 1).

Table 1 The Compositions of Chinese Herbal Decoction

Chinese Herbal Decoction	Composition	Number of Patients	Treatment Time	Improvement Indicators (Before Treatment vs After Treatment)	Ref
Sijunzi decoction	Ginseng, Poria cocos, Atractylodes macrocephala, Licorice	—	—	—	Huang et al (2019)
Linggui Zhugan Tang	Cassia twig, Poria cocos, Atractylodes macrocephala, Licorice	1	1 month	EF (20 vs 50%) LVEDd (64 vs 47 mm) LA (50 vs 34 mm) BNP (5000 vs 350 pg/mL)	Shao et al (2023)
Shengmaisan	Ginseng, Ophiopogon japonicus, Schisandra chinensis	63	1 year	EF (31.2 ± 7.8 vs 56.1 ± 7.9%) LVIDs (52.4 ± 8.6 vs 46.7 ± 7.3 mm) LVEDd (61.3 ± 8.7 vs 55.7 ± 7.3 mm)	Gong et al (2015)
Kuanxin recipe	Astragalus membranaceus, Polygonatum sibiricum Red, Trichosanthes kirilowii, Ganoderma lucidum, Salvia miltiorrhiza, Medical leech, Cassia twig, Vitex negundo, Hair holly root, Cat ginseng	88	6 month	NYHA ($P < 0.05$) LVEF (0.34 ± 0.15 vs 0.49 ± 0.08) LVEDd (68.77 ± 7.53 vs 61.11 ± 4.39 mm) BNP (356.03 ± 61.58 vs 282.68 ± 47.80 pg/mL)	Wang et al (2017)
Yiqi Xiefei prescription	Astragalus membranaceus, Codonopsis pilosula, Poria cocos, Polyporus umbellatus, lepidium seed, Salvia miltiorrhiza	1	7 month	EF (28 vs 51.8%) LVIDs (58 vs 37.3 mm) LVEDd (63 vs 50.9 mm)	Li et al (2021)
Qishen Yiqi Huoxue Formula	Roasted Astragalus membranaceus, Red Ginseng, Ophiopogon japonicus, Cornus officinalis, Cattail pollen, Lu Lu Tong, Seaweed, Cassia twig	72	3 month	NYHA ($P < 0.05$) NT-proBNP (4624.87 ± 436.81 vs 4034.48 ± 410.56 pg/mL) IGF-1 (115.26 ± 12,78 vs 139.88 ± 12.14 ng/mL) cTnT (89.24 ± 5.91 vs 67.59 ± 7.16 pg/mL)	Lu et al (2021)
Renshen Yangrong Decoction	Ginseng, Astragalus membranaceus, Poria cocos, Atractylodes macrocephala, Poria cocos, Atractylodes macrocephala, Rehmannia glutinosa, Paeonia lactiflora, Dried orange peel, Cinnamomum cassia, Schisandra chinensis, Polygala tenuifolia, Licorice	1	12 day	LA (45 vs 43 mm) LVID (77 vs 73 mm) EF (25 vs 36%) NT-proBNP (3320 vs 146 pg/mL) 6 WMD (264 vs 366 m)	Zhang et al (2021)
Yixin Xiaozhang Decoction	Astragalus membranaceus, Poria cocos, Atractylodes macrocephala, Almond, Ligusticum wallichii, Cattail pollen, Aspongopus, Dried orange peel, Pinellia ternata, Acorus tatarinowii, Polygala tenuifolia, Lily, Licorice, Pericarpium trichosanthis	1	1 year	LA (42 vs 41 mm) LV (84 vs 62 mm) RA (41 vs 34.6 mm) EF (28 vs 58%)	Yu et al (2021)
Huangqi Baoxin Decoction	Astragalus membranaceus, Codonopsis pilosula, Forsythia suspensa, Poria cocos, Ophiopogon japonicus, Crab armor, Salvia miltiorrhiza, Chinese angelica, Cassia twig, Schisandra chinensis	94	3 month	MEE (107.44 ± 9.23 vs 81.79 ± 8.65 cal/min) LVFS (17.68 ± 3.45 vs 27.93 ± 4.23%) LVEF (35.78 ± 6.37 vs 48.38 ± 5.37%) ET (94.53 ± 8.14 vs 58.14 ± 5.43 ng/L) BNP (2135.27 ± 423.26 vs 465.39 ± 87.56 ng/L) Ang-II (148.76 ± 9.85 vs 81.67 ± 6.83 ng/L) 6 WMD (298.37 ± 50.45 vs 546.37 ± 59.63 m)	Xu et al (2024)
Kangxian Yixin Formula	Radix Astragali Mongolici, Red ginseng, Radix Salviae Miltiorrhizae, Poria cocos, Cimicifuga, Motherwort, Eupatorium, Radix Ophiopogonis Japonici, Atractylodes macrocephala	79	6 month	LVEDD (68.13 ± 8.05 vs 56.10 ± 7.33 mm) LVEF (33.00 ± 9.66 vs 52.31 ± 11.37%) RVEDD (21.93 ± 4.94 vs 21.37 ± 2.24 mm) FS (16.65 ± 5.13 vs 27.31 ± 6.77%) IVSD (9.17 ± 0.99 vs 10.15 ± 1.06 mm) LVPWD (16.65 ± 5.13 vs 27.31 ± 6.77 mm) HR (79.93 ± 12.83 vs 68.44 ± 9.46 /min) BP (115.44 ± 13.12/76.62 ± 9.83 vs 112.06 ± 10.95/67.27 ± 7.97 mmHg)	Li et al (2021)

Patent Medicines for the Treatment of DCM

Injection

Traditional Chinese medicine injections are sterile solutions extracted and refined using different methods based on the different active metabolites of Chinese botanical drugs. They can be used for subcutaneous, acupoint, muscle, intravenous injection, etc. Quick onset of action is the advantage. On the basis of Western medicine treatment, adding Astragalus injection, Danshen injection, Shenfu injection, Shenmai injection, Xinmailong injection, etc. to DCM patients can better alleviate clinical symptoms and improve heart function.[21–25] Astragalus injection, Danshen injection, and Shenfu injection can significantly reduce the level of serum BNP.[21–23] Shenfu injection also has a regulatory effect on the levels of angiotensin and endothelin.[26] Xinmailong injection can improve the levels of serum NT-proBNP and hs-CRP.[25] Cell experiments have shown that Shenmai injection has antioxidant stress and repairing effects on hypoxic/reoxygenated myocardial cells.[27] Clinical trial has confirmed that Shenmai injection has a significant improvement effect on the levels of myocardial injury markers (including cardiac myosin binding protein-C, cTnI, serum periosteal protein, and NT-proBNP) in DCM patients.[24]

Oral Medicine

Oral traditional Chinese patent medicines are stable in nature, effective, relatively minor toxic side effects, and easy to take, carry, store and keep. Many oral medicines also have good therapeutic effects on DCM. A meta-analysis[28] compared the therapeutic effects of 11 commonly used Chinese patent medicines. The results showed that Getong Tongluo Capsules, Yangxinshi Tablets, Shenqi Yiqi Dropping Pills, Shensong Yangxin Capsules, Huangqi Mixture, Tongxinluo Capsules, Wenxin Granules, and Qili Qiangxin Capsules were superior to conventional Western medicine in improving the overall clinical efficacy rate. Getong Tongluo Capsules, Yangxinshi Tablets, Shenqi Yiqi Dropping Pills, Shexiang Baoxin Pills, Xinshuai Mixture, Huangqi Mixture, Tongxinluo Capsules, Wenxin Granules, and Qili Qiangxin Capsules are all superior in improving LVEF. Yangxinshi Tablets, Yixinshu Capsules, Shenqi Yiqi Dropping Pills, Wenxin Granules, and Qili Qiangxin Capsules are superior in improving 6MWT (6 minute walk test). In addition, Shenqi Yiqi Dripping Pills and Xinshuai Mixture can better reduce serum BNP, and Shenqi Yiqi Dripping Pills and Qili Qiangxin Capsules can lower hs-CRP.

Single Medicinal Herb for the Treatment of DCM

Apart from the above, studies have shown that single medicinal herb and their effective extracts also have the effect of improving DCM, such as Astragalus membranaceus, Salvia miltiorrhiza, Panax ginseng, Ophiopogon japonicus, Scutellaria baicalensis, etc. Modern pharmacological research shows that Astragalus membranaceus can treat DCM by regulating energy metabolism. The saponins in it have the effect of regulating energy metabolism of myocardial cells and inhibiting ventricular remodeling in rats.[29] At the same time, flavonoids in it play an immunomodulatory and anti-inflammatory role by regulate the NF-κB and MAPK signaling pathways.[30] Salvia miltiorrhiza can reduce the progression of coronary atherosclerosis, improve coronary blood flow microcirculation, stabilize the cell membrane of vascular endothelial cells, and protect myocardium.[31] Tanshinone IIA can inhibit the release of inflammatory factors TNF-α, IL-1, and IL-6 in DCM patients with cachexia, and has a protective effect on the heart.[32]

Ginseng and its active metabolites can protect the myocardium through various pathways such as improving energy metabolism, inhibiting apoptosis, regulating autophagy, and suppressing inflammatory responses.[33–35] Ophiopogon japonicus and its active metabolites have various cardioprotective effects, such as reducing the rate of apoptosis, regulating autophagy of myocardial cells, regulating Ca^{2+} homeostasis in myocardial cells, anti-inflammatory and antioxidant effects.[36] Baicalin can significantly improve cardiac function indicators and reduce myocardial cell apoptosis in DCM rats. The mechanism may be related to the β1-AR/PKA/CaMK II signaling pathway.[37]

Other Traditional Alternative Strategies for DCM Treatment

Acupoint Application

Acupoint application is a characteristic external treatment therapy of TCM, which has the advantages of convenience, economy, and practicality. It achieves the effect of unblocking meridians and qi, adjusting the yin and yang of organs, and maintaining the balance of the body. LIU Hongxia et al treated DCM heart failure patients with acupoint application in

addition to conventional Western medicine. The results showed that the total effective rate, urine output, NT proBNP, clinical symptoms and heart function of the acupoint application group were significantly improved.[38]

Mild Moxibustion

Mild moxibustion has the function of tonifying deficiency, warming and promoting circulation. It has a good therapeutic effect on chronic obstructive diseases. Zhang Jie et al performed mild moxibustion treatment on patients with DCM qi deficiency and blood stasis syndrome. The results showed a significant decrease in the levels of serum periosteal protein and cardiac myosin binding protein-C in patients. The combination of mild moxibustion can delay the process of ventricular remodeling.[39]

TCM Characteristic Nursing

TCM characteristic nursing is a therapy based on the theory of TCM and the organic unity of the human body and environment. It can effectively alleviate patients' tension and anxiety, improve their quality of life and mental state.[40] ZHANG Minxia et al randomly divided 200 severe DCM patients into groups for observation. The living standards and psychological status of patients in the TCM characteristic nursing group were significantly better than those in the control group, and the nursing satisfaction rate was higher.[41]

DCM Mechanism and TCM Intervention Based on Modern Medicine

Genetic Mutations

Contemporary series using genetic screening suggest that up to 40% of DCM is genetically determined. So far, more than 50 genes have been implicated in DCM. These pathogenic genes are mostly encoding genes related to the structure and function of the heart, including sarcomeric proteins, cytoskeleton, nuclear envelope, sarcolemma, ion channels and intercellular junctions.[42] Genetic mutations alter the coding sequence of amino acids, disrupt RNA synthesis and transcription, and produce abnormal structures or quantities of proteins. Pathologically, it manifests as myocardial cell hypertrophy, apoptosis, and myocardial tissue fibrosis. Functionally, it manifests as impaired generation and conduction of myocardial contractile force, ion channel defects, disruption of ion homeostasis, increased nuclear membrane fragility, and obstructed energy supply. Ultimately, myocardial contraction disorders and ventricular dilation occur, leading to DCM.[43]

The most common is TTN (encoding for titin), which is estimated to cause or contribute to approximately 15–25% of familial DCM. Other important genes involved in the pathogenesis of DCM include cytoskeleton gene clusters (DES, DMD, FLNC, NEXN, LDB3), Encoding laminin A/C (LMNA gene) and so on.[42] Quantitative Scores and Final Classifications of Genes Curated for Dilated Cardiomyopathy are shown in Table 2.[1]

There is limited research on TCM treatment for gene deficient DCM. Our team found that the Kuoxinfang (KXF) can improve the survival rate of tnnt2a mutant zebrafish, increase ATP content, and increase the expression of bcl2/bax. It's suggested that KXF have a protective effect on the heart by improving energy metabolism and reducing myocardial cell apoptosis.[44] The application of Zhenwu Decoction (ZWD) in the treatment of $cTnT^{R141W}$ transgenic DCM mice showed that ZWD can reduce the expression of $cTnT^{R141W}$ gene, improve the cardiac structure and myocardial cell ultrastructure

Table 2 Curated Genes on Clinically Available DCM Genetic Testing Panels. Genes are Grouped by Clinical Validity Classification, Ranging from Definitive, Strong and Moderate to Limited, Disputed, and No Known Disease Relationship

Clinical Validity	DCM Genetic
Definitive	BAG3, DES, LMNA, MYH7, PLN, RBM20, SCN5A, TTN, TNNC1, TNNT2, FLNC
Strong	DSP
Moderate	ACTC1, TNNI3, TPM1, VCL, ACTN2, NEXN, JPH2,
Limited	ABCC9, LDB3, MYBPC3, MYH6, TCAP, ANKRD1, CSRP3, LAMA4, MYPN, DSG2, GATAD1, ILK, NEBL, PRDM16, SGCD, EYA4, NKX2-5, TBX2-, DTNA, MYL2, CTF1, PLEKHM2, PSEN2, TNNI3K, OBSCN
Disputed	PDLIM3, PKP2, MYL3, PSEN1
No	MIB1, LRRC10, NPPA

Note: Adapted from Jordan E, Peterson L, Ai T, et al. Evidence-based assessment of genes in dilated cardiomyopathy. Circulation. 2021;144(1):7–19. Creative Commons.[1]

of transgenic mice. It is also possible to inhibit myocardial cell apoptosis by regulating apoptosis factors Bcl-2 and Bax.[45,46] Ginsenoside-Rb1 (Rb1) intervention in cTnT^{R141W} mice not only significantly reduces mortality, ventricular dilation, and systolic dysfunction but also improves cardiac hypertrophy, interstitial fibrosis, ultrastructural degeneration, and intervertebral disc remodeling. The mechanism may be related to reducing the expression of HB-EGF and activating STAT3.[47] Tetramethylpyrazine phosphate (TMPP) inhibits the activation of the Ca^{2+}/CaM/CaMKII pathway in cTnT^{R141W} transgenic mice. Compared with the use of Rb1 or TMPP alone, the combined treatment of Rb1 and TMPP has a synergistic effect on improving chamber dilation, systolic dysfunction, interstitial fibrosis, and ultrastructural degeneration in cTnT^{R141W} mice[48] (Figure 2).

Cardiac Remodeling and Fibrosis

Cardiac remodeling is a crucial step in the development of DCM, involving changes in myocardial cells, non myocardial cells, and extracellular matrix (ECM). During this process, myocardial cells undergo morphological and functional changes. They may experience hypertrophy, apoptosis, or necrosis, leading to dysfunction of myocardial tissue.[49] The remodeling of ECM is mainly manifested by myocardial fibrosis, including excessive deposition of ECM proteins such as collagen. Several studies using LGE-CMR have reported that one third to two thirds (30–66%) of DCM patients suffer from focal myocardial fibrosis. The levels of several fibrosis markers in the serum of DCM patients are significantly elevated, including procollagen type III (PCIII), connective tissue growth factor (CTGF), matrix metalloproteinases (MMP)-2, MMP-9 and tissue inhibitor of metalloproteinases (TIMP)-1.[50]

The architecture of the cardiac muscle is heavily defined by a network of extracellular matrix (ECM) proteins. ECM is a very dynamic structure, which proteins mainly mediated by the CFs, while broke down by MMPs.[51] The balance between synthesis and degradation of ECM proteins is disturbed, leading to excess fibrous connective tissue formation.[52] The most famous fibrogenic factor in this process is TGF-β. Pirfenidone and tranilast have an effect on fibrosis by inhibition of the TGF-β signaling pathway. The renin-angiotensin-aldosterone system (RAAS) has a regulatory effect on myocardial fibrosis. AngII and aldosterone can stimulate collagen synthesis. Additionally, AngII can reduce MMP-1 activity and can induce TGF-β1 expression. Western medicine such as AT1 receptor antagonist losartan was shown to suppress myocardial fibrosis in patients with end-stage renal disease.[53] The use of aliskiren (a renin inhibitor) has been shown to prevent myocardial collagen deposition in a mouse model of myocardial fibrosis.[54]

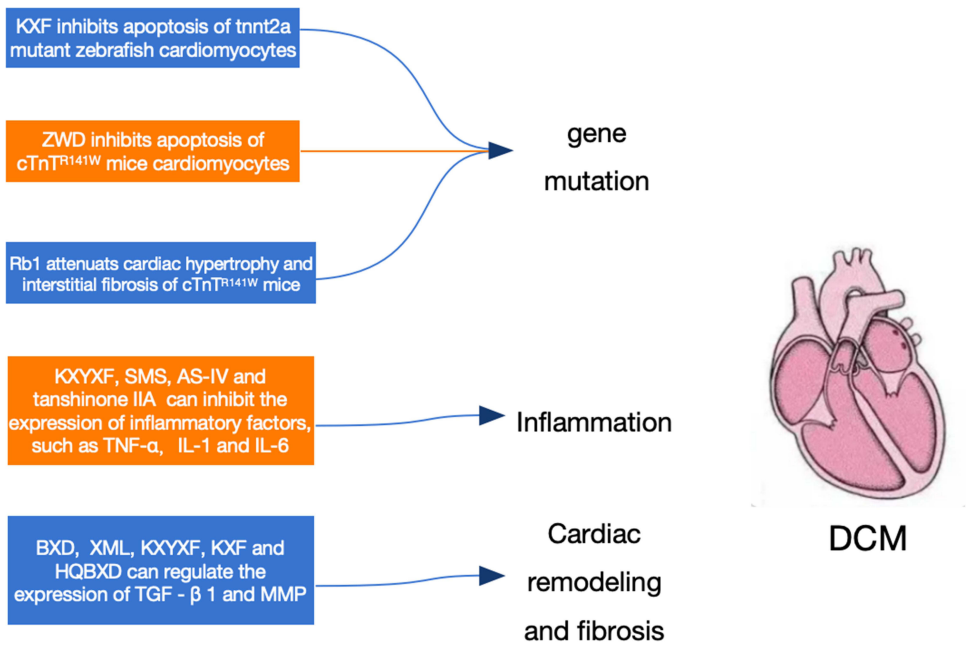

Figure 2 The effect of traditional Chinese medicine on the pathogenesis of DCM.

Baoxin decoction (BXD) can significantly reduce the volume fraction of myocardial collagen in DCM rats. It can downregulate galectin-3, collagen I and III, and is associated with high expression of fibrosis markers. In addition, BXD downregulated the expression of TGF-β1 and Smad3 in myocardial fibrosis rats. It suggests that BXD may improve DCM cardiac function and alleviate myocardial fibrosis by inhibiting the TGF-β1 signaling pathway.[55] XML treatment significantly enhanced the survival rate of rats from epirubicin-induced heart failure. It was observed that the accumulation of collagen was inhibited, and the mRNA levels of MMP-9 and TGF-β1 were reduced in rat heart. So the role of XML in improving cardiac function may be achieved by inhibiting cardiac fibrosis remodeling and preventing left ventricular dilation.[56] Other decoction such as Kangxian Yixin Formula,[57] Kuoxin Recipe,[58] Huangqibaoxin Decoction[59] also have regulatory effects on fibrosis markers such as TGF-β1 and MMP, and reduce collagen deposition (Figure 2).

Inflammation

Inflammation is a common pathological manifestation of DCM. Pathological examination of myocardial biopsy samples of patients with DCM frequently uncovers evidence of an inflammatory cell infiltrate and gene expression patterns compatible with immune cell activation. The most common causes of inflammatory DCM are infections and autoimmunity. They damage the myocardium, then trigger inflammation and recruit immune cells to the heart to repair the myocardium. Immune cells that contribute to remodelling include mast cells, M2 macrophages, T helper 2 (TH2) and TH17 cells and, in the case of autoimmune aetiologies, B cells that produce autoantibodies. Immune cells release cytokines, such as TGF-β1, IL-4, IL-1β, IL-17A, IL-33 and TNF, that promote remodelling, collagen deposition and fibrosis. With time, fibrotic scar tissue eventually replaces the damaged tissue, thereby stiffening the heart and further amplifying the progression to dilation and heart failure.[2]

Many traditional Chinese medicines have a regulatory effect on the inflammatory response of the heart. The combination of Kangxian Yixin Concentrated Pills and Western medicine can better improve the heart function and heart failure degree of DCM patients (Qi deficiency and blood stasis syndrome), enhance their quality of life and clinical efficacy. Compared with the use of Western medicine alone, they have lower levels of TGF-β1, MMP-2, MMP-9, sST2, TNF-α, IL-1, and IL-6 in their blood, and higher levels of TIMP-1 and IL-10.[60] Subsequently, Zeng et al used Kangxian Yixin Formula to intervene in a rat model of doxorubicin induced dilated cardiomyopathy. It was found that Kangxian Yixin Formula can reduce the expression of TNF-α, TGF-β1 by regulating the MCP-1/CCR2 signaling pathway, alleviate myocardial injury and fibrosis.[57] Shengmaisan can regulate the TLR-4/NF-κB signaling pathway in DCM rats, inhibit the expression of downstream inflammatory factors (such as TNF-α and IL-6), ultimately improve cardiac function.[61]

Chinese herbal monomers such as Astragaloside IV (AS-IV) can alleviate inflammatory cell infiltration and cell hypertrophy in the myocardial tissue of DCM rats. Experiments have shown that AS-IV regulates the expression of RORγt and FoxP3, inhibits the differentiation of Th17 cells in spleen tissue, reduces serum levels of IL-17, IL-21, and TNF-α, and improves cardiac function.[62] Sodium tanshinone IIA sulfonate injection can protect the heart of DCM patients with cachexia by inhibiting the release of TNF-α, IL-1, and IL-6 mediated by the TLR4/JNK MAPK pathway.[63] In addition, animal experiments have shown that tanshinone IIA can inhibit myocardial cell apoptosis, reduce serum TNF-α and IL-6 levels, and improve cardiac function by activating the PI3K/Akt signaling pathway in DCM rats[64] (Figure 2).

Related Pathways of TCM Treatment

At present, research on the pathogenesis of DCM is not clear. Known pathways include NF -κB, AMPK/mTOR, TGF-β/Smarts, PI3K/Akt, β-catenin/PPARγ, CaN signaling pathway and so on (Table 3).

TCM Intervention in the NF-κB Signaling Pathway

Cardiac remodeling and heart failure have been implicated in activation of the NF-κB signaling pathway.[65–67] Doxorubicin-induced expression of IKKε, IκBα, p65, RelB, and p100 in the heart tissues of DCM phenotype mice was significantly increased, and knockdown of IKKε ameliorated cardiac insufficiency and myocardial fibrosis in DCM mice.[68]

Huoxue Huayu formula (HXHYF) improved myocardial collagen volume fraction and cardiac mass index, reduced cardiomyocyte apoptosis in DCM mice, as well as decreased NF-κB mRNA and protein content in myocardial tissues of DCM mice.[69] Shenqi Yangxin decoction decreased gene and protein expression of HMGB1, TLR4, RAGE and NF-κB in

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Table 3 Related Pathways of TCM in the Treatment of DCM

Drug	Model	Dosage and Route of Administration	Mechanism	The Herbal Composition (Including the Scientific Name)	Ref
HXHYF A	BALB/c mice	20.5g /kg/day Gavage	Down-regulating NF-κB expression	Astragalus membranaceus, Red ginseng, Birthplace, polygala tenuifolia, Ligusticum wallichii, Platycodon grandiflorum, Salvia miltiorrhiza, silk tree, isatis leaf, rattletop	Wang et al (2015)
HXHYF B	BALB/c mice	20.5g /kg/day Gavage	Down-regulating NF-κB expression	Angelica sinensis, Ligusticum wallichii, prepared rhizome of rehmannia, Carthamus tinctorius, peach kernel, white peony	Wang et al (2015)
SQYX	SD rats	1.87mg/kg/day Gavage	Down-regulating HMGB1, TLR4, RAGE, NF-κB expression	Radix Astragali Mongolici, Radix Ginseng Rubra, Radix Ophiopogonis Japonici, Fructus Schisandrae Chinensis, Radix Salviae Miltiorrhizae, Radix Paeoniae Alba, and Radix Glycyrrhizae	Shen et al, (2018)
SMS	SD rats	0.875g/kg/day Gavage	Down-regulating myocardial tissue TLR-4 and NF- κ B expression	Radix Ginseng Rubra, Radix Ophiopogonis Japonici, Fructus Schisandrae Chinensis	Xing et al, (2018)
ZWD	C57BL/6J mice and $cTnT^{R141W}$ mice	18.2 g/kg/d Gavage	Up-regulating p-AMPKα expression, down-regulating AMPKα, p-mTOR, p62, p-ULK1 and P-TCS2 expression	Poria cocos, Atractylodes macrocephala, monkshood, Chinese herbaceous peony, ginger	Sui et al, (2023)
KXYXF	Wistar rats	High dose: 3.6 g/kg/d, Low dose: 0.9 g/kg/d Gavage	Up-regulating LC3-II/LC3-I, Beclin1 and p-AMPK/AMPK expression, down-regulating p62 and p-mTOR/mTOR expression	Radix Astragali Mongolici, Red ginseng, Radix Salviae Miltiorrhizae, Poria cocos, Cimicifuga, Motherwort, Eupatorium, Radix Ophiopogonis Japonici, Atractylodes macrocephala	Chang et al, (2021)
Mulberry leaf	Lewis rats	Normal powder diet mixed with 5% ML powder fed	Down-regulating p67phox, GRP78, ET-1, p38 MAPK, akt, VEGF, and TGF-β1 expression	Mulberry leaf	Somasundaram Arumugam, (2013)
HSY	SD rats	High dose:5.4mL/kg/d, Low dose: 2.7mL/kg/d Gavage	Down-regulating TGF-β, Smad2, 3 and 4, TIMP-1 expression, up regulating Sirt3, Smad7, MMP2, MMP9 expression	Radix Astragali Mongolici, Codonopsis pilosula Nannf., Ophiopogon japonicus Ker Gawl., Schisandra chinensis Baill	Pan et al, (2021)
KXF	Wistar rats	High dose:7.2g/kg/d, Middle dose: 3.6g/kg/d Low dose: 1.8g/kg/d Gavage	Down-regulating TGF-β1, smad2 expression	Astragalus membranaceus, Polygonatum sibiricum Red, Trichosanthes kirilowii, Ganoderma lucidum, Salvia miltiorrhiza, medical leech, cassia twig, Vitex negundo, Hair holly root, Cat ginseng	Wu et al, (2022)
HQBXD	SD rats	High dose:30g/kg/d, Middle dose: 176g/kg/d Low dose: 7.5g/kg/d Gavage	Down-regulating Galectin-3, TGF-β, smad3 expression	Radix Astragali Mongolici, Codonopsis pilosula Nannf., Radix Salviae Miltiorrhizae, Angelica sinensis, Turtle shell, Forsythia suspensa, Cinnamon twig, Poria cocos, Radix Ophiopogonis Japonici, Fructus Schisandrae Chinensis	Sun, (2017)
KXYXR	Wistar rats	High dose: 18.8g/kg/d, Low dose: 4.7 g/kg/d Gavage	Down-regulating TGF-β1, smad2/3/4/7 expression	Codonopsis pilosula, Astragalus membranaceus, Poria cocos, Atractylodes macrocephala, Salvia miltiorrhiza, motherwort, Ligusticum wallichii, Red peony, Eupatorium, Carthamus tinctorius	Nie et al, (2017)
SDP	SD rats	High dose:5.84g/kg/d, Middle dose: 2.92g/kg/d Low dose: 1.46g/kg/d Gavage	Up-regulating PI3K, Akt, Bcl-2 expression, down-regulating Bax, caspase3, caspase9, expression	Salvia miltiorrhiza, ginseng, Astragalus membranaceus, Angelica sinensis, Carthamus tinctorius, Plantain seed, Cassia twig	Chen et al, (2023)
QSYQ	Lewis rats	High dose:540mg/kg/d, Middle dose: 270mg/kg/d Low dose: 135mg/kg/d Gavage	Up-regulating p-PI3K/PI3K, p-Akt/Akt and p-mTOR/mTOR ratios	Astragalus membranaceus, Salvia miltiorrhiza, pseudo-ginseng, Dalbergia	Lv et al, (2020)

KXYXF	Wistar rats	High dose:3.6g/kg/d, Low dose:0.9g/kg/d Gavage	Up-regulating PPARγ expression, down-regulating β-catenin expression	Radix Astragali Mongolici, Red ginseng, Radix Salviae Miltiorrhizae, Poria cocos, Cimicifuga, Motherwort, Eupatorium, Radix Ophiopogonis Japonici, Atractylodes macrocephala	Liu et al, (2021)
KXYXF	Rat cardiac fibroblasts	0.25 mg /mL Gavage	Up-regulating PPARγ, Sirt3 expression, down-regulating β-catenin, α-SMA, TGF-β1 expression	Radix Astragali Mongolici, Red ginseng, Radix Salviae Miltiorrhizae, Poria cocos, Cimicifuga, Motherwort, Eupatorium, Radix Ophiopogonis Japonici, Atractylodes macrocephala	Wang et al, (2021)
ECYXT	New Zealand rabbits	High dose:8.4g/kg/d, Middle dose: 4.2g/kg/d Low dose: 2.1g/kg/d Gavage	Up-regulating SERCA2a expression, down-regulating CaN expression	Astragalus membranaceus, Salvia miltiorrhiza, Polyporus umbellatus, Alisma, safflower carthamus	LI et al, (2021)
KXYXF	Wistar rats	High dose:3.6g/kg/d, Low dose: 1.8g/kg/d Gavage	Down-regulating CaN, NAFT3 expression	Radix Astragali Mongolici, Red ginseng, Radix Salviae Miltiorrhizae, Poria cocos, Cimicifuga, Motherwort, Eupatorium, Radix Ophiopogonis Japonici, Atractylodes macrocephala	Zeng et al, (2022)
Baicalin	Wistar rats	High dose:100mg/kg/d, Middle dose: 50mg/kg/d, Low dose: 25mg/kg/d Gavage	Down-regulating β1-AR, PKA, CaMKII expression	Baicalin	Wang et al, (2018)

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rat myocardial tissues. The mechanism of its treatment for DCM may be related to the regulation of the HMGB1-TLR4/RAGE/NF-κB signaling pathway.[70] SMS effectively inhibited myocardial injury and improved cardiac function in DCM rats, which may be achieved by regulating the TLR4/NF-κB signaling pathway and downstream inflammatory factors.[61]

TCM Intervention in the AMPK/mTOR Signaling Pathway

SUNG et al studied skeletal muscle-specific deletion of β1 and β2 subunits (β1β2 M-KO) mice. They found that these mice exhibited DCM-like cardiac structural alterations and cardiac dysfunction. It suggested that there is a certain synchronization between AMPK deletion in the skeletal and cardiac muscles, and that DCM can be induced as a result.[71] Zhang et al showed that adriamycin inhibits AMPK activity, activates mTOR, aggravates oxidative stress and impairs metabolism, down-regulates autophagy, and increases the number of cardiomyocyte apoptosis, leading to heart failure in DCM.[72]

ZWD significantly improved cardiac function and reduced myocardial fibrosis in DCM mice. The mechanism may be related to the regulation of AMPKα/mTOR pathway to increase autophagy.[73] KXYXF can improve cardiac function, reduce mitochondrial damage, and regulate AMPK and mTOR expression levels in DCM rats. It is hypothesized that KXYXF activates the AMPK/mTOR signaling pathway, enhances autophagy and inhibits the progression of DCM.[74] Morus alba (ML) not only attenuates myocardial fibrosis but also improves left ventricular ejection fraction and shortening fraction in rats after myocarditis. The mechanism may be related to the reduction of myocardial endothelin-1, activated members of the MAPK pathway and vascular endothelial growth factor.[75]

TCM Intervention in TGF-β/Smads Signaling Pathway

The TGF-β/Smads signaling pathway has a wide range of biological activities, and its excessive activity can contribute to MF.[76] In contrast, the severity of MF is strongly associated with other markers of adverse ventricular remodeling as well as all-cause mortality.[77]

Huangqi Shengmai Yin up-regulates FS and EF and attenuates left ventricular systolic dysfunction in rats with myocardial fibrosis. It inhibits the TGF-β/Smad pathway primarily by increasing the expression of silencing message regulator 3, which inhibits fibroblast activation and improves ventricular remodeling.[78] KXF significantly reduced the levels of TGF-β1 and Smad2 proteins, as well as Col 1 I and Col III in myocardial tissues. It was shown that KXF improved myocardial fibrosis in DCM rats by inhibiting the TGF-β1/Smad2 signaling pathway.[58] Other Chinese medicines, such as HQBXD[59] and KXYXR,[79] can also treat DCM by inhibiting the TGF-β/Smad signaling pathway to alleviate collagen deposition.

TCM Intervention in the PI3K/Akt Signaling Pathway

Intracellular and extracellular information is transmitted by the PI3K/Akt signaling pathway to regulate cell survival, apoptosis, differentiation, etc.[80] After PI3K binds to Akt, it can promote the phosphorylation of downstream substrates such as Caspase - 3 and mTOR to inhibit apoptosis.[81] Experiments have confirmed that up-regulating microRNA-132 promoted the proliferation of cardiomyocytes, reduced the apoptosis of cardiomyocytes, and inhibited myocardial fibrosis (MF) by activating the PI3K/Akt signaling pathway in rats with dilated cardiomyopathy (DCM).[82] DONG et al found that the PI3K/Akt/HK II signaling pathway was involved in the pathological process of DCM by regulating cardiomyocyte apoptosis in cTnTR141W transgenic mice.[83]

Qishen Yiqi Pill (QSYQ) has the effect of improving myocardial remodeling. It improved the cardiac function of rats induced by cardiac myosin, and reduced the histological score of muscle inflammation and the collagen volume fraction. QSYQ increased the ratios of p-PI3K/PI3K, p-Akt/Akt, and p-mTOR/mTOR in the rat myocardium, indicating that it can effectively inhibit myocardial fibrosis by regulating the PI3K/Akt - mTOR pathway in rats.[84] Shendan Formula (SDP) reduced plasma NT-proBNP, cTnT, and CK, and increased the expressions of PI3K and Akt in DCM rats, which confirmed that SDP may inhibit cardiomyocyte apoptosis and myocardial fibrosis in DCM rats through the PI3K/AKT signaling pathway.[85]

TCM Intervention in the β-Catenin/PPARγ Signaling Pathway

β-catenin is the key molecule in the Wnt signaling pathway and plays an important regulatory role in embryonic development, cell-specific differentiation, etc.[86,87] PPARγ, the downstream protein of β–catenin, is a growth-limiting factor, which widely

expressed in the myocardium, smooth muscle, and adipose tissue.[88] Experimental studies have shown that the β-catenin/PPARγ signaling pathway can promote myocardial fibrosis (MF) and aggravate heart failure in dilated cardiomyopathy (DCM).[87]

Administration of the KXYXF regulated the expression of β-catenin and PPARγ in the myocardial tissue of DCM rats, and improved cardiac function and MF degree. It suggested KXYXF improved myocardial fibrosis in DCM by regulating the β- catenin/PPARγsignaling pathway.[89] Further mechanism verification has shown that the KXYXF inhibited the trans-differentiation of rat fibroblasts induced by AngII by regulating the Sirt3/β-catenin/PPARγ pathway.[90]

TCM Intervention in the CaN Signaling Pathway

CHU et al found that the expression, and activity of CaN were increased in cardiomyocytes in neonatal rats induced by AngII with increased intracellular Ca^{2+}, which suggests that the CaN signaling pathway is related to cardiomyocyte hypertrophy.[91] Based on the results of myocardial tissue biopsies of DCM patients, VIGLIANO et al confirmed that cardiomyocyte hypertrophy and autophagic vacuolation are prognostic predictors for idiopathic DCM and severe heart failure.[92]

Yixintai improved heart failure by increasing the expression of SERCA2a, reducing the concentration of Ca^{2+}, and inhibiting the expression of CaN in the myocardial tissue of DCM rabbits.[93] KXYXF also decreased the CaN and NAFT3 proteins in the myocardial tissue of DCM rats.[94]

Conclusion

DCM, as a type of primary cardiomyopathy, has complex pathological and physiological mechanisms. The long-term efficacy of conventional Western medicine treatment is limited. Although some new treatment methods, such as gene therapy and stem cell transplantation, are emerging, they have not yet been popularized due to their immaturity and high economic costs. Many studies have shown that TCM can not only significantly alleviate clinical symptoms and reduce the toxic side effects of Western medicine but also improve myocardial abnormalities and reverse myocardial fibrosis at the cellular and molecular levels, with its unique individualized treatment method based on syndrome differentiation. It has achieved good therapeutic effects in reducing mortality rate, improving quality of life, and improving prognosis. But potential adverse effects such as herb-drug interactions (eg, anticoagulant herbs with antiplatelet drugs) and hepatotoxicity require further evaluation.

However, research on the treatment of TCM also has certain limitations, such as: ①The lack of standardized disease names, classifications, and medication for DCM, making it difficult to promote effective TCM diagnosis and treatment methods; ②In clinical research of TCM, the clinical sample size is relatively small, and lack of long-term follow-up research. The scientific research design is also not rigorous. So the statistical results may also have certain deviations; ③The animal model research of DCM in experimental research lags behind. The credibility of experimental evidence needs to be improved. It is necessary to draw on cutting-edge research data and advanced technologies at home and abroad; ④The characteristic of TCM is that it has multiple links and targets. So, a single molecular study cannot fully explain the mechanism of TCM.

Therefore, we still need to conduct large-scale, multicenter clinical studies to gradually form systematic and standardized clinical standards for TCM. In terms of basic research, we should focus on the research experiments of multiple targets and pathways of TCM, introduce modern medical scientific research techniques and methods, integrate multi-omics approaches (eg, transcriptomics, metabolomics) to elucidate the network pharmacology of TCM and validate its multi-target effects.

Author Contributions

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

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