

Preclinical cardiovascular mechanisms of SGLT2 inhibitors in heart failure: evidence from in vivo and in vitro studies

 Paniz Negareshifard¹, Saeedeh Keshavarzi¹, Anoosha Habibian¹, Kosar Bagheriha¹, Seyedeh Zahra Banihashemian¹, Bahador Bagheri², Marzieh Noruzi^{3,4*} 

1. School of medicine, Semnan University of Medical Sciences, Semnan, Iran

2. Department of Pharmacology and Toxicology, School of Pharmacy, Iran University of Medical Sciences, Tehran, Iran

3. Research Center of Physiology, Neuroscience Research Institute, Semnan University of Medical Sciences, Semnan, Iran

4. School of pharmacy, Semnan University of Medical Sciences, Semnan, Iran

ABSTRACT

Introduction: Heart failure (HF) remains a major global health challenge, particularly among aging populations and patients with type 2 diabetes (T2D). Sodium-glucose cotransporter 2 (SGLT2) inhibitors, originally developed as glucose-lowering agents, have demonstrated significant cardiovascular benefits in patients with HF regardless of diabetic status. The reviewed studies indicate that SGLT2 inhibitors may exert cardioprotective effects through the attenuation of oxidative stress, inflammation, mitochondrial dysfunction, apoptosis, and cardiac fibrosis. Several studies have shown that modulation of signaling pathways involving NADPH oxidases, Sirtuin 1, AMPK, and STAT3 contributes to reducing myocardial injury and adverse cardiac remodeling. These findings suggest that the cardiovascular benefits of SGLT2 inhibitors extend beyond glycemic control and may directly influence molecular pathways involved in HF progression.

In conclusion, the reviewed evidence suggests that SGLT2 inhibitors play an important role in attenuating oxidative stress, improving cardiac function, and slowing the progression of heart failure through multiple cardioprotective mechanisms. These findings also highlight that SGLT2 inhibitors may have potential implications for the prevention of cardiovascular diseases and provide important directions for future research.

Keywords:

Heart failure

SGLT2 inhibitors

Oxidative stress

Cardioprotective effects

Inflammation

Introduction

Heart failure (HF) is a growing global health problem, with increasing prevalence across different populations. The principal risk factors include age, sex, genetic predisposition, hypertension, diabetes mellitus, and obesi-

ty. Recent epidemiological data indicate that the relative increase in heart failure-associated mortality has been more pronounced among individuals aged 15–44 years than among older adults (Fedacko et al., 2024; Khan et al., 2024). HF develops as a result of multiple interact-

* Corresponding author: Marzieh Noruzi, marziyehnoruzi@semums.ac.ir

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ing pathological processes, including persistent cardiac injury and systemic inflammation. These processes promote adverse cardiac remodeling, interstitial fibrosis, and dysregulation of neurohumoral pathways, ultimately leading to significant cellular dysfunction (Boulet et al., 2024; Schwinger, 2021). At the molecular level, this structural and functional deterioration is driven by profound alterations in myocardial gene expression, typically characterized by the pathological reactivation of fetal gene programs and the downregulation of critical adult metabolic transcripts. Cellular redox homeostasis is normally maintained through a tightly regulated balance between reactive oxygen and nitrogen species and antioxidant systems, including NADPH and glutathione. In heart failure, this balance is disrupted by excessive oxidative stress and depletion of antioxidant reserves, including impaired NADPH generation and reduced glutathione availability. This redox imbalance contributes to cardiomyocyte death and maladaptive transcriptional reprogramming through multiple mechanisms, among which ATF4 (Activating Transcription Factor 4) deficiency represents a key pathway. ATF4 is a stress-responsive transcription factor that regulates genes involved in cellular adaptation, redox homeostasis, and metabolic control (Wang et al., 2022; Xiang et al., 2021). The use of sodium-glucose cotransporter 2 (SGLT2) inhibitors—which include dapagliflozin, canagliflozin, empagliflozin, and ertugliflozin—has become increasingly common. These inhibitors are considered to be one of the four fundamental components of pharmacological treatment for HF. In recent clinical guidelines, these medicines are recommended for all patients with heart failure, regardless of their left ventricular ejection fraction (LVEF) status (Crispino et al., 2025; Komaniecka et al., 2024; McDonagh et al., 2023). SGLT2 inhibitors have demonstrated efficacy in both chronic and acute HF by enhancing myocardial energy utilization, reducing fibrosis, and improving endothelial function (Cinti et al., 2025). SGLT2 inhibitors primarily exert their effects by blocking glucose and sodium reabsorption in the proximal renal tubules, thereby promoting glycosuria and restoring tubuloglomerular feedback, which helps preserve renal hemodynamics. Beyond their glucose-lowering and natriuretic actions, these agents mitigate oxidative stress by reducing NOX function, enhancing mitochondrial efficiency, and promoting a metabolic shift toward ketogenesis. Increased produc-

tion of β -hydroxybutyrate (β -OHB) further upregulates antioxidant gene expression and facilitates the clearance of reactive oxygen species (ROS). In addition, SGLT2 inhibitors possess potent anti-inflammatory properties through inhibition of the NLRP3 inflammasome, leading to reduced secretion of pro-inflammatory cytokines such as IL-1 β , TNF- α , and IL-6. They also promote macrophage polarization from the pro-inflammatory M1 phenotype toward the reparative M2 phenotype. Collectively, these mechanisms attenuate oxidative stress, inflammatory responses, and profibrotic signaling pathways, ultimately limiting cardiomyocyte injury and contributing to improved outcomes in HF (Kim et al., 2020; Lopaschuk and Verma, 2020; Palmiero et al., 2021; Piccirillo et al., 2025; Yarbeygi et al., 2019). Mechanistically, SGLT2 inhibitors may restore antioxidant defenses, reduce mitochondrial oxidative stress, and preserve redox signaling. They also appear to suppress inflammatory and pyroptotic pathways, particularly NLRP3 inflammasome activation, thereby limiting cytokine release, cardiomyocyte injury, and adverse remodeling. Additionally, SGLT2 inhibitors may improve ionic homeostasis by reducing intracellular sodium and calcium overload and enhancing mitochondrial function. Collectively, these actions may contribute to broad cardioprotective effects that extend beyond glycemic control.

Based on the favorable cardiovascular effects of SGLT2 inhibitors observed in diabetes-associated cardiac dysfunction, we hypothesize that these agents may represent an effective therapeutic and preventive strategy for HF. We further hypothesize that their beneficial effects are mediated, at least in part, through anti-inflammatory and antioxidative stress mechanisms. Accordingly, this review aimed to characterize the key signaling pathways regulated by SGLT2 inhibitors, thereby providing a comprehensive mechanistic framework for their therapeutic and preventive effects in HF.

Materials and Methods

A comprehensive narrative review was conducted to summarize current preclinical evidence regarding the molecular mechanisms of sodium–glucose cotransporter 2 inhibitors (SGLT2) inhibitors in HF. Literature searches were performed in PubMed, Embase, and the Cochrane Library from database inception through February 2026.

Search terms included combinations of “heart failure,” “SGLT2 inhibitors,” “dapagliflozin,” “empagliflozin,” “canagliflozin,” “ertugliflozin,” “oxidative stress,” “neuroinflammation,” “NLRP3,” “AMPK,” “SIRT1,” “mitochondrial dysfunction,” “NADPH oxidase (NOX),” and “Na⁺/H⁺ exchanger.

Studies were eligible for inclusion if they:

- evaluated experimental models of HF or cardiomyocyte injury;
- investigated molecular or cellular effects of SGLT2 inhibitors;
- used in vivo animal models or in vitro cardiac/endothelial cell systems; and
- reported outcomes related to oxidative stress, inflammation, mitochondrial function, fibrosis, autophagy, apoptosis, ion homeostasis, or intracellular signaling pathways.

Review articles, conference abstracts, editorials, and studies focusing exclusively on renal or glycemic outcomes without cardiac mechanistic evaluation were excluded.

Data extraction focused on experimental model characteristics, SGLT2 inhibitor type and dosage, treatment duration, and major mechanistic findings. Due to substantial heterogeneity in study design and experimental methodology, a qualitative synthesis approach was used.

Results

A comprehensive review of the literature revealed that diabetic cardiomyopathy (DCM) and heart failure (HF) share several interconnected pathophysiological mechanisms. DCM was considered in this review because studies investigating the effects of SGLT2 inhibitors in DCM may provide useful mechanistic insights into their potential effects in HF. This is particularly relevant because several of the pathophysiological pathways implicated in DCM, including oxidative stress, chronic low-grade inflammation, mitochondrial dysfunction, and progressive myocardial remodeling, are also involved in HF. Therefore, examining the effects of SGLT2 inhibitors on these shared pathways in DCM may help identify potential mechanisms that could contribute to their beneficial effects in HF, including in patients without diabetes. Across the studies included in this review, both conditions were consistently characterized by increased oxidative stress, chronic low-grade inflammation, mitochondrial dysfunction, and progressive myocardial

remodeling. Further analysis identified oxidative stress and inflammatory signaling as central mechanistic drivers in the development and progression of both disease entities. Several studies reported consistent alterations in key biomarkers associated with oxidative stress and inflammation, highlighting their critical contribution to disease severity and adverse cardiac outcomes. In addition, myocardial fibrosis emerged as an important pathological feature linking DCM and HF. Based on these findings, the following sections will examine the most frequently reported relevant biomarkers of oxidative stress, inflammation, and cardiac fibrosis, with particular emphasis on their roles in HF pathophysiology and the potential beneficial effects of SGLT2 inhibitors in modulating these pathways.

Common pathophysiological pathways of HF and DCM

Following a myocardial infarction, activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system triggers a series of maladaptive cellular responses. These responses include oxidative stress, mitochondrial dysfunction, accumulation of advanced glycation end-products, dysregulated autophagy, and heightened inflammation (Kenny and Abel., 2019; Schwinger., 2021). The relative contribution of inflammation and ischemic injury differs between heart failure phenotypes. In HFpEF, inflammation is considered a major driver of endothelial dysfunction, whereas in HFrEF, disease progression is more closely linked to ischemia-induced cardiomyocyte loss and disturbances in cytosolic and mitochondrial Na⁺ and Ca²⁺ homeostasis (Maack et al., 2018). Diabetes mellitus is also a major contributor to heart failure, particularly HFpEF. Chronic hyperglycemia promotes inflammation and vascular smooth muscle cell proliferation, both of which accelerate cardiovascular damage. The development of diabetic cardiomyopathy has been associated with increased mitochondrial reactive oxygen species production, inflammatory activation, apoptosis, dysregulated autophagy and mitophagy, and myocardial fibrosis pathways. Persistent hyperglycemia ultimately contributes to cardiomyocyte death and progressive myocardial fibrosis (Dunlay et al., 2019; Huo et al., 2023; Marwick et al., 2018; Ritchie and Abel., 2020; Tan et al., 2020).

SGLT2 inhibitors' roles in heart failure-related molec-

ular pathways

1- The effect of SGLT2 inhibitors on cardiovascular ROS generation

Oxidative stress is a key mechanism in the development and progression of heart failure. Excessive production of reactive oxygen species (ROS) contributes to vascular dysfunction and damages critical cellular components such as proteins, membrane lipids, and DNA. This imbalance between oxidant production and antioxidant defence promotes cardiomyopathy and progressive cardiac dysfunction. Beyond their glucose-lowering properties, SGLT2 inhibitors have been shown to reduce the risk of heart failure, partly through their ability to attenuate oxidative stress (Koniari et al., 2022). SGLT2 inhibitors reduce oxidative stress by limiting ROS generation, decreasing lipid peroxidation, and enhancing endogenous antioxidant defences. These effects may involve improvements in intracellular calcium handling, modulation of Na^+/H^+ exchanger activity, and suppression of NADPH oxidase (NOX) activity. Because mitochondrial dysfunction is a major source of ROS production in heart failure, SGLT2 inhibitors' protective effects on mitochondrial function are particularly important. Dapagliflozin, for example, has been shown to reduce ROS production and protect cardiomyocytes against hypoxia–reoxygenation injury (Tsai et al., 2021). Similarly, empagliflozin alleviates cardiac microvascular ischemia–reperfusion injury by preserving mitochondrial structure and function, thereby improving cellular energy metabolism and reducing oxidative stress. These effects are associated with improved mitochondrial homeostasis, including better mitochondrial dynamics and reduced mitochondrial damage (Zou et al., 2022). Ertugliflozin has also been reported to decrease mitochondrial ROS production and improve mitochondrial function in Gαq mouse models, suggesting cardioprotective effects that extend beyond glycemic control (Chambers et al. 2025). More recently, canagliflozin was shown to attenuate oxidative stress and structural cardiac injury in isoproterenol-induced models by reducing lipid peroxidation and limiting further oxidative damage (Kitasato et al., 2025). In the following sections, the related molecular pathways will be discussed in greater detail.

1-1- Effects of SGLT2 inhibitors on Ca^{2+} homeostasis

Intracellular Ca^{2+} mobilization plays a central role in ROS signaling and is essential for regulating excitation–

contraction coupling (ECC) in cardiomyocytes. This process is controlled by several key proteins, including sarco/endoplasmic reticulum Ca^{2+} -ATPase (SERCA), ryanodine receptors (RyR), and calcium/calmodulin-dependent protein kinase II (CaMKII) (Prosser et al., 2011). CaMKII is activated by binding of Ca^{2+} /calmodulin to its regulatory domain, leading to the phosphorylation of multiple ion channels and transporters involved in intracellular Ca^{2+} handling. These targets include RyR (Currie et al., 2004; Zhang et al., 2003), L-type Ca^{2+} channels (Hudmon et al., 2005; Wu et al., 1999), and SERCA (Picht et al., 2007; Tsui et al., 2005). In addition, CaMKII-mediated phosphorylation of phospholamban (PLN), a physiological inhibitor of SERCA2a, enhances Ca^{2+} reuptake into the sarcoplasmic reticulum. Several pathological conditions associated with atrial fibrillation (AF), including hyperglycemia, oxidative stress, and β -adrenergic stimulation, are known to increase CaMKII activity. In patients with chronic AF, enhanced phosphorylation of the RyR complex promotes abnormal Ca^{2+} leakage from the sarcoplasmic reticulum, contributing to arrhythmogenic ROS signaling. Empagliflozin has been shown to attenuate these pathological changes by reducing CaMKII activity and reducing RyR-mediated Ca^{2+} leak, thereby decreasing Ca^{2+} -dependent ROS signaling in AF (Durak et al., 2018; Erickson et al., 2013; Mangmool et al., 2010; Vafiadaki et al., 2007). In addition to disturbances in Ca^{2+} homeostasis, endoplasmic reticulum (ER) stress also contributes to cardiomyocyte injury. ER stress arises when the protein-folding capacity of the ER becomes impaired, triggering the unfolded protein response (UPR) through signaling pathways mediated by IRE1 α , PERK, and ATF6. Persistent activation of these pathways can lead to cellular dysfunction and apoptosis. When combined with mitochondrial dysfunction, ER stress further aggravates cardiac injury. Recent evidence suggests that SGLT2 inhibitors can alleviate ER stress by modulating these dysregulated pathways, thereby supporting cellular recovery and contributing to cardioprotection in heart failure (Pham et al., 2024; Read and Schröder, 2021). In human cardiac fibroblasts exposed to hyperglycemic conditions, canagliflozin has been shown to reduce mitochondrial oxidative stress and normalize abnormalities in calcium handling. These findings suggest that SGLT2 inhibitors help stabilize intracellular Ca^{2+} homeostasis while simultaneously improving mitochondrial redox balance (Varzideh et al.,

2024). Overall, SGLT2 inhibition appears to mitigate CaMKII-driven Ca^{2+} dysregulation, ROS signaling, and ER stress, thereby improving cardiomyocyte function and contributing to cardioprotection in atrial fibrillation and heart failure.

1-2- The effect of SGLT2 inhibitors on nitric oxide function

NADPH oxidase (NOX) is a major source of superoxide (O_2^-) production in the vasculature and plays an important role in both redox signaling and cardiovascular disease. NOX isoforms, particularly NOX1 and NOX2, are expressed in endothelial cells, vascular smooth muscle cells, fibroblasts, and perivascular adipocytes. Their activation can be influenced by disturbances in intracellular Ca^{2+} homeostasis and by signaling molecules such as Rac1 and p47phox, which are required for NOX complex assembly (Bedard and Krause 2007; Konior et al., 2014; Zhou et al., 2021). In heart failure, oxidative stress and endothelial nitric oxide synthase (eNOS) uncoupling create a self-perpetuating cycle that sustains NOX activation. This process is driven by oxidation and depletion of tetrahydrobiopterin (BH_4), an essential cofactor for eNOS. Loss of BH_4 shifts eNOS from nitric oxide (NO) production toward superoxide generation, further increasing oxidative stress and endothelial dysfunction (Meza et al., 2019). SGLT2 inhibitors have been shown to interrupt this cycle. Canagliflozin suppresses NOX1 and NOX2 activity, reduces oxidative stress, and preserves BH_4 availability, thereby improving eNOS coupling (Forstermann and Sessa., 2012; Roe and Ren., 2012). These effects are linked to inhibition of Rac1 activation and prevention of p47phox translocation, both essential steps in NOX activation (Kondo et al., 2021). In endothelial cell studies, SGLT2 inhibitors reduced ROS production and restored NO bioavailability under inflammatory conditions (Uthman et al., 2019). Canagliflozin has also shown rapid vascular and myocardial protective effects during ischemia–reperfusion injury, including improved vasorelaxation, enhanced eNOS phosphorylation, and reduced lipid peroxidation (9102 „la te ruoyaS). Similarly, empagliflozin decreases NOX activity through modulation of the NHE/ Na^+ /NCX/ Ca^{2+} /PKC signaling pathway, resulting in lower ROS production in coronary endothelial cells (Li et al., 2024). Overall, the available evidence suggests that SGLT2 inhibitors may reduce oxidative stress in HF by suppressing NOX activation, preserving eNOS func-

tion, and improving vascular endothelial function.

2- Effects of SGLT2 inhibitors on cardiac inflammation

Inflammation plays a major role in the progression of heart failure by exacerbating cardiac dysfunction through several interconnected mechanisms, including activation of the NLRP3 inflammasome, which can contribute to cardiomyocyte death (Luo et al., 2017; Pickering et al., 2018). These processes can create a persistent inflammatory cycle that promotes myocardial remodeling and heart failure progression. Recent evidence suggests that SGLT2 inhibitors may counter these effects by reducing oxidative stress and suppressing downstream inflammatory signaling. In the following sections, the related molecular pathways will be discussed in greater detail.

2-1-The effect of SGLT2 inhibitors on NLRP3 inflammasome

Elevated ROS levels can activate the NLRP3 inflammasome (Zhang et al., 2024). Assembly of the NLRP3 inflammasome through the recruitment of apoptosis-associated speck-like protein (ASC) promotes caspase-1 activation, which subsequently facilitates the maturation and release of pro-inflammatory cytokines, particularly interleukin-1 β (IL-1 β) and interleukin-18 (IL-18), and induces inflammatory cell death through pyroptosis. The relationship between the NLRP3 inflammasome and inflammatory cytokines is bidirectional. Although NLRP3 activation stimulates IL-1 β and IL-18 release, inflammatory cytokines such as tumor necrosis factor- α (TNF- α) can further amplify NLRP3 activation, creating a sustained pro-inflammatory loop that contributes to myocardial dysfunction and adverse cardiac remodeling. SGLT2 inhibitors appear to attenuate this inflammatory pathway. Experimental studies have shown that dapagliflozin suppresses NLRP3 inflammasome activation, reduces inflammation and fibrosis, and may slow the progression of heart failure in animal models (Butts et al., 2015; Kim et al., 2020; Toldo and Abbate., 2024). In addition to their direct anti-inflammatory effects, SGLT2 inhibitors may regulate inflammasome activity through the modulation of autophagy. For example, dapagliflozin reduced myocardial ischemia/reperfusion injury by suppressing NLRP3 activation while simultaneously modulating autophagy, leading to reduced caspase-1 activation and decreased IL-1 β release (Yu et

al., 2022). Overall, these findings suggest that SGLT2 inhibitors may protect against inflammation-driven myocardial injury by limiting NLRP3 inflammasome activation and reducing downstream inflammatory responses.

3- The effect of SGLT2 inhibitors on apoptosis, autophagy and cardiac fibrosis

Oxidative stress and chronic low-grade inflammation contribute to cardiac dysfunction through activation of interconnected pathways such as the NLRP3 inflammasome and STAT3 signaling. These pathways promote apoptosis, pyroptosis, ferroptosis, dysregulated autophagy, and ultimately myocardial fibrosis. Growing evidence suggests that SGLT2 inhibitors can attenuate these pathological processes by reducing oxidative stress, suppressing inflammatory signaling, and modulating autophagic activity, thereby limiting adverse cardiac remodeling. Several experimental studies have demonstrated anti-ferroptotic and anti-fibrotic effects of SGLT2 inhibitors. Empagliflozin has been shown to improve mitochondrial function and autophagy-related signaling while reducing ROS production and cytochrome c release in experimental heart failure models (Li et al., 2022). In Dahl salt-sensitive rat models, canagliflozin reduced myocardial iron accumulation, lipid peroxidation, and ROS generation (Ma et al., 2022; Ma et al., 2023). Similarly, dapagliflozin attenuated ferroptosis through activation of the Nrf2/HO-1 pathway and increased GPX4 expression (Zhang et al., 2025).

SGLT2 inhibitors also exert important anti-fibrotic effects. Empagliflozin has been shown to reduce endoplasmic reticulum Ca^{2+} release and cardiac fibrogenesis in human atrial fibroblasts, together with decreased Na^+/H^+ exchanger (NHE) activity, which plays a role in cardiac cell volume regulation (Chung et al., 2023). In addition, SGLT2 inhibitors suppress several profibrotic signaling pathways, including TGF- β 1/ATF4, SMAD, and Wnt/ β -catenin signaling, leading to reduced collagen deposition, cardiac hypertrophy, and myocardial fibrosis (Rolski and Mączewski 2025; Yuan et al., 2024). In chronic heart failure models, canagliflozin has also been shown to significantly ameliorate myocardial fibrosis and improve cardiac function in a dose-independent manner, highlighting its potential anti-remodeling effects in established cardiac dysfunction (Yu et al., 2025). In the following sections, the related molecular

pathways will be discussed in greater detail.

3-1- The effect of SGLT2 inhibitors on AMPK function

AMP-activated protein kinase (AMPK) is a central regulator of cellular energy homeostasis. In the heart, AMPK supports cardiomyocyte survival by promoting autophagy, reducing apoptosis under stress conditions, and suppressing fibrosis through inhibition of pro-fibrotic signaling pathways. In heart failure, impaired AMPK activity contributes to disrupted myocardial energy metabolism and progression of cardiac dysfunction (Lu et al., 2019). The effects of SGLT2 inhibitors on AMPK signaling are context-dependent and vary with disease state and baseline AMPK activity. Under metabolic stress, these agents generally activate AMPK, leading to increased SIRT1 signaling, inhibition of mTOR, and enhanced autophagy. These changes improve mitochondrial function, reduce oxidative stress and inflammation, and promote cellular adaptation. However, their effects may be diminished or altered when AMPK is already strongly activated in response to severe injury (Packer 2022). Dapagliflozin has been shown to restore phosphorylation of p38 and JNK and to decrease interstitial fibrosis in murine models (Shi et al., 2019). Empagliflozin restores PPAR α expression and fatty acid oxidation pathways, leading to improved metabolic balance and reduced fibrosis in experimental models (Lee et al., 2019). Empagliflozin also protects mitochondrial function and modulates AMPK signaling in ischemia-reperfusion injury models (Lu et al., 2020). Dapagliflozin has been reported to reduce ventricular arrhythmias after myocardial infarction through an AMPK-dependent mechanism (Lee et al., 2021). Empagliflozin also alleviates cardiac microvascular ischemia-reperfusion injury via activation of the AMPK α 1/ULK1/FUNDC1 pathway, enhancing mitophagy and preserving mitochondrial integrity (Cai et al., 2022). Similar findings have been reported in pressure overload models, where canagliflozin prevented hypertensive heart failure in Dahl salt-sensitive rats through activation of the AMPK/SIRT1/PGC-1 α pathway, resulting in improved energy metabolism and reduced oxidative stress (He et al., 2022). In line with these findings, canagliflozin has also been reported to inhibit ERK1/2 activation in rat hearts (Sun et al., 2024). In addition, Canagliflozin likely shifted AMPK signaling from a chronically overactivated, maladaptive state to a balanced level, because excessive

AMPK activation was driving pathological mitophagy and ferroptosis in stressed cardiomyocytes. Thus, reducing p-AMPK in this context was cardioprotective by suppressing excessive mitophagy and restoring GPX4 levels, thereby improving cell survival (Xiong et al., 2026). Collectively, inhibition of MAPK signaling contributes to the broader anti-inflammatory and anti-fibrotic effects of this drug class.

3-2- Effects of SGLT2 inhibitors on Sirtuin 1 function

Sirtuin 1 (SIRT1) plays an important role in the development and progression of heart failure by regulating cellular stress responses and energy metabolism. When SIRT1 is activated, it supports mitochondrial function, reduces oxidative stress, and promotes protective autophagy partly through hypoxia-inducible factor 1- α (HIF-1 α) signaling. It also helps suppress inflammatory and fibrotic pathways (Chen et al., 2012; Schönenberger et al., 2015; Semenza 2011; Silter et al., 2010; Wei et al., 2012). However, if HIF-1 α remains chronically elevated, it can negatively affect cardiac performance by reducing ATP production and promoting lipid accumulation (Sato and Takeda., 2023). In heart failure, reduced SIRT1 activity is linked to impaired cardiac energy metabolism and adverse structural remodeling, making SIRT1 enhancement a promising therapeutic target (Packer 2020; Tanno et al., 2012). Interestingly, SGLT2 inhibitors may exert part of their cardioprotective effects through activation of SIRT1, improving mitochondrial efficiency and reducing oxidative stress (Hoong and Chua., 2021). In experimental studies, dapagliflozin has been shown to increase the expression of SIRT1, SIRT3, and SIRT6 while suppressing HIF-1 α signaling, thereby reducing cardiac hypertrophy and dysfunction. Similarly, empagliflozin has been reported to downregulate HIF-1 α in models of atrial fibrillation (Badreldin et al., 2024; Lin et al., 2024; Yang et al., 2023). Activation of SIRT1 contributes to the broader anti-fibrotic effects of this drug class.

3-3- Effects of SGLT2 inhibitors on signal transducer and activator of transcription 3 (STAT3) pathway

Under pathological cardiac conditions, activation of STAT3 has been associated with increased expression of pro-fibrotic genes in cardiomyocytes. At the same time, phosphorylation of STAT3 may also exert protective effects by reducing inflammation through modula-

tion of the JNK and MAPK signaling pathways in heart failure. The involvement of STAT3 further supports the therapeutic relevance of SGLT2 inhibitors in cardiac disease. In this context, dapagliflozin has been shown to reduce cardiac fibrosis in rat models, partly through macrophage polarization mediated by STAT3 signaling (Harhous et al., 2019; Lee et al., 2017). Similarly, empagliflozin has been reported to modulate STAT3 activity, and long-term treatment has been linked to a reduction in myocardial infarct size, an effect partially attributed to STAT3 activation (Andreadou et al., 2017; Nikolaou et al., 2021). Notably, crosstalk between STAT3 and TGF- β signaling pathways may further contribute to cardioprotection. Interaction between STAT3 and TGF- β signaling may contribute to cardioprotective effects. In particular, early STAT3 activation during reperfusion has been associated with increased TGF- β expression, suggesting a coordinated response that may help limit myocardial injury (Mylonas et al., 2021).

3-4- Effects of SGLT2 inhibitors on mTORC1 Function

The mechanistic target of rapamycin complex 1 (mTORC1) is a central regulator of cellular metabolism, growth, and protein synthesis, and it plays a key role in the development of cardiac hypertrophy. Excessive activation of mTORC1 has been identified as an important contributor to hypertrophic cardiomyopathy (Sciarretta et al., 2022). Emerging evidence suggests that SGLT2 inhibitors can suppress mTORC1 signaling. In addition to direct effects on this pathway, these agents also act on upstream metabolic and stress-related mechanisms that regulate mTOR activity. For instance, ertugliflozin has been shown to enhance cardiac substrate metabolism while simultaneously reducing mTOR signaling, endoplasmic reticulum stress, and apoptosis in experimental models of cardiac dysfunction (Moellmann et al., 2022). Collectively, these findings suggest that the beneficial effects of SGLT2 inhibitors on mTOR signaling are closely linked to improved cellular metabolism and proteostasis.

Discussion

In this review, we summarized current evidence regarding the cardioprotective effects of SGLT2 inhibitors in heart failure and highlighted that these agents exert beneficial actions through multiple interconnected molecular pathways beyond glucose lowering. The studies

TABLE 1: A summary of preclinical studies examining SGLT2 inhibitor effects on heart failure

Author, year	Design	Drugs	Rout of administration	Duration of intervention	Molecular pathways	Reference
In vivo studies						
Ma et al., 2022	Dahl salt-sensitive Rats as a HFpEF model	Canagliflozin	Oral gavage (20mg/kg/day)	12 weeks	Reduced myocardial iron deposition, decreased lipid peroxidation (MDA levels), and downregulated ROS generation, while GPX4 expression remained unchanged.	(Ma et al., 2022)
Yu et al., 2025	SD rats	Canagliflozin	Oral gavage (10mg/kg/day)	4 weeks	Downregulated myocardial fibrosis-related genes, including collagen I, collagen III, and fibronectin	(Yu et al., 2025)
Kitasato et al., 2025	SD rats	Canagliflozin	Oral gavage (10mg/kg/day)	2 weeks	Reduced oxidative ROS, MDA, improved mitochondrial function by decreasing cytochrome-c release, attenuated apoptosis related markers like decreasing cleaved caspase-3 levels	(Kitasato et al., 2025)
Sayour et al., 2019	In vivo rat ischemia–reperfusion model	Canagliflozin	Intravenous bolus (3 µg/kg)	120 min reperfusion	Increased phosphorylated eNOS and reduced BAX/BCL2 ratio and lowered 4 hydroxynonenal positivity	(Sayour et al., 2019)
He et al., 2022	Dahl salt-sensitive (DSS) rats	Canagliflozin	Oral gavage (20mg/kg/day)	9 weeks	Activated the AMPK/SIRT1/PGC-1 α pathway to restore disrupted energy metabolism and alleviate oxidative stress	(He et al., 2022)
Xiong et al., 2026	isoproterenol-induced HF mouse model	Canagliflozin	Oral gavage (10 mg/kg/day)	28 days	Decreased p-AMPK levels suppressed excessive mitophagy Restored GPX4 protein levels (anti-ferroptosis effect)	(Xiong et al., 2026)
Ma et al., 2023	Dahl salt-sensitive (DSS) rats	Canagliflozin	Oral gavage (20mg/kg/day)	12 weeks	Decreased iron accumulation without altering GPX4 expression, restored reduced AMPK/PGC-1 α /Nrf2-related proteins and HO-1 levels	(Ma et al., 2023)
Sun et al., 2024	SD rats	canagliflozin	Oral gavage (3 mg/kg/day)	4 weeks	Decreased phosphorylation of AKT and ERK1/2	(Sun et al., 2024)
Zhang et al., 2019	pig HFpEF model	Dapagliflozin	Oral gavage (10mg/day)	9 weeks	Reduced inflammatory cytokines levels like IL-6 and TNF- α , and decreased eNOS expression	(Zhang et al., 2019)
Shi et al., 2019	C57bl/6j mice	Dapagliflozin	Oral gavage (1mg/kg/day)	4 weeks	Reduced phosphorylation of p38 and JNK, and attenuated interstitial fibrosis	(Shi et al., 2019)
Lee et al., 2021	male Wistar rats	Dapagliflozin	Oral gavage (0.1 mg/kg/day)	4 weeks	attenuated ROS and increased AMPK phosphorylation, improved ventricular arrhythmias	(Lee et al., 2021)
Yu et al., 2022	C57bl/6j mice	Dapagliflozin	Oral gavage (40mg/kg/day)	7 days (pre-treatment)	Lowered IL-1 β levels, inhibited caspase-1 activity, and reduced NLRP3 and NHE/NCX activation in cardiomyocytes	(Yu et al., 2022)
Tsai et al., 2021	SD rats	Dapagliflozin	Oral gavage (0.1 mg/kg/day)	10 days	Reduced oxidative stress and apoptosis via modulation of AMPK and NADPH oxidase signaling	(Tsai et al., 2021)
Zhang et al., 2025	Male new Zealand white rabbits heart failure model	Dapagliflozin	Oral gavage (10 mg/kg/day)	weeks 10	Attenuated oxidative stress, ferroptosis, and inflammation by increasing Nrf2, HO-1, and GPX4, and decreasing MDA, IL-1 β , IL-6, and TNF- α	Zhang et al., 2025
Lee et al., 2019	spontaneous hypertensive rats (SHR) with high fat diet	empagliflozin	Oral gavage (20 mg/kg/day)	12 weeks	Restored PPAR α , ACADM, NPPA, NPPB, and TNF- α levels and reduced cardiac fibrosis	(Lee et al., 2019)

Continuation of Table 1:

Author, year	Design	Drugs	Rout of ad-ministration	Duration of intervention	Molecular pathways	Reference
In vivo studies						
Lu et al., 2020	C57BL/6J mice/	Empagliflozin	Oral gavage (10 mg/kg/day), (10 μ M)	Pretreatment, for seven days 12 h In vitro incubation	improved mitochondrial oxidative stress, mitochondrial respiration and adenosine triphosphate , repressing mitochondrial fission, protect the microvasculature by inhibiting the DNA-PKcs/Fis1/mitochondrial fission pathway during myocardial I/R	(Zou et al., 2022)
Li et al., 2022	Male C57B/6J mice	Empagliflozin	Oral gavage (10 mg/kg/day)	4 weeks	Inhibited ROS production, reduced cytochrome c release, increased Beclin1 and Atg7 expression, increased LC3II/I ratio and enhanced mitochondrial biogenesis	(Li et al., 2022)
Chung et al., 2023	In vivo murine heart failure model	Empagliflozin	Oral gavage (10 mg/kg/day)	28 days	reducing ER Ca ²⁺ release, extracellular Ca ²⁺ entry and the profibrotic action	(Chung et al., 2023)
Yuan et al., 2024	Male C57B/6J mice	Empagliflozin	Oral gavage (10 mg/kg/day)	7 days	Inhibited Wnt/ β -catenin signaling, leading to reduced cardiac hypertrophy	(Yuan et al., 2024)
Cai et al., 2022	mutant C57B/6J mice	Empagliflozin	Oral gavage (10 mg/kg/day)	7 days (pre-treatment)	Prevented mitochondrial apoptosis through an activation of AMPK-dependent mitophagy	(Cai et al., 2022)
Croteau et al., 2021	C57B/6J mice	Ertugliflozin	0.5 mg/g of diet	4 months	Reduced cardiac H ₂ O ₂ production and downregulated oxidative stress-related genes	(Croteau et al., 2021)
Chambers et al. 2025	Gaq mice	Ertugliflozin	0.5 mg/g chow	16 weeks	Reduced mitochondrial ROS generation and improved mitochondrial dysfunction	(Chambers et al. 2025)
Chambers et al. 2025	C57BL/6J mice	Ertugliflozin	(225 mg/kg at a chow diet)	10 weeks	Reduced downstream mTOR signaling	(Chambers et al. 2025)
Mylonas et al., 2021	C57BL/6 mice	Empagliflozin, Dapagliflozin, Ertugliflozin	Oral gavage EMPA (10mg/kg/day), DAPA (9.0mg/kg/day), ERTU (9.7mg/kg/day)	7 days (pre-treatment)	Increased STAT3 phosphorylation (Y705) increased TGF- β mRNA levels, suggesting cardioprotection via STAT3/TGF- β crosstalk.	(Mylonas et al., 2021)
In vitro studies						
Kondo et al., 2021	in vitro human cardiomyocytes	Canagliflozin	In vitro incubation (3–100 μ M)	1 hour	Reduced NADPH oxidase activity; improved NOS coupling through increased BH4; suppressed Rac1 activation and p47phox translocation	(Kondo et al., 2021)
Varzideh et al., 2024	Human cardiac fibroblasts	Canagliflozin	In vitro incubation (100 nM)	48 hours	Ameliorated calcium-handling disturbances and improved mitochondrial function by reducing ROS production	(Varzideh et al., 2024)
Lin et al., 2024	H9c2 cells	Dapagliflozin	In vitro incubation (2.5 and 5 μ M)	48 hours	increased the gene and protein expression of SIRT1, 3 and 6, upregulated the hypoxia-induced gene downregulation	(Lin et al., 2024)
Uthman et al., 2019	endothelial cells Human coronary arterial endothelial cells (HCAECs) and human umbilical vein endothelial cells (HUVECs)	Empagliflozin or Dapagliflozin	In vitro incubation: 1 μ M	hours 24	Decreased ROS and restored NO bio-availability under TNF- α stimulation	(Uthman et al., 2019)

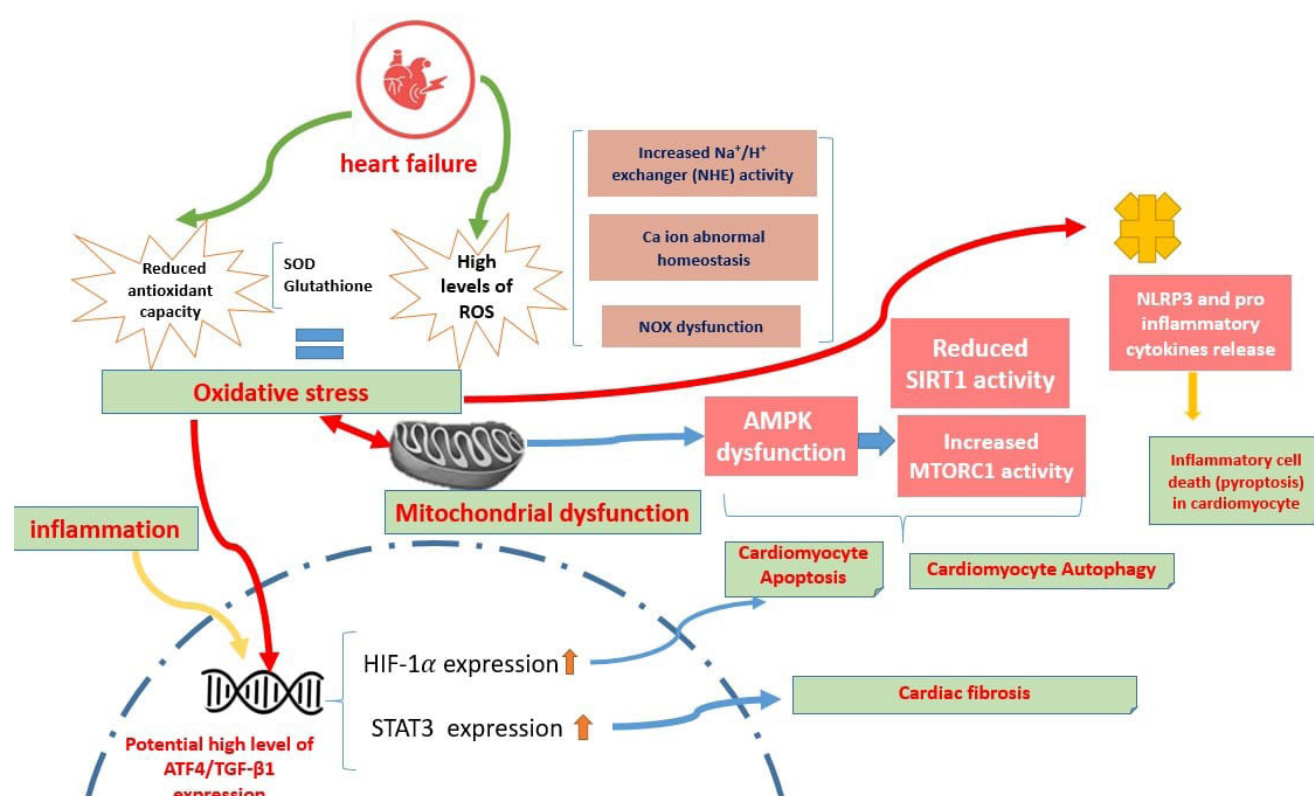


FIGURE 1. The potential molecular mechanisms of heart failure, highlighting the interplay between oxidative stress, mitochondrial dysfunction, and inflammation. In heart failure, the deficiency of myocardial antioxidant system and high production of reactive oxygen species (ROS) via dysregulation of intracellular calcium (Ca^{2+}) and NADPH oxidase (NOX) homeostasis happened. Consequently, the heightened oxidative stress leads to the onset and amplification of mitochondrial dysfunction. The compromised mitochondria initiate a cascade of detrimental events: impaired Adenosine Monophosphate-activated Protein Kinase (AMPK) activity, diminished Sirtuin 1 (SIRT1) deacetylase function, and hyperactivated mechanistic Target of Rapamycin Complex 1 (MTORC1) signaling. Collectively, these molecular perturbations drive cardiomyocyte apoptosis, induce autophagic dysregulation, and promote cardiac fibrosis. Furthermore, mitochondrial impairment establishes a deleterious positive feedback loop that intensifies oxidative stress. In parallel, inflammatory pathways, including the activation of the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome and the subsequent release of pro-inflammatory cytokines, contribute substantially to the development of cardiomyopathy and inflammatory-mediated cell death. Aberrant transcriptional regulation, characterized by augmented expression of Hypoxia-inducible factor 1-alpha (HIF-1 α), and Signal Transducer and Activator of Transcription 3 (STAT3), further exacerbates the progression of heart failure. Activating Transcription Factor 4 (ATF4)/Transforming Growth Factor beta 1 (TGF- β 1) gene expression is a potential molecular mechanism that needs further research.

identified through our literature search (Table 1) indicate that SGLT2 inhibitors mitigate oxidative stress, inflammation, fibrosis, apoptosis, and mitochondrial dysfunction in preclinical heart failure models. These effects are accompanied by reductions in ROS generation, lipid peroxidation, and pro-inflammatory cytokine production, as well as modulation of key signaling pathways, including AMPK, SIRT1, STAT3, and mTORC1.

As illustrated in Figure 1, heart failure is characterized by impaired antioxidant defenses, disrupted calcium handling, and dysregulated NOX activity, all of which contribute to excessive ROS generation. Increased oxidative stress promotes mitochondrial dysfunction and is associated with reduced AMPK and SIRT1 activity to-

gether with mTORC1 hyperactivation. These alterations collectively promote cardiomyocyte apoptosis, impaired autophagy, and myocardial fibrosis. In parallel, activation of inflammatory pathways, particularly the NLRP3 inflammasome, further exacerbates cardiac remodeling and disease progression. Downstream transcriptional dysregulation involving HIF-1 α and STAT3 may also contribute to worsening myocardial dysfunction.

Consistent with previously published reports, particularly those by Pabel et al. (Pabel et al., 2021), the available evidence supports the concept that SGLT2 inhibitors exert multifaceted cardioprotective effects through attenuation of oxidative stress and inflammation, improvement of mitochondrial function, and

modulation of cardiac remodeling. Among these mechanisms, reduction of oxidative stress appears to represent one of the most central and reproducible pathways underlying the cardiovascular benefits of SGLT2 inhibitors. In agreement with earlier investigations (Wichaiyo and Saengklub., 2022), inhibition of cardiac NHE1 by SGLT2 inhibitors may reduce intracellular sodium accumulation and subsequently limit mitochondrial calcium overload. This process may decrease excessive ROS generation, preserve mitochondrial membrane integrity, and improve cellular bioenergetics. Preservation of mitochondrial homeostasis is particularly important in heart failure, where impaired energy metabolism and oxidative injury contribute substantially to progressive myocardial dysfunction. In addition to their antioxidant properties, accumulating evidence indicates that SGLT2 inhibitors possess important anti-inflammatory effects. Several experimental studies suggest that these agents suppress activation of the NLRP3 inflammasome pathway (Chen et al., 2022), thereby reducing the release of pro-inflammatory cytokines and attenuating chronic low-grade inflammation. This mechanism is particularly relevant to ventricular remodeling and myocardial fibrosis, both of which play central roles in the progression of HFrEF and HFpEF. By limiting inflammatory signaling and fibrotic responses, SGLT2 inhibitors may contribute not only to functional improvement but also to long-term structural preservation of the myocardium.

Another important aspect highlighted in this review is the potential role of SGLT2 inhibitors in regulating autophagy and cellular quality-control mechanisms. Emerging evidence suggests that these drugs may restore autophagic balance through activation of the AMPK/SIRT1 signaling pathway and inhibition of mTORC1 activity, pathways closely linked to cellular metabolism, stress adaptation, and survival. Enhanced autophagic flux may facilitate the removal of damaged organelles and dysfunctional mitochondria, thereby protecting cardiomyocytes from further injury. However, despite these promising findings, available evidence remains somewhat inconsistent across studies (Piperis et al., 2024). While many experimental models demonstrate improved autophagic activity following SGLT2 inhibitor therapy, other investigations report variable or context-dependent effects influenced by disease stage, experimental model, treatment duration, and drug dosage (Duan et al., 2024). These discrepancies suggest that the precise con-

tribution of autophagy to the overall clinical benefits of SGLT2 inhibitors has not yet been fully elucidated.

Although substantial mechanistic evidence supports direct myocardial effects of SGLT2 inhibitors, some investigators propose that the observed cardiovascular benefits may be driven predominantly by systemic hemodynamic and metabolic changes rather than direct cardiac signaling pathways, particularly given the relatively low myocardial expression of SGLT2. Proposed systemic mechanisms include reductions in preload and afterload, osmotic diuresis, natriuresis, improved vascular function, and decreased plasma volume, all of which may alleviate cardiac workload and improve heart failure outcomes (Cowie and Fisher 2020). It is therefore likely that both direct cellular mechanisms and indirect systemic effects contribute to the cardioprotective actions of SGLT2 inhibitors.

The strength of this review is the integration of both in vitro and in vivo evidence to provide a comprehensive overview of the molecular mechanisms underlying SGLT2 inhibitor therapy in heart failure. By simultaneously addressing oxidative stress, mitochondrial dysfunction, inflammation, fibrosis, pyroptosis, and autophagy, this review moves beyond single-pathway interpretations of SGLT2 inhibitor action. Furthermore, comparison between dapagliflozin and empagliflozin provides additional insight into potential class effects and shared molecular targets.

Several limitations should be considered when interpreting the current evidence. Most available data originate from preclinical studies, whereas mechanistic investigations in humans remain relatively limited. In addition, variability in experimental protocols, including differences in drug dosage, treatment duration, and heart failure models, reduces direct comparability among studies. Evidence regarding the long-term molecular effects of SGLT2 inhibitors in heart failure with preserved ejection fraction (HFpEF) and heart failure with mildly reduced ejection fraction (HFmrEF) also remains insufficient. Current findings suggest that attenuation of oxidative stress, preservation of mitochondrial function, and modulation of inflammatory signaling represent the most clinically relevant and consistently reproducible mechanisms observed across experimental studies. In contrast, the roles of autophagy, ferroptosis, mTORC1 signaling, and transcriptional regulation remain less clearly established and require further trans-

lational investigation.

Future studies should focus on inflammatory and oxidative stress-related biomarkers in heart failure, particularly pathways involving NF- κ B, AGE/RAGE signaling, Nrf2, and HIF-1 α . Although current data suggest these pathways may contribute to the anti-inflammatory and antifibrotic effects of SGLT2 inhibitors, direct mechanistic validation remains limited. Additional research is also needed to clarify the efficacy and safety of SGLT2 inhibitors in HFpEF and HFmrEF populations, as well as their potential effects when combined with SGLT1 inhibition and across different stages of heart failure (Heidenreich et al., 2022; Pabel et al., 2021). Unlike previous reviews that primarily focused on the clinical benefits of SGLT2 inhibitors in heart failure, the present review specifically integrates recent preclinical evidence regarding oxidative stress- and inflammation-related molecular pathways involved in cardiac remodeling and myocardial dysfunction. By combining findings from both in vivo and in vitro studies, this review provides a more comprehensive mechanistic framework explaining how SGLT2 inhibitors may attenuate myocardial injury beyond glycemic control. Particular emphasis was placed on the interconnected roles of mitochondrial dysfunction, ROS generation, NLRP3 inflammasome activation, AMPK/SIRT1 signaling, and autophagy, which collectively represent central drivers of heart failure progression and potential therapeutic targets across different heart failure phenotypes.

Conclusion

SGLT2 inhibitors exert cardioprotective effects in heart failure through multiple interconnected mechanisms that extend beyond glucose lowering. Among the proposed pathways, modulation of oxidative stress and preservation of mitochondrial homeostasis appear to be among the most consistently supported mechanisms across preclinical studies, whereas the contributions of autophagy and inflammasome signaling remain more context-dependent. Although current evidence is promising, further translational and clinical studies are needed to clarify the relative importance of these mechanisms in different heart failure phenotypes and stages.

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[art/44490050-heart-attack-icon-design](https://www.vecteezy.com/vector-art/420730-vector-dna-icon); <https://www.vecteezy.com/vector-art/420730-vector-dna-icon>)

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

Data curation and Original draft preparation were done by Paniz Negareshifard, Saeedeh Keshavarsi, Anoosha Habibian, Kosar Bagheriha and Seyedeh Zahra Banihashemian. Investigation was done by Paniz Negareshifard and Saeedeh Keshavarsi. Methodology and Project administration were done by Bahador Bagheri and Marzieh Noruzi. Resources were checked by Anoosha Habibian, Kosar Bagheriha. Study supervision, Validation and Review and editing were done by Marzieh Noruzi. Visualization was done by Seyedeh Zahra Banihashemian. Formal analysis and Conceptualization of the manuscript for important intellectual content were done by Bahador Bagheri. All authors are responsible for drafting and revising the article and contributed equally.

References

- Andreou I, Efentakis P, Balafas E, Togliatto G, Davos C H, Varela A, et al. Empagliflozin Limits myocardial infarction in vivo and cell death in vitro: role of STAT3, mitochondria, and redox aspects. *Frontiers in Physiology* 2017; 8: 1077. <https://doi.org/10.3389/fphys.2017.01077>
- Badreldin H, Elshal M, El-Karef A, Ibrahim T. Empagliflozin protects the heart from atrial fibrillation in rats through inhibiting the NF- κ B/HIF-1 α regulatory axis and atrial remodeling. *International Immunopharmacology* 2024; 143: 113403. <https://doi.org/10.1016/j.intimp.2024.113403>
- Bedard K, Krause K H. The NOX family of ROS-generating NADPH oxidases: physiology and pathophysiology. *Physiological Reviews* 2007; 87: 245-313. <https://doi.org/10.1152/physrev.00044.2005>
- Boulet J, Sridhar V S, Bouabdallaoui N, Tardif J-C, White M. Inflammation in heart failure: pathophysiology and therapeutic strategies. *Inflammation Research* 2024; 73: 709-723. <https://doi.org/10.1007/s00011-023-01845-6>
- Butts B, Gary R A, Dunbar S B, Butler J. The Importance of NLRP3 Inflammasome in Heart Failure. *Journal of Cardiac Failure* 2015; 21: 586-593. <https://doi.org/10.1016/j.cardfail.2015.04.014>

- Cai C, Guo Z, Chang X, Li Z, Wu F, He J, et al. Empagliflozin attenuates cardiac microvascular ischemia/reperfusion through activating the AMPK α 1/ULK1/FUNDC1/mitophagy pathway. *Redox Biology* 2022; 52: 102288. <https://doi.org/10.1016/j.redox.2022.102288>
- Chambers JM, Croteau D, Pimentel DR, Gower AC, Panagia M, Baka T, Qin F, Luptak I, Colucci WS. SGLT2 inhibitor upregulates myocardial genes for oxidative phosphorylation and fatty acid metabolism in Gαq-mice. *J Mol Cell Cardiol Plus*. 2025 Apr 9;12:100296. <https://doi.org/10.1016/j.jmccpl.2025.100296>
- Chen R, Xu M, Hogg R T, Li J, Little B, Gerard R D, et al. The acetylase/deacetylase couple CREB-binding protein/Sirtuin 1 controls hypoxia-inducible factor 2 signaling. *Journal of Biological Chemistry* 2012; 287: 30800-30811. <https://doi.org/10.1074/jbc.M111.244780>
- Chen S, Coronel R, Hollmann M W, Weber N C, Zuurbier C J. Direct cardiac effects of SGLT2 inhibitors. *Cardiovascular Diabetology* 2022; 21: 45. <https://doi.org/10.1186/s12933-022-01480-1>
- Chung C-C, Lin Y-K, Chen Y-C, Kao Y-H, Yeh Y-H, Trang N N, et al. Empagliflozin suppressed cardiac fibrogenesis through sodium-hydrogen exchanger inhibition and modulation of the calcium homeostasis. *Cardiovascular Diabetology* 2023; 22: 27. <https://doi.org/10.1186/s12933-023-01756-0>
- Cinti F, Laborante R, Cappannoli L, Morciano C, Gugliandolo S, Pontecorvi A, et al. The effects of SGLT2i on cardiac metabolism in patients with HFpEF: Fact or fiction? *Cardiovascular Diabetology* 2025; 24: 208. <https://doi.org/10.1186/s12933-025-02767-9>
- Cowie M R, Fisher M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. *Nature Reviews Cardiology* 2020; 17: 761-772. <https://doi.org/10.1038/s41569-020-0406-8>
- Crispino S P, Segreti A, Nafisio V, Valente D, Crisci F, Ferro A, et al. The role of SGLT2-inhibitors across all stages of heart failure and mechanisms of early clinical benefit: from prevention to advanced heart failure. *Biomedicines* 2025; 13: 608. <https://doi.org/10.3390/biomedicines13030608>
- Croteau D, Luptak I, Chambers J M, Hobai I, Panagia M, Pimentel D R, et al. Effects of sodium-glucose linked transporter 2 inhibition with ertugliflozin on mitochondrial function, energetics, and metabolic gene expression in the presence and absence of diabetes mellitus in mice. *Journal of the American Heart Association* 2021; 10: e019995. <https://doi.org/10.1161/JAHA.120.019995>
- Currie S, Loughrey C M, Craig M A, Smith G L. Calcium/calmodulin-dependent protein kinase II δ associates with the ryanodine receptor complex and regulates channel function in rabbit heart. *Biochemical Journal* 2004; 377: 357-366. <https://doi.org/10.1042/bj20031043>
- Duan H-Y, Barajas-Martinez H, Antzelevitch C, Hu D. The potential anti-arrhythmic effect of SGLT2 inhibitors. *Cardiovascular Diabetology* 2024; 23: 252. <https://doi.org/10.1186/s12933-024-02312-0>
- Dunlay S M, Givertz M M, Aguilar D, Allen L A, Chan M, Desai A S, et al. Type 2 diabetes mellitus and heart failure: a scientific statement from the American Heart Association and the Heart Failure Society of America: this statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update. *Circulation* 2019; 140: e294-e324. <https://doi.org/10.1161/CIR.0000000000000691>
- Durak A, Olgar Y, Degirmenci S, et al. A SGLT2 inhibitor dapagliflozin suppresses prolonged ventricular-repolarization through augmentation of mitochondrial function in insulin-resistant metabolic syndrome rats. *Cardiovascular Diabetology* 2018; 17:144. <https://doi.org/10.1186/s12933-018-0790-0>
- Erickson J R, Pereira L, Wang L, Han G, Ferguson A, Dao K, et al. Diabetic hyperglycaemia activates CaMKII and arrhythmias by O-linked glycosylation. *Nature* 2013; 502: 372-6. <https://doi.org/10.1038/nature12537>
- Fedacko J, Tuppo E E, Singh R B, Elkilany G N, Hristova K. Chapter 2 - Epidemiology and mortality due to heart failure. In: Singh RB, Fedacko J, Hristova K and Elkilany GN, editors. *Pathophysiology, risk factors, and management of chronic heart failure*: Academic Press, 2024: 23-40. <https://doi.org/10.1016/B978-0-12-822972-9.00017-1>
- Forstermann U, Sessa W C. Nitric oxide synthases: regulation and function. *European Heart Journal* 2012; 33: 829-837, 837a-837d. <https://doi.org/10.1093/eurheartj/ehr304>
- Harhous Z, Booz G W, Ovize M, Bidaux G, Kurdi M. An update on the multifaceted roles of STAT3 in the heart. *Frontiers in Cardiovascular Medicine* 2019; 6: 150. <https://doi.org/10.3389/fcvm.2019.00150>
- He L, Ma S, Zuo Q, Zhang G, Wang Z, Zhang T, et al. An effective sodium-dependent glucose transporter 2 inhibition, canagliflozin, prevents development of hypertensive heart failure in dahl salt-sensitive rats. *Frontiers in Pharmacology* 2022; 13: 856386. <https://doi.org/10.3389/fphar.2022.856386>
- Heidenreich P A, Bozkurt B, Aguilar D, Allen L A, Byun J J, Colvin M M, et al. 2022 AHA/ACC/HFSA guideline for

- the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Journal of the American College of Cardiology* 2022; 79: e263-e421. <https://doi.org/10.1161/CIR.0000000000001063>
- Hoong C W, Chua M W. SGLT2 inhibitors as calorie restriction mimetics: insights on longevity pathways and age-related diseases. *Endocrinology* 2021; 162: bqab079. <https://doi.org/10.1210/endo/bqab079>
- Hudmon A, Schulman H, Kim J, Maltez J M, Tsien R W, Pitt G S. CaMKII tethers to L-type Ca²⁺ channels, establishing a local and dedicated integrator of Ca²⁺ signals for facilitation. *Journal of Cell Biology* 2005; 171: 537-47. <https://doi.org/10.1083/jcb.200505155>
- Huo J-L, Feng Q, Pan S, Fu W-J, Liu Z, Liu Z. Diabetic cardiomyopathy: Early diagnostic biomarkers, pathogenetic mechanisms, and therapeutic interventions. *Cell Death Discovery* 2023; 9: 256. <https://doi.org/10.1038/s41420-023-01553-4>
- Kenny H C, Abel E D. Heart failure in type 2 diabetes mellitus: impact of glucose-lowering agents, heart failure therapies, and novel therapeutic strategies. *Circulation Research* 2019; 124: 121-141. <https://doi.org/10.1161/CIRCRESA-HA.118.311371>
- Khan M S, Shahid I, Bennis A, Rakisheva A, Metra M, Butler J. Global epidemiology of heart failure. *Nature Reviews Cardiology* 2024; 21: 717-734. <https://doi.org/10.1038/s41569-024-01046-6>
- Kim S R, Lee S G, Kim S H, Kim J H, Choi E, Cho W, et al. SGLT2 inhibition modulates NLRP3 inflammasome activity via ketones and insulin in diabetes with cardiovascular disease. *Nature Communications* 2020; 11: 2127. <https://doi.org/10.1038/s41467-020-15983-6>
- Kitasato L, Murayama Y, Ishizue N, Kobayashi S, Oikawa J, Fukaya H, et al. Canagliflozin restores electrical properties and suppresses structural damage in isoproterenol-induced myocardial injury models. *Scientific Reports* 2025; 15: 44958. <https://doi.org/10.1038/s41598-025-29126-8>
- Komaniecka N, Maroszek S, Drozdziak M, Oswald S, Drozdziak M. Transporter proteins as therapeutic drug targets-with a focus on SGLT2 inhibitors. *International Journal of Molecular Sciences* 2024; 25: 6926. <https://doi.org/10.3390/ijms25136926>
- Kondo H, Akoumianakis I, Badi I, Akawi N, Kotanidis C P, Polkinghorne M, et al. Effects of canagliflozin on human myocardial redox signalling: clinical implications. *European Heart Journal* 2021; 42: 4947-4960. <https://doi.org/10.1093/eurheartj/ehab420>
- Koniari I, Velissaris D, Kounis N G, Koufou E, Artopoulou E, de Gregorio C, et al. Anti-diabetic therapy, heart failure and oxidative stress: an update. *Journal of Clinical Medicine* 2022; 11. <https://doi.org/10.3390/jcm11164660>
- Konior A, Schramm A, Czesnikiewicz-Guzik M, Guzik T J. NADPH oxidases in vascular pathology. *Antioxid Redox Signal* 2014; 20: 2794-2814. <https://doi.org/10.1089/ars.2013.5607>
- Lee C-C, Chen W-T, Chen S-Y, Lee T-M. Dapagliflozin attenuates arrhythmic vulnerabilities by regulating connexin43 expression via the AMPK pathway in post-infarcted rat hearts. *Biochemical Pharmacology* 2021; 192: 114674. <https://doi.org/10.1016/j.bcp.2021.114674>
- Lee H-C, Shiou Y-L, Jhuo S-J, Chang C-Y, Liu P-L, Jhuang W-J, et al. The sodium-glucose co-transporter 2 inhibitor empagliflozin attenuates cardiac fibrosis and improves ventricular hemodynamics in hypertensive heart failure rats. *Cardiovascular Diabetology* 2019; 18: 45. <https://doi.org/10.1186/s12933-019-0849-6>
- Lee T M, Chang N C, Lin S Z. Dapagliflozin, a selective SGLT2 Inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts. *Free Radical Biology and Medicine* 2017; 104: 298-310. <https://doi.org/10.1016/j.freeradbiomed.2017.01.035>
- Li X, Flynn E R, do Carmo J M, Wang Z, da Silva A A, Mouton A J, et al. Direct cardiac actions of sodium-glucose cotransporter 2 inhibition improve mitochondrial function and attenuate oxidative stress in pressure overload-induced heart failure. *Frontiers in Cardiovascular Medicine* 2022; 9: 859253. <https://doi.org/10.3389/fcvm.2022.859253>
- Li X, Wang M, Kalina J-O, Preckel B, Hollmann M W, Albrecht M, et al. Empagliflozin prevents oxidative stress in human coronary artery endothelial cells via the NHE/PKC/NOX axis. *Redox Biology* 2024; 69: 102979. <https://doi.org/10.1016/j.redox.2023.102979>
- Lin Y-H, Tsai W-C, Chiu C-C, Chi N-Y, Liu Y-H, Huang T-C, et al. The beneficial effect of the SGLT2 inhibitor dapagliflozin in alleviating acute myocardial infarction-induced cardiomyocyte injury by increasing the sirtuin family SIRT1/SIRT3 and cascade signaling. *International Journal of Molecular Sciences* 2024; 25: 8541. <https://doi.org/10.3390/ijms25158541>
- Lopaschuk G D, Verma S. Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (sglt2) inhibitors: a perspective. *JACC: Basic to Translational Science* 2020; 5:

- 632-644. <https://doi.org/10.1016/j.jacbts.2020.02.004>
- Lu Q, Li X, Liu J, Sun X, Rousselle T, Ren D, et al. AMPK is associated with the beneficial effects of antidiabetic agents on cardiovascular diseases. *Bioscience Reports* 2019; 39: BSR20181995. <https://doi.org/10.1042/BSR20181995>
- Lu Q, Liu J, Li X, Sun X, Zhang J, Ren D, et al. Empagliflozin attenuates ischemia and reperfusion injury through LKB1/AMPK signaling pathway. *Molecular and Cellular Endocrinology* 2020; 501: 110642. <https://doi.org/10.1016/j.mce.2019.110642>
- Luo B, Huang F, Liu Y, Liang Y, Wei Z, Ke H, et al. NLRP3 inflammasome as a molecular marker in diabetic cardiomyopathy. *Frontiers in Physiology* 2017; 8: 519. <https://doi.org/10.3389/fphys.2017.00519>
- Ma S, He L-L, Zhang G-R, Zuo Q-J, Wang Z-L, Zhai J-L, et al. Canagliflozin mitigates ferroptosis and ameliorates heart failure in rats with preserved ejection fraction. *Naunyn-schmiedeberg's Archives of Pharmacology* 2022; 395: 945-962. <https://doi.org/10.1007/s00210-022-02243-1>
- Ma S, He L, Zuo Q, Zhang G, Guo Y. Canagliflozin regulates ferroptosis, potentially via activating AMPK/PGC-1 α /Nrf2 signaling in HFpEF Rats. *Cardiovascular Innovations and Applications* 2023; 7: 987. <https://doi.org/10.15212/CVIA.2022.0024>
- Maack C, Lehrke M, Backs J, Heinzel F R, Hulot J-S, Marx N, et al. Heart failure and diabetes: metabolic alterations and therapeutic interventions: a state-of-the-art review from the Translational Research Committee of the Heart Failure Association-European Society of Cardiology. *European Heart Journal* 2018; 39: 4243-4254. <https://doi.org/10.1093/eurheartj/ehy596>
- Mangmool S, Shukla A K, Rockman H A. β -Arrestin-dependent activation of Ca²⁺/calmodulin kinase II after β 1-adrenergic receptor stimulation. *Journal of Cell Biology* 2010; 189: 573-587. <https://doi.org/10.1083/jcb.200911047>
- Marwick T H, Ritchie R, Shaw J E, Kaye D. Implications of underlying mechanisms for the recognition and management of diabetic cardiomyopathy. *Journal of the American College of Cardiology* 2018; 71: 339-351. <https://doi.org/10.1016/j.jacc.2017.11.019>
- McDonagh T A, Metra M, Adamo M, Gardner R S, Baumbach A, Böhm M, et al. 2023 focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. *European Heart Journal* 2023; 44: 3627-3639. <https://doi.org/10.1093/eurheartj/ehad195>
- Meza C A, La Favor J D, Kim D-H, Hickner R C. Endothelial dysfunction: is there a hyperglycemia-induced imbalance of NOX and NOS? *International Journal of Molecular Sciences* 2019; 20: 3775. <https://doi.org/10.3390/ijms20153775>
- Moellmann J, Mann P A, Kappel B A, Kahles F, Klinkhammer B M, Boor P, et al. The sodium-glucose co-transporter-2 inhibitor ertugliflozin modifies the signature of cardiac substrate metabolism and reduces cardiac mTOR signaling, endoplasmic reticulum stress and apoptosis. *Diabetes, Obesity and Metabolism* 2022; 24: 2263-2272. <https://doi.org/10.1111/dom.14814>
- Mylonas N, Nikolaou P-E, Efentakis P, Dimitriadis G, Iliodromitis E, Andreadou I. Comparative study on the cardioprotective effects against ischemia/reperfusion injury of the selective SGLT2 inhibitors, empagliflozin, dapagliflozin and ertugliflozin in non-diabetic mice. *European Heart Journal* 2021; 42: ehab724. 3250. <https://doi.org/10.1093/eurheartj/ehab724.3250>
- Nikolaou P E, Efentakis P, Abu Qourah F, Femminò S, Makridakis M, Kanaki Z, et al. Chronic empagliflozin treatment reduces myocardial infarct size in nondiabetic mice through STAT-3-mediated protection on microvascular endothelial cells and reduction of oxidative stress. *Antioxidants & Redox Signaling* 2021; 34: 551-571. <https://doi.org/10.1089/ars.2019.7923>
- Pabel S, Hamdani N, Luedde M, Sossalla S. SGLT2 inhibitors and their mode of action in heart failure-has the mystery been unravelled? *Current Heart Failure Reports* 2021; 18: 315-328. <https://doi.org/10.1007/s11897-021-00529-8>
- Packer M. Cardioprotective effects of sirtuin-1 and its downstream effectors: potential role in mediating the heart failure benefits of SGLT2 (sodium-glucose cotransporter 2) inhibitors. *Circulation: Heart Failure* 2020; 13: e007197. <https://doi.org/10.1161/CIRCHEARTFAILURE.120.007197>
- Packer M. Critical reanalysis of the mechanisms underlying the cardiorenal benefits of SGLT2 inhibitors and reaffirmation of the nutrient deprivation signaling/autophagy hypothesis. *Circulation* 2022; 146: 1383-1405. <https://doi.org/10.1161/CIRCULATIONAHA.122.061732>
- Palmiero G, Cesaro A, Vetrano E, Pafundi P C, Galiero R, Caturano A, et al. Impact of SGLT2 inhibitors on heart failure: from pathophysiology to clinical effects. *International Journal of Molecular Sciences* 2021; 22: 5863. <https://doi.org/10.3390/ijms22115863>
- Pham L T T, Mangmool S, Parichatikanond W. Sodium-glu-

- cose cotransporter 2 (SGLT2) inhibitors: guardians against mitochondrial dysfunction and endoplasmic reticulum stress in heart diseases. *ACS Pharmacology & Translational Science* 2024; 7: 3279-3298. <https://doi.org/10.1021/ac-sptsci.4c00240>
- Piccirillo F, Lanciotti M, Nusca A, Frau L, Spanò A, Liporace P, et al. Sodium-glucose transporter-2 inhibitors (SGLT2i) and myocardial ischemia: another compelling reason to consider these agents regardless of diabetes. *International Journal of Molecular Sciences* 2025; 26: 2103. <https://doi.org/10.3390/ijms26052103>
- Picht E, DeSantiago J, Huke S, Kaetzel M A, Dedman J R, Bers D M. CaMKII inhibition targeted to the sarcoplasmic reticulum inhibits frequency-dependent acceleration of relaxation and Ca²⁺ current facilitation. *Journal of Molecular and Cellular Cardiology* 2007; 42: 196-205. <https://doi.org/10.1016/j.yjmcc.2006.09.007>
- Pickering R J, Rosado C J, Sharma A, Buksh S, Tate M, de Haan J B. Recent novel approaches to limit oxidative stress and inflammation in diabetic complications. *Clinical & Translational Immunology* 2018; 7: e1016. <https://doi.org/10.1002/cti2.1016>
- Piperis C, Marathonitis A, Anastasiou A, Theofilis P, Mourouzis K, Giannakodimos A, et al. Multifaceted impact of SGLT2 inhibitors in heart failure patients: exploring diverse mechanisms of action. *Biomedicines* 2024; 12: 2314. <https://doi.org/10.3390/biomedicines12102314>
- Prosser B L, Ward C W, Lederer W. X-ROS signaling: rapid mechano-chemo transduction in heart. *Science* 2011; 333: 1440-1445. <https://doi.org/10.1126/science.1202768>
- Read A, Schröder M. The unfolded protein response: an overview. *Biology* 2021; 10: 384. <https://doi.org/10.3390/biology10050384>
- Ritchie R H, Abel E D. Basic mechanisms of diabetic heart disease. *Circulation research* 2020; 126: 1501-1525. <https://doi.org/10.1161/CIRCRESAHA.120.315913>
- Roe N D, Ren J. Nitric oxide synthase uncoupling: a therapeutic target in cardiovascular diseases. *Vascular Pharmacology* 2012; 57: 168-72. <https://doi.org/10.1016/j.vph.2012.02.004>
- Rolski F, Mączewski M. Cardiac Fibrosis: Mechanistic discoveries linked to SGLT2 inhibitors. *Pharmaceutics* 2025; 18: 313. <https://doi.org/10.3390/ph18030313>
- Sato T, Takeda N. The roles of HIF-1 α signaling in cardiovascular diseases. *Journal of Cardiology* 2023; 81: 202-208. <https://doi.org/10.1016/j.jjcc.2022.09.002>
- Sayour AA, Korkmaz-Icöz S, Loganathan S, Ruppert M, Sayour VN, Oláh A, Benke K, Brune M, Benkő R, Horváth EM, Karck M. Acute canagliflozin treatment protects against in vivo myocardial ischemia-reperfusion injury in non-diabetic male rats and enhances endothelium-dependent vasorelaxation. *Journal of Translational Medicine* 2019. 17(1), 127. <https://doi.org/10.1186/s12967-019-1881-8>
- Schönenberger M J, Krek W, Kovacs W J. EPAS1/HIF-2 α is a driver of mammalian pexophagy. *Autophagy* 2015; 11: 967-969. <https://doi.org/10.1080/15548627.2015.1045180>
- Schwinger R H G. Pathophysiology of heart failure. *Cardiovascular Diagnosis and Therapy* 2021; 11: 263-276. <https://doi.org/10.21037/cdt-20-302>
- Sciarretta S, Forte M, Frati G, Sadoshima J. The complex network of mTOR signalling in the heart. *Cardiovascular Research* 2022; 118: 424-439. <https://doi.org/10.1093/cvr/cvab033>
- Semenza G. Regulation of metabolism by hypoxia-inducible factor 1. In *Cold Spring Harbor symposia on quantitative biology*, vol. 76, pp. 347-353. Cold Spring Harbor Laboratory Press, 2011. <https://doi.org/10.1101/sqb.2011.76.010678>
- Shi L, Zhu D, Wang S, Jiang A, Li F. Dapagliflozin attenuates cardiac remodeling in mice model of cardiac pressure overload. *American Journal of Hypertension* 2019; 32: 452-459. <https://doi.org/10.1093/ajh/hpz016>
- Silte M, Kögler H, Zieseniss A, Wilting J, Schäfer K, Toischer K, et al. Impaired Ca²⁺-handling in HIF-1 α +/- mice as a consequence of pressure overload. *Pflügers Archiv-European Journal of Physiology* 2010; 459: 569-577. <https://doi.org/10.1007/s00424-009-0748-x>
- Sun H, Du B, Fu H, Yue Z, Wang X, Yu S, et al. Canagliflozin combined with aerobic exercise protects against chronic heart failure in rats. *Iscience* 2024; 27. <https://doi.org/10.1016/j.isci.2024.109014>
- Tan Y, Zhang Z, Zheng C, Wintergerst K A, Keller B B, Cai L. Mechanisms of diabetic cardiomyopathy and potential therapeutic strategies: preclinical and clinical evidence. *Nature Reviews Cardiology* 2020; 17: 585-607. <https://doi.org/10.1038/s41569-020-0339-2>
- Tanno M, Kuno A, Horio Y, Miura T. Emerging beneficial roles of sirtuins in heart failure. *Basic Research in Cardiology* 2012; 107: 273. <https://doi.org/10.1007/s00395-012-0273-5>
- Toldo S, Abbate A. The role of the NLRP3 inflammasome and pyroptosis in cardiovascular diseases. *Nature Reviews Cardiology* 2024; 21: 219-237. <https://doi.org/10.1038/s41569-023-00946-3>
- Tsai K-L, Hsieh P-L, Chou W-C, Cheng H-C, Huang Y-T,

- Chan S-H. Dapagliflozin attenuates hypoxia/reoxygenation-caused cardiac dysfunction and oxidative damage through modulation of AMPK. *Cell & Bioscience* 2021; 11: 44. <https://doi.org/10.1186/s13578-021-00547-y>
- Tsui J, Inagaki M, Schulman H. Calcium/calmodulin-dependent protein kinase II (CaMKII) localization acts in concert with substrate targeting to create spatial restriction for phosphorylation. *Journal of Biological Chemistry* 2005; 280: 9210-6. <https://doi.org/10.1074/jbc.M407653200>
- Uthman L, Homayr A, Juni RP, Spin EL, Kerindongo R, Boomsma M, Hollmann MW, Preckel B, Koolwijk P, van Hinsbergh VW, Zuurbier CJ. Empagliflozin and dapagliflozin reduce ROS generation and restore NO bioavailability in tumor necrosis factor α -stimulated human coronary arterial endothelial cells. *Cellular Physiology and Biochemistry* 2019; 53: 865-886. <https://doi.org/10.33594/000000178>
- Vafiadaki E, Sanoudou D, Arvanitis D A, Catino D H, Kranias E G, Kontrogianni-Konstantopoulos A. Phospholamban interacts with HAX-1, a mitochondrial protein with anti-apoptotic function. *Journal of Molecular Biology* 2007; 367: 65-79. <https://doi.org/10.1016/j.jmb.2006.10.057>
- Varzideh F, Kansakar U, Wilson S, Jankauskas S S, Santulli G. The SGLT2 inhibitor canagliflozin attenuates mitochondrial oxidative stress and alterations of calcium handling induced by high glucose in human cardiac fibroblasts. *Cell Cycle* 2024; 23: 923-930. <https://doi.org/10.1080/15384101.2025.2492423>
- Wang X, Zhang G, Dasgupta S, Niewold E L, Li C, Li Q, et al. ATF4 protects the heart from failure by antagonizing oxidative stress. *Circulation Research* 2022; 131: 91-105. <https://doi.org/10.1161/CIRCRESAHA.122.321050>
- Wei H, Bedja D, Koitabashi N, Xing D, Chen J, Fox-Talbot K, et al. Endothelial expression of hypoxia-inducible factor 1 protects the murine heart and aorta from pressure overload by suppression of TGF-beta signaling. *Proceedings of the National Academy of Sciences of the United States of America* 2012; 109: E841-850. <https://doi.org/10.1073/pnas.1202081109>
- Wichaiyo S, Saengklub N. Alterations of sodium-hydrogen exchanger 1 function in response to SGLT2 inhibitors: what is the evidence? *Heart Failure Reviews* 2022; 27: 1973-1990. <https://doi.org/10.1007/s10741-022-10220-2>
- Wu Y, MacMillan L B, McNeill R B, Colbran R J, Anderson M E. CaM kinase augments cardiac L-type Ca^{2+} current: a cellular mechanism for long Q-T arrhythmias. *American Physiological* 1999; 276: H2168-2178. <https://doi.org/10.1152/ajpheart.1999.276.6.H2168>
- Xiang D, Liu Y, Zhou S, Zhou E, Wang Y. Protective effects of estrogen on cardiovascular disease mediated by oxidative stress. *Oxidative Medicine and Cellular Longevity* 2021; 2021: 5523516. <https://doi.org/10.1155/2021/5523516>
- Xiong W, Xiong N, Wu Y, Sui Y, Xiao M, Qi X, et al. Canagliflozin alleviates pressure overload-induced cardiac dysfunction via PINK1 regulation by inhibiting mitophagy-driven ferroptosis. *Canadian Journal of Cardiology* 2026. <https://doi.org/10.1016/j.cjca.2026.04.015>
- Yang J, Li L, Zheng X, Lu Z, Zhou H. Dapagliflozin attenuates myocardial hypertrophy via activating the SIRT1/HIF-1 α signaling pathway. *Biomedicine & Pharmacotherapy* 2023; 165: 115125. <https://doi.org/10.1016/j.biopha.2023.115125>
- Yaribeygi H, AU - Butler A E, AU - Barreto G E. Antioxidative mechanisms of SGLT2 inhibitors in cardiometabolic complications. *Experimental Physiology* 2019; 104: 243-249.
- Yu H, Han Z, Chang W, Zhou H, Du B, Jia B, et al. Canagliflozin ameliorates myocardial fibrosis and cardiac function in chronic heart failure: a dose-independent therapeutic approach. *Journal of Cellular and Molecular Medicine* 2025; 29: e70718. <https://doi.org/10.1111/jcmm.70718>
- Yu Y-W, Que J-Q, Liu S, Huang K-Y, Qian L, Weng Y-B, et al. Sodium-glucose co-transporter-2 inhibitor of dapagliflozin attenuates myocardial ischemia/reperfusion injury by limiting NLRP3 inflammasome activation and modulating autophagy. *Frontiers in Cardiovascular Medicine* 2022; 8: 768214. <https://doi.org/10.3389/fcvm.2021.768214>
- Yuan X, Pan L, Zhang C, Zhu Q, Huang Z, Qin Y, et al. Empagliflozin improves pressure-overload-induced cardiac hypertrophy by inhibiting the canonical Wnt/ β -catenin signaling pathway. *Frontiers in Pharmacology* 2024; 15: 1499542. <https://doi.org/10.3389/fphar.2024.1499542>
- Zhang J, Chen X, Lv S, Hao Q. Dapagliflozin inhibits ferroptosis to improve chronic heart failure by regulating Nrf2/HO-1/GPX4 signaling pathway. *PLOS One* 2025; 20: e0317295. <https://doi.org/10.1371/journal.pone.0317295>
- Zhang N, Feng B, Ma X, Sun K, Xu G, Zhou Y. Dapagliflozin improves left ventricular remodeling and aorta sympathetic tone in a pig model of heart failure with preserved ejection fraction. *Cardiovascular Diabetology* 2019; 18: 107. <https://doi.org/10.1186/s12933-019-0914-1>
- Zhang R, Xie Q, Lu X, Fan R, Tong N. Research advances in the anti-inflammatory effects of SGLT inhibitors in type 2 diabetes mellitus. *Diabetology & Metabolic Syndrome* 2024; 16: 99. <https://doi.org/10.1186/s13098-024-01325-9>
- Zhang T, Maier L S, Dalton N D, Miyamoto S, Ross Jr J,

- Bers D M, et al. The δ C isoform of CaMKII is activated in cardiac hypertrophy and induces dilated cardiomyopathy and heart failure. *Circulation Research* 2003; 92: 912-919. <https://doi.org/10.1161/01.RES.0000069686.31472.C5>
- Zhou L, Liu Y, Wang Z, Liu D, Xie B, Zhang Y, et al. Activation of NADPH oxidase mediates mitochondrial oxidative stress and atrial remodeling in diabetic rabbits. *Life Sciences* 2021; 272: 119240. <https://doi.org/10.1016/j.lfs.2021.119240>
- Zou R, Shi W, Qiu J, Zhou N, Du N, Zhou H, et al. Empagliflozin attenuates cardiac microvascular ischemia/reperfusion injury through improving mitochondrial homeostasis. *Cardiovascular Diabetology* 2022; 21: 106. <https://doi.org/10.1186/s12933-022-01532-6>