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Mitochondrial calcium uniporter complex: An emerging therapeutic target for cardiovascular diseases (Review)

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Abstract. Cardiovascular disease (CVD) is currently a major factor affecting human physical and mental health. In recent years, the relationship between intracellular Ca^{2+} and CVD has been extensively studied. Ca^{2+} movement across the mitochondrial inner membrane plays a vital role as an intracellular messenger, regulating energy metabolism and calcium homeostasis. It is also involved in pathological processes such as cardiomyocyte apoptosis, hypertrophy and fibrosis in CVD. The selective mitochondrial calcium uniporter complex (MCU complex) located in the inner membrane is essential for mitochondrial Ca^{2+} uptake. Therefore, the MCU complex is a potential therapeutic target for CVD. In this review, recent research progress on the pathophysiological mechanisms and therapeutic potential of the MCU complex in various CVDs was summarized, including myocardial ischemia-reperfusion injury, pulmonary arterial hypertension, other peripheral vascular diseases, myocardial remodeling and arrhythmias. This review contributes to a deeper understanding of these mechanisms at the molecular level and highlights potential intervention targets for CVD treatment in clinical practice.

Contents

1. Background

Cardiovascular diseases (CVD) remain the leading cause of mortality and morbidity worldwide, with the number of deaths from CVD having increased by 12.5% globally over the past decade (1). Common risk factors include hypertension, hyperlipidemia, hyperglycemia and smoking. Abnormal substance metabolism is ultimately linked to the onset of CVD (2). However, the mechanisms underlying CVD are highly complex. Currently, it is thought that one of the key features of CVD pathogenesis is abnormal energy metabolism, leading to cellular dysfunction, pathological aging of cardiomyocytes, apoptosis and myocardial fibrosis (3). Intracellular Ca^{2+} serves as an essential messenger involved in these processes (4-6). Research suggests that elevated Ca^{2+} levels may predict the development of CVD (7). Ca^{2+} has a significant role in regulating the excitation-contraction coupling mechanism of cardiomyocytes. Furthermore, Ca^{2+} is central to adaptive tissue regulation (8,9). In vascular smooth muscle cells (VSMCs), Ca^{2+} is critical for controlling blood flow and vessel lumen diameter. It induces VSMC contraction by forming a complex with the calcium-binding protein calmodulin, which activates myosin light-chain kinase (10). Under prolonged stress, elevated Ca^{2+} levels in cardiomyocytes and VSMCs result in cellular stress, eventually leading to cell death (11). In summary, Ca^{2+} plays a crucial regulatory role in the initiation, progression and outcomes of CVD.

Mitochondrial Ca^{2+} (mCa^{2+}) transport plays a critical role in regulating ATP production, intracellular calcium signaling, energy metabolism, reactive oxygen species (ROS) production and cell death (12). The mitochondrial calcium uniporter (MCU) complex is a highly selective calcium ion channel located in the inner mitochondrial membrane and is the primary pathway for calcium ions entering the mitochondrial matrix (13). Ca^{2+} from the endoplasmic reticulum

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and cytoplasm permeates the intermembrane space (IMS) through the voltage-dependent anion channel 1 (VDAC1) and is subsequently transported into the mitochondrial matrix via the MCU complex (14). When the Ca^{2+} load exceeds the system's capacity, it disrupts cellular energy metabolism and oxidative stress, eventually leading to necrosis or apoptosis (6). Therefore, the MCU complex appears to have a central role in regulating mCa^{2+} flux, which directly affects intracellular Ca^{2+} homeostasis. The disruption of this balance is closely associated with the progression of numerous diseases. This review focuses on exploring the biological effects and regulatory mechanisms of the MCU complex in CVD. A comprehensive summary of the MCU complex's role in mCa^{2+} flux-related cardiovascular conditions was provided, including myocardial ischemia-reperfusion (I/R) injury, pulmonary arterial hypertension (PAH), peripheral arterial disease (PAD) and arrhythmias (Fig. 1, Table I). The significant biological functions of the MCU complex in regulating mCa^{2+} flux, inducing cardiomyocyte apoptosis and promoting vascular proliferation were highlighted. The review's objective was to identify new predictive indicators for CVD in clinical settings and to explore potential therapeutic targets that have yet to be developed.

2. Introduction to the MCU complex

The MCU complex is a crucial protein complex with a molecular weight of ~480 kDa (15). It comprises channel subunits and regulatory components, including the pore-forming subunit MCU, its dominant-negative subunit MCUb, essential MCU regulator (EMRE), mitochondrial calcium uptake family members (MICU1, MICU2 and MICU3) and mitochondrial calcium uniporter regulator 1 (MCUR1) (16). The MCU complex is present in all mammals, though its activity differs across various tissues. For instance, MCU currents in mouse skeletal muscle are higher than those in cardiac tissue, which may be related to the differing mitochondrial content in these tissues (17). Cardiomyocytes are among the most mitochondria-rich cells in the human body, with mitochondria accounting for 30-40% of the cell volume. By contrast, mitochondria occupy only 5.3% of skeletal muscle cells. In beating cardiomyocytes, mitochondria can produce up to 90% of the ATP (18,19) needed to sustain contraction. When a substantial amount of Ca^{2+} accumulates in the cytoplasm, it continuously stimulates the MCU complex, leading to mCa^{2+} influx (20). Therefore, it may be hypothesized that to maintain orderly cardiomyocyte contraction, mitochondria require lower MCU current levels, whereas skeletal muscle cells, with fewer mitochondria, do not need to limit MCU activity. Further experimental validation is required and investigating these mechanisms will offer clearer insights for targeted disease therapies.

MCU is a 40-kDa protein containing two coiled-coil (CC) domains and two transmembrane domains (TMD), connected by a short loop, with both the N-terminus and C-terminus oriented toward the mitochondrial matrix. The channel entry is formed by the 'DIME' motif (amino acids 261-264 in human MCU), which is critical for Ca^{2+} permeability (21,22). Studies have demonstrated that silencing MCU in both *in vivo* and *in vitro* experiments eliminates mCa^{2+} uptake, while mitochondrial morphology and membrane potential remain unaffected. Conversely, MCU overexpression significantly increases agonist-induced mCa^{2+} uptake (21,23).

MCUb, discovered in 2013 by Raffaello *et al* (24), is an alternative isoform of MCU with a molecular weight of 33 kDa, sharing high structural similarity with MCU. A key distinction between the two lies in the substitution of essential amino acids in the loop region (E256V) and the first transmembrane helix (R251W). Silencing MCUb increases mCa^{2+} uptake, confirming its role as a negative regulator of the channel (25). This effect is likely due to structural differences. In cardiac tissue, MCUb is not expressed under normal conditions but is upregulated following I/R injury, where it helps to limit mCa^{2+} overload and prevent cell apoptosis during elevated intracellular Ca^{2+} levels (26). The MCU/MCUb ratio varies significantly across tissues and cells; for instance, the heart has a high MCUb/MCU ratio (3:1), while skeletal muscle has a much lower ratio (1:40), which may influence the tissue's ability to rapidly accumulate Ca^{2+} in mitochondria (27). Given the differential expression of MCU and MCUb across tissues and cancer types, the capacity of the MCU complex to accumulate Ca^{2+} in mitochondria varies, making this an important area of investigation.

EMRE is a 10-kDa protein encoded by the single-pass membrane protein with aspartate rich tail 1 (gene and contains a single TMD (28). Specific knockout of EMRE in cells leads to impaired mCa^{2+} uptake, exhibiting a phenotype similar to that observed with MCU silencing, confirming EMRE as an essential component of the MCU complex (28). Likewise, studies in yeast cells have shown that MCU alone is insufficient to activate uniporter activity, as both MCU and EMRE must be co-expressed for the channel to function (29). It has been shown that the 'E site' in the MCU-EMRE complex acts as a selective filter for the channel, while the 'D site' located at the pore entrance has a minimal impact on selectivity. This allows the E site to ensure precise calcium selectivity while enhancing ion throughput (30). MICU1, identified in 2010, is another key member of the MCU complex with a molecular weight of 54 kDa. EMRE interacts with MICU1's basic domain to anchor MICU1 within the complex (31). The EMRE-MICU1 complex promotes Ca^{2+} signal sensing on both sides of the inner mitochondrial membrane (IMM). When mitochondrial matrix Ca^{2+} levels are high, Ca^{2+} interacts with the EMRE tail, causing conformational changes that block the channel, preventing further mCa^{2+} influx. Conversely, when the Ca^{2+} concentration rises in the IMS, MICU1 undergoes conformational changes that allow mCa^{2+} influx (32). MICU1 is relatively scarce in the heart and recent studies claim that the mammalian heart lacks MICU1 for gating the mitochondrial calcium uniporter (mtCU). However, genetic models have not yet been tested. Hasan *et al* (33) found that in non-failing human hearts, MICU1 is present within the MCU complex.

MICU2 and MICU3 are homologs of MICU1 and play a role in regulating mCa^{2+} uptake (34). Of note, silencing MICU1 also results in the loss of MICU2, indicating a strong connection between the two proteins (35). Studies suggest that when cytosolic Ca^{2+} levels rise, the MICU1-MICU2 heterodimer is inhibited, which opens the uniporter channel (36). Research on MICU3 is more limited, but it is primarily expressed in the nervous system. Although both MICU2 and MICU3 are present in most tissues,

Table I. Evidence for an important role of the MCU complex in cardiovascular disease.

A, Cardiovascular disease

Condition	Diagnosis	Treatment assessment	Highlight
Myocardial I/R injury	Compared with the control group, the myocardial injury group exhibited increased myocardial cell apoptosis (47), decreased cardiac function (47,50), lumen narrowing, vascular wall edema or endothelial prolapse and disruption of the microvascular barrier (49,50).	Inhibition of the MCU alleviates cardiac microvascular I/R injury. Grpel2 (47), HINT2 (49), SERCA (50) and Ru360 (47) have shown protective effects against myocardial I/R injury. Activation of MCU and MCUb provides protective effects against I/R injury (25,53,54).	Inhibiting the MCU complex or overexpressing MCUb reduces mitochondrial fission and apoptosis, thereby providing cardioprotection (25,47,49,50). Activation of MCU can increase mCa^{2+} levels, maintaining normal cellular metabolic processes (53,54).
PAH	Compared to the control group, PAH patients exhibit increased arterial pressure and significant proliferation of small pulmonary arteries (64).	MiRNA-138 and miRNA-25 downregulate mitochondrial calcium transport proteins, leading to cell proliferation in PAH (64).	In PASMCs, ROCK-mediated calcium sensitization increases, leading to a persistent decline in MCU complex function, which triggers mitochondrial fragmentation and the Warburg effect, resulting in excessive pulmonary vascular proliferation (64).

B, Cardiac dysfunction

Condition	Diagnosis	Treatment assessment	Highlight
Myocardial remodeling	Compared to the control group, ischemic cardiomyopathy exhibits myocardial fibrosis, cardiac hypertrophy and impaired systolic function (71).	NA	In mice with systemic MCU knockout, ISO-induced myocardial fibrosis and cardiac hypertrophy occur (71). Overexpression of MCU restores mCa^{2+} handling, improving cardiac function in diabetic cardiomyopathy (75).
HF	Compared to the control group, the HF group shows increased LDH, CK and BNP levels, as well as dysfunction in left ventricular systolic and diastolic function (72).	Ginger enhances the therapeutic effects of aconite in treating acute HF by enhancing mitochondrial energy metabolism mediated by MCU (72).	Maintaining MCU-dependent mitochondrial energy metabolism can improve HF (72,73).
Arrhythmia	Compared to the control group, the model group shows electrocardiographic evidence of arrhythmia (82,84).	NA	MCU deficiency can lead to myocardial fiber damage and mitochondrial swelling, resulting in changes in cardiac function (82).
Atrial fibrillation	NA	The MCU inhibitor Ru360 improves cardiac function in patients with atrial fibrillation (83).	The MCU inhibitor Ru360 protects cardiac function in patients with atrial fibrillation by inhibiting mitochondrial calcium transients (83,85).

Table I. Continued.

B, Cardiac dysfunction

Condition	Diagnosis	Treatment assessment	Highlight
PVT	NA	The MCU activator kaempferol restores rhythmic cardiac contractions in zebrafish with arrhythmia and inhibits arrhythmia occurrence in mice with PVT (86).	The MCU activator can effectively improve arrhythmias in zebrafish and mice (87).

I/R, ischemia-reperfusion injury; MCU, mitochondrial Ca^{2+} uniporter; NA, information not available; Grpel2, GrpE like 2; HINT2, histidine triad nucleotide-binding protein 2; SERCA, sarcoendoplasmic reticulum calcium ATPase; mCa^{2+}, mitochondrial Ca^{2+}; miRNA, microRNA; HF, heart failure; PAH, pulmonary arterial hypertension; PASMCs, pulmonary artery smooth muscle cells; ROCK, Rho-associated protein kinase; ISO, isoproterenol; LDH, lactate dehydrogenase; CK, creatine kinase; BNP, B-type natriuretic peptide; PVT, polymorphic ventricular tachycardia.

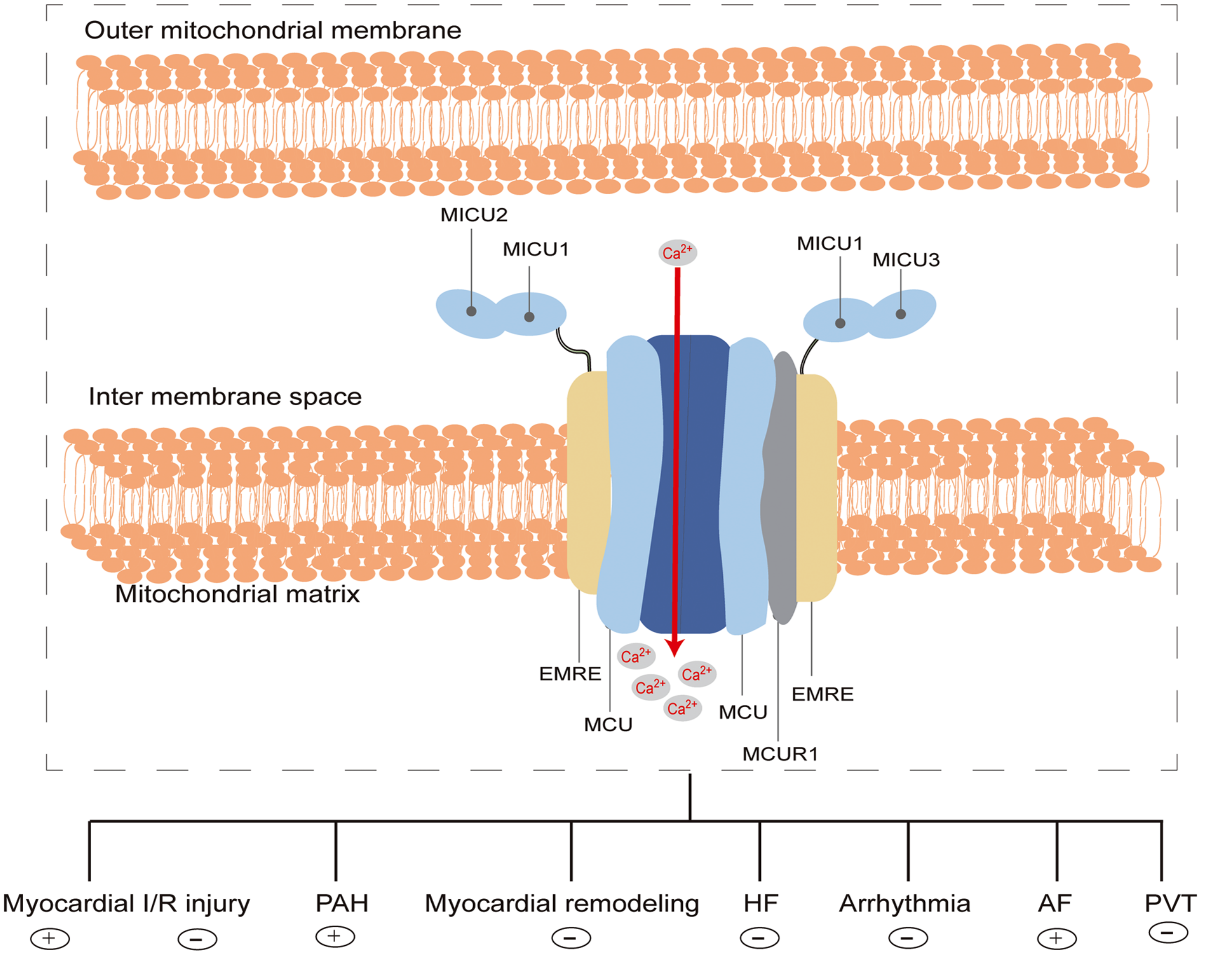

Figure 1. Role of the MCU complex in cardiovascular diseases. The core of the MCU channel consists of the transmembrane proteins MCU, MCUb and EMRE. Together, the MCU isoforms assemble into a pentamer (or tetramer) structure in the inner mitochondrial membrane, forming a Ca^{2+}-conducting pore. The activity of this pore is regulated by members of the MICU. The impact of the MCU complex on cardiovascular diseases is illustrated, with '+; indicating promoting effects and '-' indicating inhibitory effects. MCU, mitochondrial Ca^{2+} uniporter; MICU, mitochondrial Ca^{2+} uptake protein family; I/R, ischemia/reperfusion; EMRE, essential MCU regulator; PAH, pulmonary arterial hypertension; HF, heart failure; AF, atrial fibrillation; PVT, polymorphic ventricular tachycardia.

MICU3 forms a heterodimer only with MICU1, not MICU2. MICU3 appears to respond more rapidly to cytosolic Ca^{2+}, ensuring quick mCa^{2+} uptake in the nervous system, which makes further investigation into MICU3 in neural tissues particularly important (37).

MCUR1 is a 35-kDa protein encoded by the CCDC90A gene. The interaction between the CC domains of MCUR1 and MCU is essential for the proper assembly of the hetero-oligomeric MCU complex (38). It has been shown that knocking down MCUR1 disrupts MCU-mediated mCa^{2+}

uptake, highlighting the importance of MCUR1 in MCU function (39). However, MCUR1 appears to have additional roles in mitochondria. Research by Zulkifli *et al* (40) revealed that human MCUR1 can rescue defects in mitochondrial proline metabolism caused by put6Δ and put7Δ deletions. On the other hand, Paupe *et al* (41) proposed that MCUR1 is not a direct regulator of the MCU complex but rather a cytochrome c oxidase assembly factor, with MCUR1 gene silencing (CCDC90A) leading to disruptions in mitochondrial membrane potential and ATP production. Therefore, the relationship between MCUR1 and mitochondrial function requires further clarification.

The solute carrier family 25 (SLC25) family comprises nuclear-encoded EF-hand-containing mitochondrial solute carrier proteins, which mediate transmembrane transport between the cytoplasm and mitochondria. SLC25A23 is a key member of this family (42). Research indicates that SLC25A23 interacts with MCU and MICU1, enhancing MCU channel activity. Silencing SLC25A23 has been shown to reduce mCa^{2+} influx (43,44). Further investigation is needed to fully understand the complex role of SLC25A23 in mCa^{2+} uptake.

3. The MCU complex and CVD

The MCU complex and myocardial I/R injury. Myocardial ischemia occurs when blood flow to the heart is reduced, resulting in an imbalance between the oxygen supply and demand of the myocardium, which triggers ischemic damage (45). Revascularization is currently the most effective strategy to lower the mortality rate among ischemic patients; however, reperfusion at this stage can also cause additional myocardial damage, a phenomenon known as 'reperfusion injury' (46). During ischemia, myocardial cells are deprived of oxygen, nutrients and survival factors. Prolonged ischemia leads to progressive and irreversible changes in the structure and function of the myocardium, with the most significant damage being the injury or death of myocardial cells (47). While reperfusion is essential to rescue myocardial infarction, the sudden reoxygenation of previously ischemic myocardial cells causes excessive ROS production, intracellular Ca^{2+} accumulation, and ultimately, myocardial cell death (48). Research has shown that mCa^{2+} overload is a key mechanism of myocardial cell injury during I/R injury. During this process, pathological elevations of Ca^{2+} in the mitochondrial matrix led to the opening of mitochondrial permeability transition pores (mPTP), which results in the release of solutes and small proteins from the mitochondrial matrix, causing mitochondrial swelling and, eventually, cell death (49). Therefore, understanding how to regulate mCa^{2+} channels during I/R is crucial for preventing further myocardial cell loss.

Studies have shown that the MCU plays a significant role in the development of myocardial I/R injury (50,51). Recent research has highlighted the relationship between myocardial I/R and the MCU complex. By inhibiting the MCU complex, mCa^{2+} influx and subsequent Ca^{2+} overload can be reduced, which ultimately decreases mitochondrial fragmentation and apoptosis, alleviating cardiac microvascular I/R injury (50,52,53). Liang's team demonstrated that inhibiting the MCU in cardiac I/R exerts cardioprotective effects by reducing the abnormal opening of the mPTP in cardiac microvascular endothelial cells (53). One current hypothesis suggests that during ischemia and reperfusion, Ca^{2+} enters the mitochondria via the MCU, activating the PTP (54). Inhibiting MCU during I/R may be a potential strategy to reduce PTP opening (55). In addition, studies have found that MCUb expression increases following cardiac ischemic injury. Overexpression of MCUb has demonstrated protective effects against myocardial I/R injury, potentially related to reduced mCa^{2+} uptake and increased efflux (26). By contrast, Rasmussen *et al* (56) observed different outcomes. They developed a transgenic mouse model expressing a dominant-negative (DN) form of the MCU specifically in the myocardium. Unexpectedly, DN-MCU mice, which lacked MCU-mediated mCa^{2+} entry, exhibited higher oxygen consumption rates and reduced ROS generation compared to wild-type mice (56). Chapoy Villanueva *et al* (57) proposed that these differences may be due to the varying durations of MCU deficiency. Chronic disruption of MCU activity may trigger compensatory adaptations to maintain cellular metabolic processes in the absence of rapid mCa^{2+} influx. Their team confirmed that the responses to I/R injury differ between chronic and acute MCU deficiency mouse models. Furthermore, using both short-term and long-term EMRE-deficient adult mouse models, they showed that the protective effects against I/R injury were lost in long-term EMRE-deficient mice (57). MICU1, a crucial regulator of mCa^{2+} homeostasis, has also been studied in the context of I/R injury. Studies have shown that MICU1 knockout significantly exacerbates myocardial I/R injury, as evidenced by increased infarct size, impaired cardiac function and elevated myocardial cell apoptosis. The absence of MICU1 leads to pronounced mCa^{2+} overload, which disrupts mitochondrial morphology, inhibits mitochondrial function and reduces ATP production (58). However, the precise mechanisms underlying these effects require further investigation.

MCU and other vascular diseases. The pathological changes in vascular diseases primarily include three conditions: i) Loss of elasticity in the vascular wall due to lesions, resulting in aneurysmal changes and, in severe cases, rupture and bleeding. ii) Lesions causing lumen narrowing, which can lead to ischemia and even necrosis of the affected organ or limb. iii) Lesions inducing endothelial injury, which can trigger intravascular coagulation and thrombosis, potentially causing ischemia in organs or tissues. Emboli may also dislodge and obstruct distal vessels (59,60). Common vascular diseases include PAH, aneurysms, PAD and aortic coarctation (61-64). These conditions have complex and varied etiologies, with mCa^{2+} playing a role in their pathogenesis. As a unidirectional channel for mCa^{2+} influx, the MCU is also involved in the development of these vascular diseases.

PAH is a life-threatening obstructive arterial disease characterized by excessive pulmonary vascular proliferation, loss of vascular lumen, vascular remodeling and, ultimately, right ventricular failure, which can lead to death (65). The etiology of PAH is highly complex and a reduction in mCa^{2+} has been observed in PAH for some time (66). Research has shown that vascular constriction and cell proliferation in PAH are also caused by decreased MCU expression and increased MICU1 expression, leading to reduced MCU complex function, elevated cytosolic Ca^{2+}, decreased mCa^{2+}, mitochondrial fragmentation and the Warburg effect, thereby promoting pulmonary vascular overproliferation (67,68). Given this, the role of the MCU complex in PAH deserves closer attention. Wu *et al* (68) conducted research using Fura-2 acetoxymethyl ester and fluorescence resonance energy transfer probes to assess calcium localization, demonstrating elevated cytosolic Ca^{2+} and reduced mCa^{2+} in Pulmonary artery smooth muscle cells (PASMCs) from patients with PAH. Further investigation using mRNA expression profiling and super-resolution confocal microscopy confirmed that the reduced mCa^{2+} in PAH PASMCs could be attributed to decreased MCU expression. Immunoblotting also revealed significantly increased MICU1 levels in human PAH PASMCs and similar MCU downregulation was observed in the lungs of monocrotaline-induced PAH rats (68). The study concluded that reduced MCU expression leads to decreased mCa^2, which impairs PDH activity, affects glycolysis and ultimately results in smooth muscle cell apoptosis and proliferation (67). These findings highlight the critical regulatory role of the MCU complex in PAH-related mCa^{2+} dynamics.

The decline in MCU complex function in PAH is attributed to two key factors: Epigenetic mechanisms driven by increased expression of microRNA (miR)-138 and miR-25 (67), and increased calcium sensitization mediated by Rho-associated kinase (ROCK) in PAH PASMCs. ROCK increases myosin contractility by inactivating myosin light chain phosphatase, allowing sustained vasoconstriction independent of calcium influx. As a result, ROCK activation leads to calcium sensitization, contributing to the decline in MCU complex function. Increased activity of the G protein RhoA and its downstream target ROCK has been observed in idiopathic pulmonary arterial hypertension (PAH) and animal PAH models, primarily due to serotonylation (69) and superoxide-mediated activation (70), forming a calcium-sensitivity mechanism. Therefore, the interaction between the MCU complex, G protein RhoA and ROCK may represent a potential mechanism in PAH pathogenesis.

Calcium transport is also widely studied in other vascular diseases. For instance, in familial thoracic aortic aneurysm and dissection (FTAAD), a metabolomics and transcriptomics analysis using two different mouse models by Tomida *et al* (71) revealed that increasing the cytosolic Ca^{2+} concentration can help prevent FTAAD. Similarly, in pregnancy-induced hypertension, altered calcium transport gene expression, which leads to calcium loss in urine, has been associated with preeclampsia and calcium deficiency (72). This suggests that calcium transport may play a role in vascular disease pathogenesis through calcium imbalance. Therefore, the study of the MCU complex, as a mitochondrial calcium uniporter, in vascular diseases warrants further exploration.

MCU complex and cardiac remodeling, heart failure (HF). Cardiac remodeling refers to changes in the size, shape and function of the heart resulting from molecular and genetic alterations in response to cardiac injury or hemodynamic stress. It is widely recognized as a key mechanism in the progression of HF (73). Research has shown that Ca^{2+} imbalance can damage mitochondria, leading to cardiomyocyte death, pathological hypertrophy and ultimately heart failure (74). Wang *et al* (74) used chronic administration of isoproterenol (ISO) to create MCU knockout or transgenic mice and confirmed increased levels of the MCU complex and MCU in the mitochondria of ischemic mouse hearts. Of note, ISO-induced myocardial fibrosis, cardiac hypertrophy and contractile dysfunction were exacerbated in global MCU knockout mice, whereas cardiac-specific MCU overexpression maintained intracellular Ca^{2+} homeostasis and contractility, inhibited cell hypertrophy and prevented ISO-induced cardiac dysfunction and hypertrophy (74). The study by Zhang *et al* (75) supports these findings, showing that MCU complex expression decreased in a propranolol-induced heart failure model, while maintaining MCU-dependent mitochondrial energy metabolism improved heart failure outcomes (75). Liu *et al* (76) further reinforced this perspective by demonstrating that MCU overexpression increased mCa^{2+} uptake rates in failing cardiomyocytes, reduced ROS production, corrected intracellular Ca^{2+} handling defects and improved contractile function. The authors also indicated that excessive sarcoplasmic reticulum (SR) Ca^{2+} leak leads to decreased SR Ca^{2+} load in cardiomyocytes and that MCU overexpression was sufficient to correct SR leak and cytosolic Ca^{2+} transients (76). While Garbincius and Elrod (77) praised the work by Liu *et al* (76), they raised concerns that the study was short-term, focusing only on the consequences of MCU overexpression within two weeks, without investigating potential long-term adverse effects. They questioned whether harmful consequences may emerge over a longer observation period, or if compensatory changes in unidirectional transporter channel regulation or mCa^{2+} efflux could offset negative effects. In addition, it remains elusive how mCa^{2+} homeostasis is affected in a guinea pig (ACi) model. The peak mCa^{2+} concentration was reduced during electrical stimulation in intact ACi cardiomyocytes, but interpreting this measurement may be complicated by factors such as reduced SR Ca^{2+} load and cytosolic Ca^{2+} transients (76,77). In a study of diabetic cardiomyopathy, MCU complex member protein levels were reduced and adenoviral MCU overexpression restored mCa^{2+} handling and improved cardiac function (78).

However, there are differing views on the role of the MCU complex in cardiac remodeling and heart failure. Tarazón *et al* (79) found increased MCU levels in heart transplant patients, which were associated with cardiac dysfunction caused by acute rejection. In their analysis of ventricular septal samples from patients with pressure-overload-induced cardiac hypertrophy, they observed significantly elevated MCU and MICU1 protein levels. As seen in the studies mentioned above, members of the MCU complex exhibit varied responses in cardiac remodeling and heart failure. One possible explanation is that the heart may be at different stages of disease. For instance, the samples in the study by Tarazón *et al* (79) represented moderate hypertrophy rather than end-stage hypertrophy or heart failure, and the increased MCU expression may reflect a compensatory phase of hypertrophy. In end-stage heart failure, elevated cytosolic Na^+ concentrations promote Na^+/Ca^{2+} exchange, leading to reduced mCa^{2+} levels (80,81). This reduction in mCa^{2+} efflux limits mitochondrial ATP production, further impairing contractility in the failing heart. MCU supplementation can promote mCa^{2+} uptake, compensating for mCa^{2+} deficiency due to increased efflux, thereby boosting mitochondrial ATP production and supporting cardiac bioenergetics (82). As such, targeting the expression or function of the MCU complex may offer a promising therapeutic approach for future studies on cardiac remodeling and heart failure.

The MCU complex and arrhythmias. Arrhythmias, characterized by irregular heart rhythms, are a leading cause of morbidity and mortality associated with CVD worldwide. These irregular heart rhythms present substantial treatment challenges (83). The mechanisms underlying arrhythmias are complex, with intracellular Ca^{2+} homeostasis recognized as a key factor in their development (84). Wang *et al* (85) developed a zebrafish MCU mutant model that survives into adulthood and observed weakened heart contractions in the mutants. Pathological examination revealed damaged myofibrils and swollen mitochondria in the hearts of these MCU mutants. Electrocardiograms showed conduction system defects and abnormal rhythms, including prolonged pauses resembling sinus arrest (86). This study highlights the critical role of the MCU complex in the development of arrhythmias.

MCU not only plays a significant role in the development of arrhythmias but also serves as a potential therapeutic target. Wiersma *et al* (87) identified mitochondrial changes in the atrial tissue of patients with atrial fibrillation (AF), potentially caused by mCa^{2+} transients due to increased Ca^{2+} influx mediated by the MCU. The use of the MCU inhibitor Ru360 or moderate downregulation of MCU prevented adverse mitochondrial changes induced by rapid pacing. Furthermore, treatment with Ru360 improved contractile dysfunction in a *Drosophila melanogaster* AF model, providing protection to cardiomyocytes (87). These findings suggest that targeting MCU to prevent mitochondrial dysfunction could represent a novel therapeutic approach for addressing AF remodeling. Joseph *et al* (88) demonstrated that cardiac-specific deletion of the MCU gene in high-fat diet (HFD)-induced long QT syndrome, inducible ventricular tachycardia and abnormal ventricular repolarization offered protection. Cardiac iron overload, which can lead to iron overload cardiomyopathy and arrhythmias, was shown by Sripetchwandee *et al* (89) to be fully prevented with the use of MCU blockers. Sander *et al* (90) found that the mCa^{2+} uniporter activator kaempferol restored rhythmic heart contractions in zebrafish and inhibited arrhythmias in ventricular myocytes of mice with polymorphic ventricular tachycardia. Further research revealed that only moderate increases in MCU levels provided protection against arrhythmias, though the specific mechanisms remain to be fully explored (91).

These studies significantly expand the current understanding of the MCU complex's involvement in arrhythmias, highlighting its key role in the progression of these conditions. Furthermore, the findings provide compelling evidence for the potential value of assessing and targeting MCU expression in the diagnosis and treatment of arrhythmias.

The MCU complex and myocarditis. Myocarditis is characterized by localized or diffuse inflammation in the myocardium, with a wide range of etiologies, including both infectious and non-infectious factors. In a study of viral myocarditis, Hu *et al* (92) used flow cytometry to monitor transient changes in intracellular calcium, finding that Ca^{2+} levels in cardiomyocytes infected with CVB3 were 1.7 and 4 times higher than in the control group at 6 and 12 h post-infection, respectively, leading to intracellular calcium overload. Another study followed 102 patients with dengue hemorrhagic fever from Colombia for a year, performing immunohistochemical analysis on cardiac tissues from autopsies and conducting *in vitro* studies on myotubes infected with dengue virus. This study found that disruptions in Ca^{2+} storage in infected cells may directly contribute to myocarditis in pediatric patients (93). Furthermore, Huynh *et al* (94) discovered that after treating human cardiomyocytes with the S1 protein for 72 h, there was an increase in ROS, mCa^{2+} and intracellular Ca^{2+} levels, leading to reduced mitochondrial respiratory rates and mitochondrial dysfunction, which ultimately resulted in myocarditis and cardiac dysfunction. Collectively, these studies indicate that intracellular calcium overload, both in the cytosol and mitochondria, leads to mitochondrial dysfunction, contributing to the development of myocarditis and cardiac dysfunction.

In non-viral studies, Maass *et al* (95) measured cytoplasmic and mCa^{2+} levels in cardiomyocytes from the control group and burn patients with >40% total body surface area burns. They found that 24 h post-burn, cytoplasmic Ca^{2+} levels increased from 90±3 to 293±6 nM ($P<0.05$) and mCa^{2+} levels also rose significantly from 24±1 to 75±2 nM ($P<0.05$). Similar observations were made in *in vitro* models, where lipopolysaccharide-treated groups exhibited a 112% increase in cytoplasmic Ca^{2+} (185±15 nM, $P<0.05$) and an 87% increase in mCa^{2+} ($P<0.05$) compared to a control group (95). These results align with findings from Wan-Yi *et al* (96), who reported that ruthenium red prevented burn-induced myocardial Ca^{2+} accumulation and alleviated related myocardial and mitochondrial damage. Both Maass *et al* (94) and White *et al* (97) suggested that administering Ca^{2+} antagonists post-burn could prevent the rise in cytoplasmic Ca^{2+} and improve myocardial contractility. Another significant pathophysiological mechanism in anthracycline-induced cardiotoxicity is the disruption of cellular and mitochondrial calcium signaling (98).

Currently, the most well-established and widely studied pathway for mCa^{2+} uptake is through the MCU complex (99,100). The driving force for this process is the large electrochemical gradient across the IMM, with the mitochondrial membrane potential being ~-180 mV. This suggests that the MCU complex, as the channel responsible for mCa^{2+} uptake, may be involved in the pathogenesis of myocarditis. The rapid uptake of calcium into the mitochondrial matrix is driven by the mitochondrial membrane potential and facilitated by the mitochondrial calcium ion carrier channel (101). Although current research on the role of the MCU complex in both infectious and non-infectious myocarditis is limited, this area holds great potential for further exploration.

4. Role and controversies of the MCU complex in CVD

In recent years, the role of the MCU in CVD has attracted significant attention, particularly in I/R injury. However, different studies have revealed the complex and potentially controversial roles of MCU in the heart. For instance, Liang *et al* (4) demonstrated the potential of MCU inhibition in cardiac protection, while Rasmussen *et al* (56) offered a contrasting perspective, suggesting that inhibition of MCU may not always be effective, particularly within different time frames. The study by Chapoy Villanueva *et al* (57) further indicated that the effects of EMRE deficiency differ between short-term and long-term conditions. Short-term EMRE deficiency improved cardiac function and alleviated I/R injury, whereas long-term deficiency led to a loss of this protective effect. This finding suggests a time-dependent role of the MCU complex in the heart, warranting further investigation.

In addition, a recent study by Ashok *et al* (102) presents a contrasting view to previous conclusions. By acutely knocking out MCU, they observed that MCU knockout did not significantly alter mitochondrial calcium import nor affect the recovery of the mitochondrial membrane potential during simulated I/R injury (102). Their research suggests that mCa^{2+} overload may be mediated by the reverse mode of the sodium-calcium exchanger, a novel mechanism that warrants further exploration. This finding raises important considerations regarding the role of MCU in I/R injury, particularly its direct involvement in cell death.

Interaction between MICU1 and MCU and its regulation in CVD. In addition to MCU itself, MICU1, as a regulatory factor of MCU, has an important role in cardiovascular function. Studies on MICU1 have shown that it not only acts as the 'gatekeeper' of MCU, but also regulates the mitochondrial cristae structure by interacting with the mitochondria contact site and cristae organizing system complex, thereby affecting calcium ion transport and mitochondrial function (103). However, Tomar *et al* (38), have proposed an alternative viewpoint, suggesting that MICU1 does not fully regulate calcium flux by blocking the MCU channel, but rather exerts its effect by enhancing the opening probability of MCU. This perspective offers new insights into understanding the role of MICU1 under different pathological conditions.

In a study on patients with HF, it has been observed that the protein ratio of MICU1 to MCU increased ~2-fold, whereas the protein levels of MCU or MCUb did not show significant changes in the non-HF control group (104). This change is in contrast with the upregulation of MCUb in the mouse I/R model (26). Although differences in rhythm frequency and energy demands between mouse and human hearts may lead to certain inconsistencies in results, it is noteworthy that changes in MCUb expression in mouse I/R injury typically require 2 to 3 days to become evident. Therefore, further investigation into the temporal expression pattern of MCUb in both human HF and mouse HF models will contribute to a better understanding of its role in CVD.

5. Intersection of the MCU complex and other conditions in CVD

In recent years, the role of the MCU in lipid metabolism has garnered increasing attention (105,106). In adipose tissue, the expression of MCU has been shown to increase during conditions such as obesity and diabetes (107). Zhang *et al* (108) demonstrated that inhibition of hepatic MCU could prevent liver steatosis induced by an HFD. Furthermore, MCU inhibition or depletion reduced obesity in mice and improved metabolic disturbances (109). These findings reveal a connection between MCU-mediated calcium transport and lipid metabolism.

In the context of metabolic stress, obesity and diabetes, alterations in Ca^{2+} homeostasis have significant effects on tissues including the heart and skeletal muscle (110). Diabetes increases the risk of heart failure by altering mitochondrial energy metabolism in the heart. Studies have identified diabetes as a key factor in the development of cardiac arrhythmias (6). In heart tissues from streptozotocin-induced type 1 diabetic mice, the protein levels of MCU and EMRE were reduced by 50 and 36%, respectively, while MCUb levels increased by 31% compared to control mice. This resulted in reduced mitochondrial calcium uptake and impaired cardiac function (6,111,112). In addition, in the hearts of type 2 diabetic mice, MCUb expression was similarly upregulated (78). Gene therapy, using dominant-negative MCUb transgenic mice (MCUbW245R/V251E), successfully improved cardiac contractile function, likely through transcriptional repression mediated by nuclear receptor co-repressor 2 (113). These studies highlight the pivotal role of MCUb in bridging metabolic processes and cardiac function, suggesting that MCUb plays a crucial role in the interplay between diabetes and cardiac health (114). In myocardial microvascular endothelial cells of diabetic mice, downregulation of MICU1 led to mitochondrial calcium overload, triggering endothelial damage and inflammation, thereby promoting the progression of diabetic cardiomyopathy. By contrast, overexpression of MICU1 in diabetic db/db mice preserved cardiac function, reduced cardiac hypertrophy and prevented the onset of diabetic cardiomyopathy (115).

These findings further underscore the importance of the MCU signaling pathway at the intersection of metabolism and cardiovascular health, providing promising directions for therapeutic strategies targeting metabolic diseases and CVD.

6. Pharmacology of the MCU complex

The MCU complex plays a vital role in regulating mCa^{2+} transport, mitochondrial metabolic function, cell proliferation and apoptosis. In CVD, the expression of the MCU complex appears to have phase-specific effects: Inhibiting its expression during the acute phase may offer protective benefits, while increasing its expression during the chronic phase may promote cardioprotection. Thus, the timing of administering MCU complex-targeted drugs is crucial in treating cardiovascular conditions. To date, several inhibitors of the MCU complex, such as Ruthenium Red (RuR) and its derivative Ru360 (116), DS16570511 (117) and the antibiotic Minocycline, have been studied in various disease contexts. Mitoxantrone has also been shown to block MCU activity (118). On the other hand, MCU activators like miR-124 and Kaempferol have been explored in cardiovascular research (51). Furthermore, certain herbal medicines have demonstrated cardioprotective effects via the MCU complex (Fig. 2).

Inhibitors of the MCU complex. RuR and its derivative Ru360 inhibit the MCU by binding to the selective filter DIME group of the MCU (119). Ru360 has been shown to improve postoperative cognitive dysfunction and reduce cardiac injury following ischemia-reperfusion in mice (120). A recent study

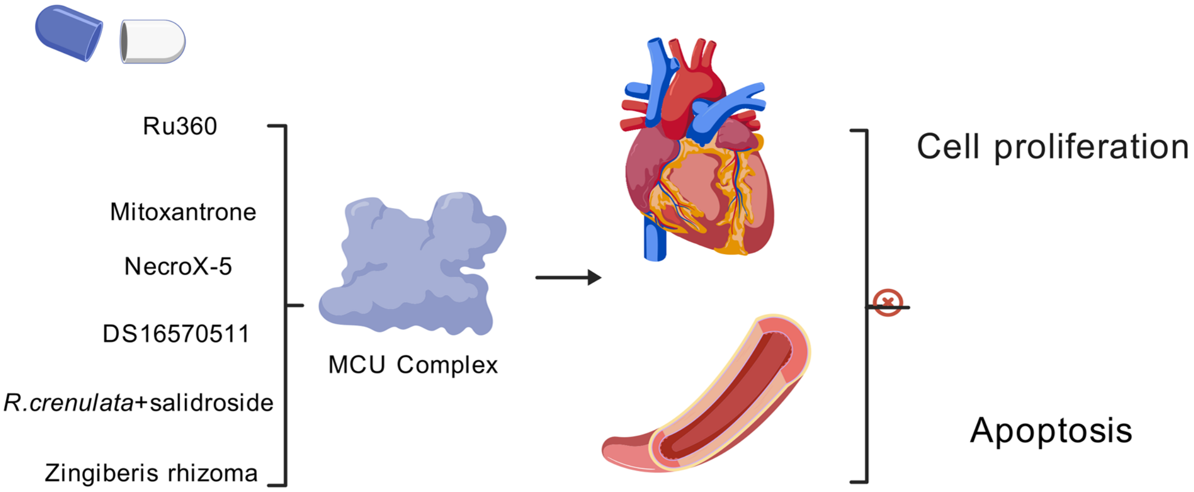

Figure 2. The impact of the MCU complex on cardiovascular diseases can induce either cell proliferation or apoptosis. These effects can be alleviated through various interventions, such as Ru360, NecroX-5, DS16570511 and certain traditional Chinese herbs. MCU, mitochondrial Ca^{2+} uniporter.

showed that, compared to the parent compounds Ru265 and Os245, their complexes exhibit stronger cellular uptake capabilities (121). Mitoxantrone has been reported to alleviate hepatic steatosis through MCU inhibition (108). A recent study by Arduino *et al* (118) characterized Mitoxantrone, an anthraquinone-derived cell inhibitor used in treating hematologic malignancies, as a specific MCU inhibitor that can increase tumor resistance. NecroX-5, a derivative of the reactive oxygen scavenger NecroX series compounds, has been found to reduce Ca^{2+} accumulation in cultured cardiomyocytes (122). In addition, Minocycline, an antibiotic, has been shown to inhibit Ca^{2+} uptake in isolated rat liver mitochondria (123). Although these inhibitors have not yet been tested in clinical trials for CVD, their widespread use in animal models highlights their potential for future clinical trials and therapeutic applications. The European Society of Cardiology recommends trimetazidine as an adjunct therapy for angina. Xiao *et al* (124) discovered through *in vivo* and *in vitro* experiments that its mechanism of action is related to the inhibition of the MCU.

Kon *et al* (117) first introduced the MCU inhibitor DS16570511, which exhibits cell-permeable and selective inhibitory properties. Compared to RuR, DS16570511 may more effectively inhibit human mitochondrial MCU rather than porcine or rat MCU. Of note, DS16570511 can increase cardiac contractility without affecting the heart rate in perfused hearts. The study also revealed that DS16570511 inhibits both endogenous mCa^{2+} uptake activity and Ca^{2+} uptake driven by exogenously expressed MCU or MICU1. This suggests that both MCU and MICU1 are potential binding targets for DS16570511, making it a promising lead compound for treating CVD, warranting further investigation (117).

Effect of Traditional Chinese Medicine on the MCU complex. In recent years, certain plant-based medicines have gained widespread attention. As an essential component of traditional medicine, Chinese herbal medicine has demonstrated significant potential in modern pharmacological research. Several studies have shown that active small molecules in Chinese herbs can regulate mitochondrial Ca^{2+} homeostasis by targeting the MCU complex, thereby exerting various biological effects such as anti-inflammatory, anti-apoptotic and antioxidant actions. This provides new insights for drug development targeting the MCU complex. This article will systematically review the research progress on the regulation of the MCU complex by active small molecules in Chinese herbal medicines and their potential applications in disease intervention, offering theoretical support and new research directions for the treatment of MCU-related diseases (Table II).

Traditional Chinese Medicine and its effect on the MCU complex in the cell cycle

i) Curcumin. Curcumin, a phenolic antioxidant extracted from turmeric, has numerous beneficial effects, including anti-apoptotic, anti-atrophy and anti-inflammatory properties (125,126). Previous studies have shown that curcumin influences intracellular Ca^{2+} pumps. Due to its low bioavailability, Kushwaha *et al* (127) developed a nano-curcumin pyrroloquinoline quinone (NCF) formulation. In *in vivo* and *in vitro* experiments, they demonstrated that NCF can inhibit MICU1-mediated mitochondrial Ca^{2+} overload, limit P53 mitochondrial translocation and enhance anti-apoptotic capabilities.

ii) Astragaloside IV (AS-IV). AS-IV is a small molecule saponin extracted from Astragalus, known for its anti-inflammatory, anti-apoptotic and antioxidant properties (128). Research has shown that AS-IV can regulate the MCU, leading to mitochondrial Ca^{2+} overload, mitochondrial dysfunction, ATP depletion, ROS generation and cytochrome c release, thus inhibiting cell apoptosis. These findings suggest that MCU may be an important target for AS-IV therapy (128).

iii) Aconitine. Aconitine is a key toxic component found in traditional Chinese herbs such as Aconitum, Northern Aconitum and Mountain Aconitum. Studies have shown that aconitine can upregulate the expression of MCU in mitochondria, leading to mitochondrial Ca^{2+} overload, reduced ATP

Table II. Chemical information and effects of Traditional Chinese Medicine.

A, Traditional Chinese Medicine targeting the MCU complex in cardiovascular disease

Name	CAS no.	Molecular formula	Target point	Basic function	(Refs.)
Yi Yi Fu Zi	NA	NA	MCU	Regulating the MCU complex to exert cardioprotective effects.	(131)
Shen Fu injection	NA	NA	MCU	Inhibiting MCU expression to reduce mitochondrial calcium overload.	(132)
Salsolinol	2774096-1	C10H13NO3	MCU	Inhibiting over-activation of the MCU pathway. Improve mitochondrial respiratory function and energy metabolism.	(75,133)

B, Traditional Chinese Medicine targeting the MCU complex in other diseases

Name	CAS no.	Molecular formula	Target point	Basic function	(Refs.)
β-Carotene	7235-40-7	C40H56	MCU	Inhibiting the STIM1-ER-IP3R/GRP75/VDAC1-MCU axis, thus mitigating endoplasmic reticulum stress and mitochondrial oxidative damage	(134)
Tian Huang formula	NA	NA	MICU1	Improving mitochondrial function via the AMPK/MICU1 pathway	(135)
Astaxanthin	472-61-7	C40H52O4	MCU	Restoring mitochondrial redox balance and Ca^{2+} homeostasis	(136,137)
R *hodiola rosea*	97404-52-9	NA	MCU	Activating the AMPK/Sirt1 signaling pathway to balance MCU-mediated mitochondrial homeostasis.	(138)
Ginkgolide K	153355 70-5	C20H22O9	MCU	Reducing MCU expression. Providing neuroprotection in AD pathology. Decreasing mCa^{2+} levels.	(139)

C, Traditional Chinese Medicine and its effect on the MCU complex in the cell cycle

Name	CAS no.	Molecular formula	Target point	Basic function	(Refs.)
Curcumin	458-37-7	C21H20O6	MICU1	Inhibiting MICU1-mediated mitochondrial calcium overload and limiting the mitochondrial translocation of P53.	(125-127)
Astragaloside IV	8320758-3	C41H68O14	MCU	Activating the MCU prevents mitochondrial dysfunction leading to mCa^{2+} overload, ATP depletion, ROS generation and cytochrome C release.	(128)
Aconitine	302-27-2	C34H47NO11	MCU	Upregulating the expression of MCU in mitochondria leads to calcium overload, reduced ATP production and altered mitochondrial membrane potential and promotes cell apoptosis.	(129)
Aloe-emodin	NA	NA	MCU	Activating the MCU to reduce calcium ion levels, thereby stabilizing mast cells and exhibiting anti-allergic effects.	(130)

MCU, mitochondrial Ca^{2+} uniporter; NA, information not available; STIM1, stromal interaction molecule 1; ER, endoplasmic reticulum; IP3R, inositol-trisphosphate receptors; GRP75, glucose-regulated protein 75; VDAC1, voltage-dependent anion channel 1; MICU1, mitochondrial calcium uptake 1; AMPK, adenosine 5'-monophosphate-activated protein kinase; Sirt1, Sirtuin 1; ROS, reactive oxygen species; AD, Alzheimer's disease.

production, changes in mitochondrial membrane potential and promotion of cell apoptosis (129).

iv) Shuanghuanglian and Aloe-emodin. Mast cells are crucial effector cells in the immune system that can be activated through various pathways. Shuanghuanglian (SHL) has been clinically used to treat allergic reactions. Studies have shown that SHL stabilizes mast cells by activating the MCU to lower Ca^{2+} levels, exhibiting anti-allergic effects (130). In addition, Aloe-emodin, a natural mast cell stabilizer, has been found to promote mitochondrial Ca^{2+} uptake through MCU activation, inhibiting mast cell degranulation (130). These findings provide potential targeted strategies for the treatment of diseases related to mast cell activation.

Traditional Chinese Medicine targeting the MCU complex in CVD

i) Yi Yi Fu Zi (YYFZ). YYFZ, composed of Job's tears and Aconitum, is a classic Traditional Chinese Medicine formulation that may exert cardioprotective effects through its action on the MCU complex (131).

ii) Shenfu injection (SFI). SFI, a Traditional Chinese Medicine containing Aconitum, is commonly used to treat CVD. Cao *et al* (132) explored its mechanism and demonstrated that moderate doses of SFI can reduce Ca^{2+} overload through MCU regulation, exhibiting myocardial protection in an I/R rabbit model.

iii) Salsolinol (SAL). SAL, a plant-derived isoquinoline alkaloid initially isolated from prepared Aconitum (Aconiti Lateralis Radix Praeparata), was studied by Wen *et al* (133) in a rat chronic HF model induced by doxorubicin (DOX). They found that SAL may improve mitochondrial respiratory function and energy metabolism by inhibiting excessive activation of the MCU pathway, thereby alleviating DOX-induced cardiomyopathy (133). Furthermore, dried ginger has been shown to enhance its efficacy in heart failure treatment (75).

Traditional Chinese Medicine targeting the MCU complex in other diseases

i) β-Carotene. Meng *et al* (134) indicated that β-carotene exerts preventive and therapeutic effects on mastitis by inhibiting the stromal interaction molecule 1-endoplasmic reticulum (ER)-inositol-trisphosphate receptors/glucose-regulated protein 75/voltage-dependent anion channel 1/MCU axis, thus mitigating ER stress and mitochondrial oxidative damage.

ii) Tian Huang formula (THF). THF has been shown to alleviate glucose and lipid metabolic disorders in type 2 diabetes mellitus mice by improving mitochondrial function via the AMPK/MICU1 pathway in adipose tissue (135).

iii) Astaxanthin (AX). AX has been found to protect against alcoholic liver injury by restoring the mitochondrial redox balance and calcium homeostasis (136). Activated MCU may promote mitochondrial autophagy in pancreatic ductal epithelial cells by regulating the PTEN induced putative kinase 1/Parkin pathway, contributing to the development of acute pancreatitis (137).

iv) *Rhodiola crenulata* (*R. crenulata*). *R. crenulata* has been shown to alleviate high-altitude ischemic brain injury by maintaining blood-brain barrier integrity and improving energy metabolism dysfunction. Its mechanism involves balancing MCU-mediated mitochondrial homeostasis through the activation of the AMPK/Sirtuin 1 signaling pathway (138).

v) Ginkgolide K (GK). *Ginkgo biloba* extract, known for its neuroprotective and anti-inflammatory effects, has been studied in the context of Alzheimer's disease (AD). Recent research suggests that GK provides neuroprotection in AD by reducing MCU expression and mitochondrial Ca^{2+} levels. In amyloid precursor protein/presenilin 1 mouse models, GK treatment decreased MCU expression and improved cognitive function, indicating its potential for AD therapy (139).

7. Limitations and future perspective

The function and regulatory mechanisms of the MCU within cells remain largely elusive. For instance, how its regulatory mechanisms are influenced by external factors such as apoptosis, metabolic regulation, oxidative stress and inflammatory responses requires further investigation. In addition, the MCU may play a more significant role in the development and progression of CVD, making an in-depth exploration of its mechanisms of great clinical importance. It is worth noting that most current studies are focused on rodent models; however, due to species differences, the applicability of these findings to humans remains limited. For instance, compared to mice, the expression level of MCUb in human adipose tissue is significantly lower (107). Whether this difference in expression reflects a precise functional change remains elusive and it is possible that even low levels of MCUb in human tissues may play an irreplaceable role in anti-inflammatory and antioxidative stress responses (107). Therefore, future optimization of detection methods and experimental studies on human-derived cells will be of great research interest and clinical significance. In summary, as a key component in intracellular Ca^{2+} homeostasis, further research into the relationship between the MCU complex and the regulation of intracellular calcium homeostasis, particularly its role in CVD, will provide a more comprehensive understanding and is expected to offer important clues for the development of more precise therapeutic strategies.

8. Conclusion

Epidemiological studies indicate that CVD remain the leading threat to human health, with mCa^{2+} playing a critical role in their progression. The MCU complex, as the primary pathway for mCa^{2+} uptake, has been implicated in the development and progression of various cardiovascular conditions. Given its physiological properties, the MCU complex is essential for stabilizing mCa^{2+} levels and maintaining mitochondrial quality control. Through these mechanisms, targeting the MCU complex holds considerable therapeutic potential for addressing myocardial ischemia-reperfusion injury, pulmonary hypertension, other vascular diseases, myocardial remodeling and arrhythmias.

Numerous inhibitors and activators of the MCU complex have been widely studied in animal models, underscoring their potential in treating CVD. Future research focused on identifying and regulating MCU complex-related targets may help improve the prognosis and quality of life for patients with CVD.

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Authors' contributions

CC and JY conceived the project. HH analyzed the data. YL wrote this manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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