Diabetology &
Metabolic Syndrome

REVIEW

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Therapeutic potential of finerenone for diabetic cardiomyopathy: focus on the mechanisms

Jing Wang[1†], Haojie Xue[1†], Jinyu He[1†], Li Deng[2], Julong Tian[3], Yang Jiang[1*] and Jian Feng[1*]

Abstract

Diabetic cardiomyopathy (DCM) is a kind of myocardial disease that occurs in diabetes patients and cannot be explained by hypertensive heart disease, coronary atherosclerotic heart disease and other heart diseases. Its pathogenesis may be closely related to programmed cell death, oxidative stress, intestinal microbes and micro-RNAs. The excessive activation of mineralocorticoid receptors (MR) in DCM can cause damage to the heart and kidneys. The third-generation non-steroidal mineralocorticoid receptor antagonist (MRA), finerenone, can effectively block MR, thus playing a role in protecting the heart and kidneys. This review mainly introduces the classification of MRA, and the mechanism of action, applications and limitations of finerenone in DCM, in order to provide reference for the study of treatment plans for DCM patients.

Keywords Finerenone, Diabetic cardiomyopathy, Programmed cell death, Oxidative stress, Intestinal microbiota

Classification of mineralocorticoid receptor antagonists

Aldosterone is the main mineralocorticoid that can bind to the mineralocorticoid receptor (MR) to maintain water and electrolyte balance and induce pro-inflammatory activity in the body, and ultimately lead to dysfunction and failure of target organs such as the heart and kidneys [1, 2].

Mineralocorticoid receptor antagonists (MRAs) can inhibit the excessive activation of MR, thereby playing a role in protecting the heart and kidneys [3, 4]. According to molecular structure, MRA can be divided into traditional steroidal MRA and new generation non-steroidal MRA [5]. Steroid MRA mainly includes spironolactone and eplerenone, which have steroidal structures. However, spironolactone has low selectivity for MR and a higher incidence of hyperkalemia after administration [6]. Eplerenone has higher selectivity for MR, stronger anti aldosterone activity and lower side effects than spironolactone [7]. Non-steroidal MRA mainly includes finerenone, Esaxerenone, AZD9977, Aparenone, and KBP-5074, which have non steroidal structures [5, 8]. Finerenone has high selectivity for MR and is less prone to side effects such as hyperkalemia [9].

[†]Jing Wang, Haojie Xue and Jinyu He contributed equally to this work.

*Correspondence:
Yang Jiang
jy93954924@qq.com
Jian Feng
jerryfeng@swmu.edu.cn
[1] Department of Cardiology, Stem Cell Immunity and Regeneration Key Laboratory of Luzhou, The Affiliated Hospital of Southwest Medical University; Southwest Medical University Affiliated Hospital Medical Group Gulin Hospital (Gulin County People's Hospital), Luzhou, Sichuan, China
[2] Department of Rheumatology, The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan, China
[3] Department of Cardiology, The Affiliated Hospital of Panzhihua University, Panzhihua, Sichuan, China

Mechanism and function of finerenone in diabetic cardiomyopathy

Diabetic cardiomyopathy (DCM) is an organic heart disease resulting from abnormal myocardial structure and function in individuals with DM who do not have other conditions, such as coronary artery disease, hypertension, valvular heart disease and congenital heart disease. DCM arises due to dysregulated glucose and lipid metabolism associated with DM, triggering the activation of various inflammatory pathways [10]. Research has found that DCM is closely related to programmed cell death, oxidative stress, intestinal microbiota, and MicroRNAs (miRNAs) [11–14]. Finerenone is a non-steroidal MRA, and there is extensive research evidence (Phase III study FIDELIO/FIGARO) indicating that finerenone can provide protective effects on the heart and kidneys [15]. As a type of MRA, finerenone can affect programmed cell death [16]. By blocking the MR, finerenone may also inhibit the generation of reactive oxygen species (ROS), which promote oxidative stress in cells, leading to tissue injury [4] (Table 1). However, further research is needed to investigate the relationship between finerenone and intestinal microbiota as well as miRNAs.

Programmed cell death and finerenone in diabetic cardiomyopathy

In biology, cell death is broadly classified as necrosis and programmed cell death (PCD). PCD includes apoptosis [23], autophagy [23], pyroptosis [24], ferroptosis [25] and more. More and more evidence has demonstrated that PCD of cardiomyocytes is a major contributor to the development of DCM [24, 26–28]. Therefore, it is particularly important to regulate the death of cardiomyocytes in patients with diabetes cardiomyopathy. Some studies have found that finerenone can reduce cell apoptosis, restore autophagy levels and ameliorated cell pyroptosis [12, 16, 29].

Apoptosis

Apoptosis is a programmed and active death process that occurs in cells under the control of specific genes or pathways. It is carried out by proapoptotic caspases (mainly caspase-2/3/6/7/8/9/10), which cleave intracellular substrates, causing cytoplasmic contraction, chromatin concentration, nuclear dissolution, and membrane foaming, ultimately decomposing into membrane encapsulated apoptotic bodies [23]. Studies have shown that long-term hyperglycemia and excessive uptake and accumulation of free fatty acids in diabetes patients can induce cardiomyocyte apoptosis, and apoptosis promotes cardiomyocyte damage in DCM patients through a variety of signal pathways, for example, through extrinsic and intrinsic apoptotic pathways (involving caspase-3/8/9) to cause cardiomyocyte apoptosis [16, 30, 31]. And, there is an upregulation of the renin–angiotensin–aldosterone system in DCM, resulting in an increase in aldosterone levels [32, 33], and aldosterone induces cardiomyocyte apoptosis through dependence on G protein-coupled receptor-kinase (GRK) [34]. In addition, DCM can also cause vascular damage and endothelial dysfunction [30, 35].

Experiments have shown that finerenone can down-regulate the TNFa/TNFR1/CASPASE8 signaling pathway to reduce the apoptosis of cardiomyocytes [16]. And it can improve lipid metabolism in cardiomyocytes and reduce myocardial lipid uptake by down-regulating

Table 1 Basic science trials of finerenone

Target	Organ and tissue	Model	Effect
TNFa/TNFR1/CASPASE8	Heart	High-fat diet/low-dose streptozotocin-induced diabetic rats	Reduce the apoptosis of cardiomyocytes [16]
PPARγ/CD36	Heart	High-fat diet/low-dose streptozotocin-induced diabetic rats	Improve lipid metabolism in cardiomyocytes; inhibit apoptosis and oxidative stress [16]
GRK5	H9c2 cardiomyocytes	Cells endogenously express the MR and GRK5	Inhibit apoptosis, oxidative stress, and fibrosis [17]
MR	Human coronary artery SMCs and umbilical vein ECs	Cells were incubated with aldosterone	Reduce SMC proliferation and EC apoptosis [18]
PI3K/Akt/eNOS	Kidney	High-fat diet/streptozotocin-induced diabetic rats	Restore the mitophagy [19]
MR	Vascular smooth muscle cells	Noninfarcted mice incubated with low-dose angiotensin-II	Inhibit oxidative stress [20]
MR	Heart	Zucker fa/fa rats	Inhibit oxidative stress [21]
MR	Heart	Obese ZSF1 rats	Attenuate cardiac diastolic dysfunction and improve cardiac perfusion [22]

PPARγ/CD36 to indirectly improve cardiomyocyte apoptosis [16, 30, 36]. On the other hand, as a type of MRA, finerenone can block the MR of the heart, thereby blocking aldosterone induced apoptosis. GRK-5 blocks the cardiac actions of aldosterone via phosphorylation of the MR [37]. Finerenone can induce GRK-5's phosphorylation and suppress MR basal transcriptional activity in GRK5-overexpressing cardiomyocytes (finerenone's inverse agonism at the cardiac MR), which plays an important role in blocking cardiomyocyte apoptosis.

In an experiment on vascular injury, non-steroidal MRA finerenone prevents aldosterone-induced smooth muscle cell (SMC) proliferation and endothelial cell (EC) apoptosis [18]. Excessive activation of MR in ECs can lead to endothelial dysfunction, finerenone can block the excessive activation of MR and thus block this process [38, 39].

Autophagy

Autophagy is an intracellular degradation process that encapsulates intracellular substances into double layered membrane vesicles, forming autophagosomes that are then fused by lysosomes to degrade and recycle these substances. The autophagy process is strictly regulated by the body and is crucial for maintaining the homeostasis of the intracellular environment. But abnormal autophagy can lead to cell death [23]. According to current studies, autophagy is regulated mainly by the phosphatidylinositol 3-phosphate kinase-mamma-lian target of rapamycin (PI3K-mTOR) signal transduction pathway upstream of autophagy-associated genes (ATG) and the Beclin1 complex [23, 40]. Research has shown that DCM is closely related to inhibition of cellular autophagy [11, 28]. High fat environment will inhibit myocardial autophagy in patients with diabetes, and in high glucose environment, this autophagy inhibition will worsen [41].

Although the mechanism by which finerenone restores autophagy in cardiomyocytes is not clear, studies have shown that finerenone can attenuate mitochondrial autophagy disruption in renal tubular epithelial cells of patients with diabetes nephropathy by inhibiting MR [19], which may provide guidance.

Pyroptosis

Pyroptosis is a form of PCD that is related to the innate immune response (such as pathogen invasion), and it is usually activated by inflammatory caspases (mainly caspase-1/4/5/11) and caspase-3 and relies on Gasdermin family proteins to form membrane pores, leading to nuclear fragmentation and dissolution, increased cell membrane permeability, swelling and lysis, and release of cellular contents, thereby causing local inflammatory reactions [23, 26, 42]. Moreover, studies have found that pyroptosis is also involved in the formation of DCM [42, 43]. NLRP3 inflammasome activation of caspase-1-mediated pyroptosis plays an important role in the development of diabetic cardiomyopathy [42].

As a type of MRA, finerenone can block inflammation caused by excessive activation of MR [33]. However, whether finerenone can also inhibit NLRP3-mediated pyroptosis in cardiomyocytes remains to be verified.

Oxidative stress and finerenone in diabetic cardiomyopathy

Oxidative stress refers to the imbalance between oxidative and antioxidant effects in the body. The "redox state" is determined by the balance between production of reactive oxygen species (ROS) and their removal by the antioxidant defense system. When this balance is disrupted, excessive ROS production and/or inadequate ROS detoxification may result in ROS-induced damage to DNA, proteins, lipids and micro RNA, leading to irreversible cell damage and death [44, 45]. Meanwhile, studies have shown that reactive nitrogen species (RNS) are also involved in oxidative stress [46, 47].

Oxidative stress is believed to play an important role in DCM. Although pathogenic factors (such as high sugar and high fat) can lead to DCM through different mechanisms, the main contribution of these pathogenic factors to DCM is oxidative stress. And oxidative stress can also mediate programmed cell death, mitochondrial dysfunction, inflammation, and so on [46–48]. Due to the abundant energy provided by mitochondria for cardiac activity, when mitochondrial function is impaired, it can have harmful effects on the heart. Multiple signaling pathways are involved in the oxidative stress of DCM [47, 49], and understanding these signaling pathways has beneficial results for antioxidant therapy. And the antioxidant mechanism is another noteworthy issue. The elimination of ROS depends on enzymes such as catalase and superoxide dismutase (SOD) [12]. The MRA, finerenone, can effectively block oxidative stress induced by aldosterone, thereby protecting the heart [17].

Mitochondrial dysfunction

As the energy factory of cells, mitochondria play an important role in the sustained functioning of cells, and mitochondrial dysfunction is closely related to DCM [50]. The heart is an organ with high energy requirements, and most of the ATP it consumes comes from the oxidative metabolism of mitochondria. Mitochondria in the heart account for one-third of the volume of adult cardiomyocytes [51]. Therefore, the heart is greatly affected by mitochondrial dysfunction.

Mitochondria, as producers of intracellular energy, are also the main targets of oxidative stress. There are multiple main sources of ROS production in cardiomyocytes. However, mitochondrial sources of ROS are thought to represent the major ROS burden in the context of diabetes [44]. Persistent hyperglycemia can lead to excessive production of ROS by cardiomyocytes [52]. Increased mitochondrial ROS induce oxidative damage to DNA, proteins and lipids, and may trigger a variety of pathological pathways involved in mitochondrial and cellular damage [53, 54].

In recent years, many studies have shown that oxidative stress can affect mitochondrial function through various factors such as affecting calcium ion levels, mitochondrial membrane potential, and respiratory chain complexes [53, 55–57]. When cardiomyocytes are subjected to oxidative stress, the concentration of calcium ions in mitochondria increases, thus inhibiting the generation of mitochondrial ATP [55]. Mitochondrial dysfunction can lead to the generation of ROS, forming a "vicious cycle" of enhanced oxidative stress.

Signaling pathway of finerenone in oxidative stress

Finerenone has certain antioxidant potential. Research has shown that finerenone abrogated oxidative stress in vascular smooth muscle cells from noninfarcted mice incubated with low-dose angiotensin-II [20]. It was also found that finerenone reduced the production of myocardial ROS after short-term administration in Zucker fa/fa rats (a rat model of metabolic syndrome) [21]. In general, finerenone can exert certain benefits in cardiac protection by inhibiting oxidative stress. The analysis of the signaling pathway of finerenone in oxidative stress helps to deepen the understanding of the drug's mechanism of action, thus providing a basis for the formulation of disease treatment strategies.

In rat kidney fibroblast cells, activation of MR induces mitochondrial dysfunction through the PI3K/Akt/eNOS pathway. PI3K phosphorylation stimulates its downstream protein Akt, phosphorylates Akt (p-Akt) and eNOS, regulating a variety of physiological functions, triggering mitochondrial dysfunction. Finerenone normalizes mitochondrial dysfunction by blocking MR, ultimately reducing ROS production [19]. This is helpful for studying the role of finerenone in cardiac oxidative stress.

Finerenone improves cardiomyocyte metabolism and reduces ROS generation through PPARα/CD36 pathway. A nuclear receptor, peroxisome proliferator-activated receptor alpha (PPARα), plays an important role in myocardial substrate metabolism by regulating the transcription of genes involved in FA transport, esterification, and oxidation [47, 58]. Due to insulin resistance or lack of insulin in DCM, the uptake and utilization of glucose in cardiomyocytes are limited, and the expression of CD36 (FFA translocatase) in cardiomyocytes is increased [16], which mediates the entry of FFA into cells, thus activating PPARα, which will promote the β-oxidation (β-ox) of FFA in mitochondria, and thus promote the production of ROS [59–61]. The ROS and the expression of PPARγ and CD36 decreased after finerenone treatment, thus effectively blocking oxidative stress [16]. MR activation contributes to aldosterone-mediated activation of NADPH oxidase mediated generation of ROS in the heart and coronary microvascular [62]. Finerenone inhibits this process by blocking MR.

Intestinal microbiota and finerenone in diabetic cardiomyopathy

Maintaining a healthy microbiota in the gut is crucial for maintaining homeostasis. However, when intestinal microbial homeostasis is disrupted, it can induce the development of different diseases [63]. Intestinal microbiota and its metabolites can affect the development of diabetic cardiomyopathy by regulating oxidative stress [64], inflammation [65], insulin resistance [66], apoptosis [67], and autophagy [67, 68]. At present, the relationship between finerenone and intestinal microbiota is not clear, and the specific mechanism needs to be more thoroughly investigated.

MicroRNAs (miRNAs) and finerenone in diabetic cardiomyopathy

MicroRNAs (miRNAs) are a type of noncoding RNAs (ncRNAs) that are approximately 22-nucleotide (nt) long and are encoded by endogenous genes. MiRNAs participate in transcriptional or posttranscriptional regulation by binding to the untranslated regions of target mRNAs, thus participating in the regulation of human pathophysiological processes [14]. Based on previous studies it was found that more than 300 different miRNAs play a role in DCM [69]. For example, experiments have shown that miRNA-373 can participate in the mitogen-activated protein kinase (MAPK) mediated signaling pathway, playing an important role in cardiomyocytes hypertrophy by targeting the hypertrophic protein, MEF2C [70]. MiRNA-503 was involved in the progress of apoptosis in DCM via regulating Nrf2/ARE signaling pathway [71].And miRNA-30c can participate in the

Table 2 Effect of finerenone in clinical treatment

Type	Object	Follow-up period	Effect of outcome
Clinical trial (FIDELIO-DKD)	5674 patients with type 2 diabetes with CKD	Median follow-up of 2.6 years	Reduce risks of CKD progression and cardiovascular events [73]
Clinical trial (FIGARO-DKD)	7352 patients with CKD and type 2 diabetes	Median follow-up of 3.4 years	Improve cardiovascular outcomes [74]
Randomized, double-blind trial (ARTS Part B)	392 patients with HFrEF and moderate CKD	29 ± 2 days	Decrease the levels of B-type natriuretic peptide, amino-terminal proBNP, and albuminuria; have lower incidences of hyperkalaemia and worsening renal function than spironolactone [75]
Randomized, double-blind trial (ARTS-HF)	1066 patients with worsening chronic heart failure and diabetes mellitus and/or CKD	90 days	Induce a 30% or greater decrease in NT-proBNP levels in a similar proportion of patients to eplerenone [77]
Meta-analysis	51,496 patients with type 2 diabetes and CKD	Ranged from 90 days to 4 years	Reduce the risk of major adverse cardiovascular events, renal outcome and hospitalization for heart failure [78]

PPARα mediated signaling pathway, regulating cardiac oxidative stress by targeting peroxisome proliferator-activated receptor coactivator 1β (PGC-1β) [72]. Therefore, targeting a particular miRNA involved in a specific signaling pathway in the diabetic heart may provide a therapeutic effect to ameliorate diabetic cardiomyopathy. Finerenone can play a certain role in DCM through PPARγ/CD36 pathway [16]. Therefore, it remains to be further confirmed whether there is any relationship between it and miRNA-30c or other miRNAs.

Therapeutic applications and limitations of finerenone in diabetic cardiomyopathy

The data from clinical trials with finerenone has expanded the treatment options for cardiorenal disease management for patients with T2DM (Table 2). The results of the two major studies, FIDELIO-DKD and FIGARO-DKD, are mutually validated, and it is believed that finerenone can improve renal and cardiovascular outcomes, bringing more benefits to patients [15, 73, 74]. Although finerenone has shown positive effects in cardiorenal protection, it may also be accompanied by some side effects. Common side effects include hyperkalemia, headache, nausea, diarrhea and so on. In addition, some patients may experience adverse reactions such as hypoglycemia, and allergies [73–75]. Therefore, when using finerenone for disease treatment, it is necessary to pay attention to monitoring the patient's blood pressure and electrolyte levels, and closely observe the patient's condition.

In summary, finerenone is a novel and promising therapeutic drug for patients with chronic kidney disease (CKD), which has received regulatory approval with the indication of cardiorenal protection in patients with CKD associated with type 2 diabetes [76]. And, its indications include cardiovascular related benefits (reducing the risk of cardiovascular death and hospitalization due to heart failure). Although it has not yet been approved for use in DCM, with the expansion of new indications and continuous accumulation of clinical practice in China, finerenone may have broad clinical application prospects in the fields of CKD and chronic cardiovascular disease (CVD).

Conclusions and perspectives

Current studies indicate that finerenone can play an important role in cardiorenal protection. Compared with the first and second generation steroid MRA, the third generation non-steroidal MRA has higher affinity and selectivity for MR, and fewer side effects. A large number of experiments have shown that finerenone can inhibit the overactivation of MR. It can effectively block programmed cell death in the heart, including inhibiting cardiomyocyte apoptosis through the TNFa/TNFR1/CASPASE8 signaling pathway or downregulating PPARγ/CD36 and restoring autophagy in cardiomyocytes. Moreover, finerenone can inhibit oxidative stress, which reduces ROS production through the PPARα/CD36 pathway and inhibition of aldosterone mediated activation of NADPH oxidase (Fig. 1 By Figdraw). At the same time, finerenone can effectively anti-inflammatory and reduce vascular injury. These will lead to a certain therapeutic effect of finerenone in DCM patients (Fig. 2 By Figdraw), but it is also necessary to be alert to its possible side effects. It is worth noting that currently,

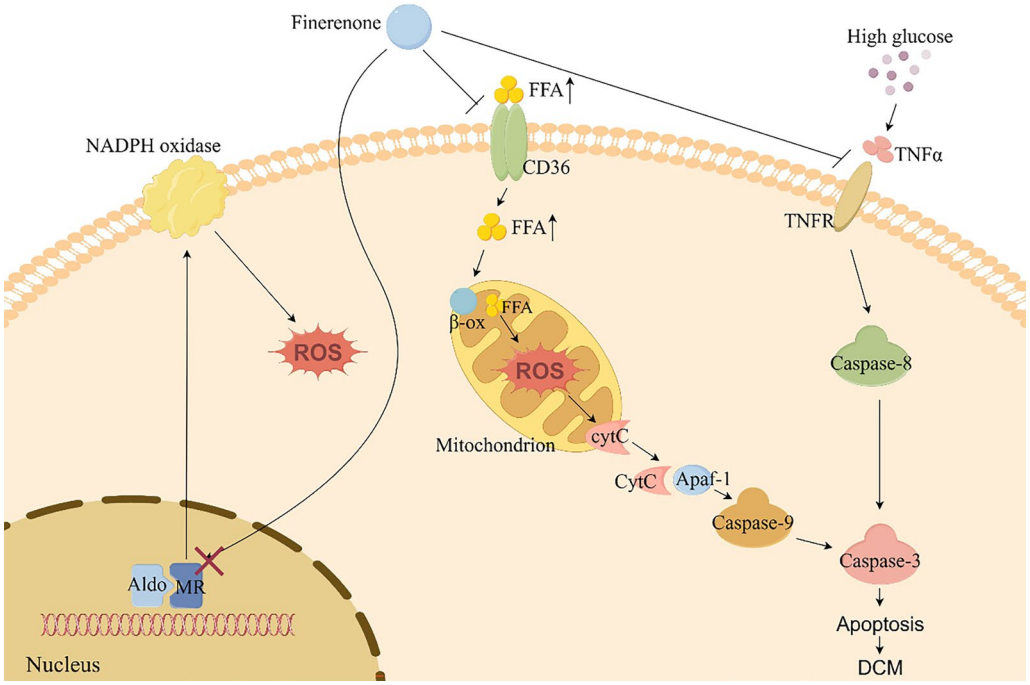

Fig. 1 Related signaling pathways of finerenone in DCM

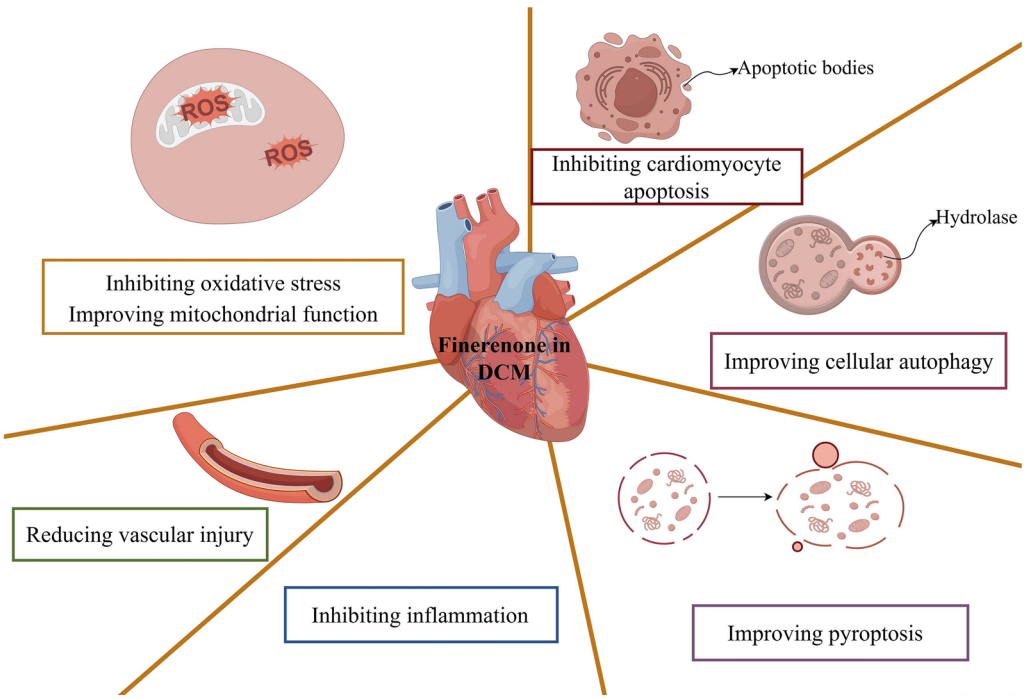

Fig. 2 Potential protective effects of finerenone in DCM

intestinal microbiota and miRNAs have become relevant factors for the onset of DCM, but further experimental research is needed to investigate the relationship between finerenone and the above two. At the same time, the mechanism of action of finerenone in DCM is not fully understood. Through continuous research in the future, it is expected to become an innovative therapeutic drug in the field of CVD.

Abbreviations

MR	Mineralocorticoid receptor
MRAs	Mineralocorticoid receptor antagonists
DCM	Diabetic cardiomyopathy
miRNAs	MicroRNAs
ROS	Reactive oxygen species
RNS	Reactive nitrogen species
PCD	Programmed cell death
GRK	G protein-coupled receptor-kinase
TNFa	Tumor necrosis factor alpha
PPAR	Peroxisome proliferators-activated receptors
FFA	Free fatty acids
SMC	Smooth muscle cell
EC	Endothelial cell
ATG	Autophagy-associated genes
SOD	Superoxide dismutase
β-ox	β-Oxidation
ncRNA	Noncoding RNAs
PGC-1β	Peroxisome proliferator-activated receptor coactivator 1β
CKD	Chronic kidney disease
CVD	Cardiovascular disease
CytC	Cytochrome *C*
Apaf-1	Apoptotic protease activating factor-1
Aldo	Aldosterone

Author contributions

JW, HX, and JH conceived, designed, and planned the manuscript. JW, HX, and JH collected and read the literature. JW drafted the manuscript and prepared Figs. 1, 2. LD made extensive revisions to the manuscript during the revision process. JT analyzed the data. JF and YJ conceived, designed, and revised the manuscript. All authors read and approved the final manuscript.

Funding

This research was funded by grants from Sichuan Science and Technology Program (2022YFS0610), Luzhou Municipal People's Government—Southwest Medical University Science and Technology Strategic Cooperation (2021LZXNYD-J33), Hejiang County People's Hospital—Southwest Medical University Science and Technology Strategic Cooperation Project (2021HJXNYD13, 2021HJXNYD04 and 2022HJXNYD05), Xuyong County People's Hospital—Southwest Medical University Science and Technology Strategic Cooperation Project (2024XYXNYD18) and Gulin County People's Hospital—Affiliated Hospital of Southwest Medical University Science and Technology strategic Cooperation (2022GLXNYDFY13), 2022-N-01-33 project of China International Medical Foundation, Provincial-level science and Technology Program Transfer Payment Special Fund project of Panzhihua Science and Technology Bureau (222ZYZF-S-01).

Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 16 July 2024 Accepted: 6 September 2024
Published online: 18 September 2024

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