Mini-Review

# SGLT2 Inhibition for Cardiovascular Diseases, Chronic Kidney Disease, and NAFLD

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## Abstract

Sodium glucose cotransporter 2 (SGLT-2) inhibitors are the latest class of antidiabetic medications. They prevent glucose reabsorption in the proximal convoluted tubule to decrease blood sugar. Several animal studies revealed that SGLT-2 is profoundly involved in the inflammatory response, fibrogenesis, and regulation of numerous intracellular signaling pathways. Likewise, SGLT-2 inhibitors markedly attenuated inflammation and fibrogenesis and improved the function of damaged organ in animal studies, observational studies, and clinical trials. SGLT-2 inhibitors can decrease blood pressure and ameliorate hypertriglyceridemia and obesity. Likewise, they improve the outcome of cardiovascular diseases such as heart failure, arrhythmias, and ischemic heart disease. SGLT-2 inhibitors are associated with lower cardiovascular and all-cause mortality as well. Meanwhile, they protect against nonalcoholic fatty liver disease (NAFLD), chronic kidney disease, acute kidney injury, and improve micro- and macroalbuminuria. SGLT-2 inhibitors can reprogram numerous signaling pathways to improve NAFLD, cardiovascular diseases, and renal diseases. For instance, they enhance lipolysis, ketogenesis, mitochondrial biogenesis, and autophagy while they attenuate the renin-angiotensin-aldosterone system, lipogenesis, endoplasmic reticulum stress, oxidative stress, apoptosis, and fibrogenesis. This review explains the beneficial effects of SGLT-2 inhibitors on NAFLD and cardiovascular and renal diseases and dissects the underlying molecular mechanisms in detail. This narrative review explains the beneficial effects of SGLT-2 inhibitors on NAFLD and cardiovascular and renal diseases using the results of latest observational studies, clinical trials, and meta-analyses. Thereafter, it dissects the underlying molecular mechanisms involved in the clinical effects of SGLT-2 inhibitors on these diseases.

**Key Words:** SGLT-2 inhibitors, molecular mechanism, ketogenesis, autophagy, inflammation, fibrosis

## Introduction

Diabetes is a major noncommunicable disease and a public health issue, which is associated with several complications such as cardiovascular diseases, chronic kidney disease (CKD), nonalcoholic fatty liver disease (NAFLD), neuropathy, and gastrointestinal complications (1-3). These complications, particularly cardiovascular diseases and CKD, are the leading causes for mortality among

diabetic patients ([4]). During the last decades, new classes of antidiabetic drugs such as dipeptidyl peptidase 4 (DDP-4) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, thiazolidinediones, and sodium glucose cotransporter 2 (SGLT-2) inhibitors improved the management of diabetes ([5],[6]). SGLT-2 inhibitors, carrying the suffix gliflozin, such as empagliflozin, dapagliflozin, canagliflozin, ipragliflozin, ertugliflozin, sotagliflozin, and luseogliflozin, increase the urinary excretion of glucose by inhibiting its reabsorption in the proximal convoluted tubule ([7]).

Previously, it was observed that SGLT-2 inhibitors can improve blood pressure, serum triglyceride, and body weight ([8-10]). Diabetic patients are often complicated with other components of metabolic syndrome such as cardiovascular diseases and SGLT-2 inhibitors showed protective effects on these complications ([7],[11],[12]). Regarding their beneficial effects on metabolic syndrome, numerous recent studies attempted to assess the effects of SGLT-2 inhibitors on cardiovascular and renal diseases. It was uncovered that SGLT-2 inhibitors can considerably protect against cardiovascular and renal diseases ([13-15]). Beyond their effects on body weight, dyslipidemia, and cardiovascular and renal diseases, they also protected against NAFLD ([16],[17]). Their great impact on cardiovascular and renal events raised the question of whether we need them for their protective effects on cardiovascular and renal diseases or for their glucose-lowering effects.

Yet, several review articles have been published that discuss the beneficial effects of SGLT-2 inhibitors on cardiovascular diseases, renal diseases, and NAFLD ([18-24]). In this review, the latest observational studies, clinical trials, and meta-analyses, particularly those published during last 4 years, have been referenced to enumerate the beneficial effects of SGLT-2 inhibitors on the liver, kidney, and cardiovascular system. This review also comprehensively explains and illustrates the pathophysiological and molecular mechanisms involved in these effects and covers recent findings in animal studies. Most of the previous reviews discussed just clinical or animal studies without making a link between them, but this review attempts to explain the underlying molecular mechanisms involved in the clinical effects of SGLT-2 inhibitors.

## Mechanism of Action, Efficacy, and Safety of SGLT-2 Inhibitors for Diabetes

SGLT-2 is located in the apical membrane of renal tubular cells in the S1 and S2 segments of proximal convoluted tubule and reabsorbs 90% of filtered glucose. SGLT-1 reabsorbs the remaining filtered glucose in the S3 segment of proximal convoluted tubule ([25]). Together they prevent urinary glucose excretion until plasma glucose concentration of ~200 mg/dL. Higher concentrations of plasma glucose exceeds their reabsorption capacity and leads to glycosuria. SGLT-2 is a cotransporter of $Na^+$ and glucose ([25]). It utilizes the downhill transport of $Na^+$ to provide energy for active reabsorption of filtered glucose. Active extrusion of $Na^+$ by $Na^+/K^+$ exchanger in the basolateral membrane of renal tubular cells results in downhill transport of $Na^+$ between 2 sides of apical membrane ([25]). SGLT-2 inhibitors can prevent 30% to 50% of glucose reabsorption and increase urinary glucose excretion in diabetic patients ([26]).

SGLT-2 inhibitors significantly decrease glycated hemoglobin (HbA1c) [mean difference (MD; 95% CI) –1.35 % (–2.36 to –0.34)], fasting plasma glucose [MD (95% CI) –1.01 mmol/L (–1.98 to –0.04)], insulin requirement [MD (95% CI) –4.85U/24h (–7.42 to –2.29)] and body weight [MD (95% CI) –2.3 kg (–3.09 to –1.50)] among patients with type 2 diabetes ([27]).

SGLT-2 inhibitors are associated with higher risk of genital tract infection. They also increase the risk of diabetic ketoacidosis, in patients with type 1 diabetes but not in patients with type 2 diabetes. Despite concerns, SGLT-2 inhibitors do not increase the risk of urinary tract infection, bone fracture and hypoglycemia. Likewise they do not increase the risk of amputation, even in diabetic patients with peripheral artery disease ([27-32]).

## The Effect of SGLT-2 Inhibitors on Cardiovascular Diseases
### Clinical Findings

Diabetes and hyperglycemia are heavily associated with higher incidence and exacerbation of cardiovascular diseases such as hypertension (HTN), ischemic heart disease, stroke, heart failure and peripheral artery disease ([33],[34]). Meta-analyses of several observational studies and clinical trials disclosed that use of SGLT-2 inhibitors is associated with markedly improved outcome of cardiovascular diseases among diabetic patients ([15],[35],[36]). Zheng et al uncovered that use of SGLT-2 inhibitors is associated with significant decrease in all-cause mortality [hazard ratio (HR; 95% credible interval (Crl) 0.80 (0.71-0.89)], cardiovascular mortality [HR (95% Crl) 0.89 (0.69-0.91)], heart failure events [HR (95% Crl) 0.62 (0.54-0.72)] and myocardial infarction ([HR (95% Crl) 0.86 (0.77-0.97)] among diabetic patients ([35]). They can also protect against nonfatal myocardial infarction or nonfatal stroke [relative risk (RR; 95% CI) 0.8 (0.70-0.94)] ([37]). Moreover, it was unveiled that use of SGLT-2 inhibitors is associated with lower hospitalization rate and decreased cardiovascular

mortality among heart failure patients with or without reduced ejection fraction (38,39). The meta-analysis performed by Malik et al uncovered that SGLT-2 inhibitors led to 22% reduction in myocardial infarction, 39% decrease in heart failure hospitalization, and 20% decrease in major adverse cardiac events among diabetic patients with CKD grade 3 or higher (40). The authors also reported that there was a decremental pattern in the incidence of stroke and cardiovascular mortality in their study (40). Interestingly, it was found that SGLT-2 inhibitors are associated with reduced risk of atrial fibrillation and atrial flutter among diabetic patients [RR (95% CI) 0.76 (0.65–0.90)] regardless of their age, blood pressure, body weight, and HbA1c (41). Even, it was shown that SGLT-2 inhibitors are superior to GLP-1 receptor agonists and other antidiabetic drugs regarding their cardioprotective effects (35,42,43). Likewise, it was observed that SGLT-2 inhibitors significantly decrease both systolic and diastolic blood pressure in diabetic patients (10,44). Further evaluations indicated that their blood pressure–lowering property is comparable to hydrochlorothiazide as a diuretic (45).

Empagliflozin provided slightly more protection among patients with atherosclerotic cardiovascular disease, while empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin were nearly similar regarding their effect on patients without atherosclerotic cardiovascular disease and patients with heart failure (46-50).

## Pathophysiological Mechanisms

There are also several animal studies reporting the beneficial effects of SGLT-2 inhibitors on cardiovascular diseases and explaining the underlying molecular mechanisms. Here, these molecular and cellular mechanisms and their effect on cardiovascular system are separately discussed.

### Hormonal and metabolic alterations induced by SGLT-2 inhibitors improve cardiovascular health

SGLT-2 inhibitors lead to weight loss, which indirectly improves cardiovascular health condition (10). SGLT-2 inhibitors augment lipolysis and decrease insulin requirement, resulting in decreased body weight (51,52). These drugs lead to calorie loss by increasing urinary excretion of glucose. However, calorie loss can partly increase food intake, but their effect on calorie loss is greater than calorie intake (53). Meanwhile, these drugs can decrease the release of positive regulators of appetite and body weight such as ghrelin and neuropeptide Y (53-55) (Fig. 4).

Overactivation of insulin and insulin-like growth factor 1 signaling pathways is critically involved in the pathogenesis of heart failure and myocardial hypertrophy (56,57). As mentioned previously, SGLT-2 inhibitors can significantly

decrease insulin requirement in diabetic patients (27). In addition to its beneficial effects on blood sugar and insulin dosage, empagliflozin attenuated the detrimental effects of insulin on the heart. This effect was mediated by decreasing protein kinase B phosphorylation, and glucose transporter 4 expression (58). Long-term phosphorylation and activation of Protein kinase B results in pathological cardiac hypertrophy and heart failure (59). SGLT-2 inhibitors can directly and indirectly modulate the cardiovascular effect of insulin and other hormones.

### Activation of Sestrin2/5' adenosine monophosphate-activated protein kinase signaling pathway and autophagy by SGLT-2 inhibitors protects against different cardiovascular diseases such as heart failure, ischemic heart disease, and arrhythmia

Empagliflozin promoted Sestrin2-mediated activation of 5' adenosine monophosphate-activated protein kinase (AMPK), thereby inhibiting mammalian target of rapamycin complex 1 (mTORC1) signaling pathway. Activation of the Sestrin2/AMPK/mTORC1 signaling pathway by empagliflozin mitigated myocardial oxidative stress, inflammation, and cardiac fibrosis (60,61). Consistently, it has been reported that Sestrin2 provides immense protection against several cardiovascular diseases such as hypertension, myocardial infarction, arrhythmias, cardiomyopathy, and atherosclerosis (62). SGLT-2 inhibitors activate the Sestrin2/AMPK signaling pathway. Thereafter, AMPK activates tuberous sclerosis complex 2, a tumor suppressor gene. Tuberous sclerosis complex 2 directly inhibits mTORC1 (63). Similar to Sisterin2, liver kinase B1 (LKB1) was upregulated by empagliflozin in the mice model of myocardial ischemia/reperfusion (64). LKB1 is a downstream of Sestrin2 and phosphorylates and activates AMPK to improve the outcome of cardiovascular diseases (65). LKB1 deletion in myocardial cells has been associated with spontaneous onset of atrial fibrillation and atrial fibrosis in mice (66) (Fig. 1).

Sestrin2 also regulates mTORC1 through GATORs. Sestrin2 attenuates the inhibitory effect of GATOR2 on GATOR1. When liberated from GATOR2, GATOR1 inhibits RagB, a GTPase needed for mTORC1 activation (67). During nutrient deficiency Sestrin2 inhibits GATOR2 and downregulates mTORC1 (68). mTORC1 is a negative regulator of autophagy, and its inhibition strongly enhances autophagy (63) (Fig. 1). Autophagy is crucial for removal of dysfunctional organelles and misfolded proteins aggregate (69). It provides the opportunity for self-renewal and prevents cardiomyocytes death (69). Sufficient autophagic response is crucial for maintenance of cardiovascular homeostasis, improves cardiovascular health, and prevents cardiac hypertrophy and cardiomyopathy (70).
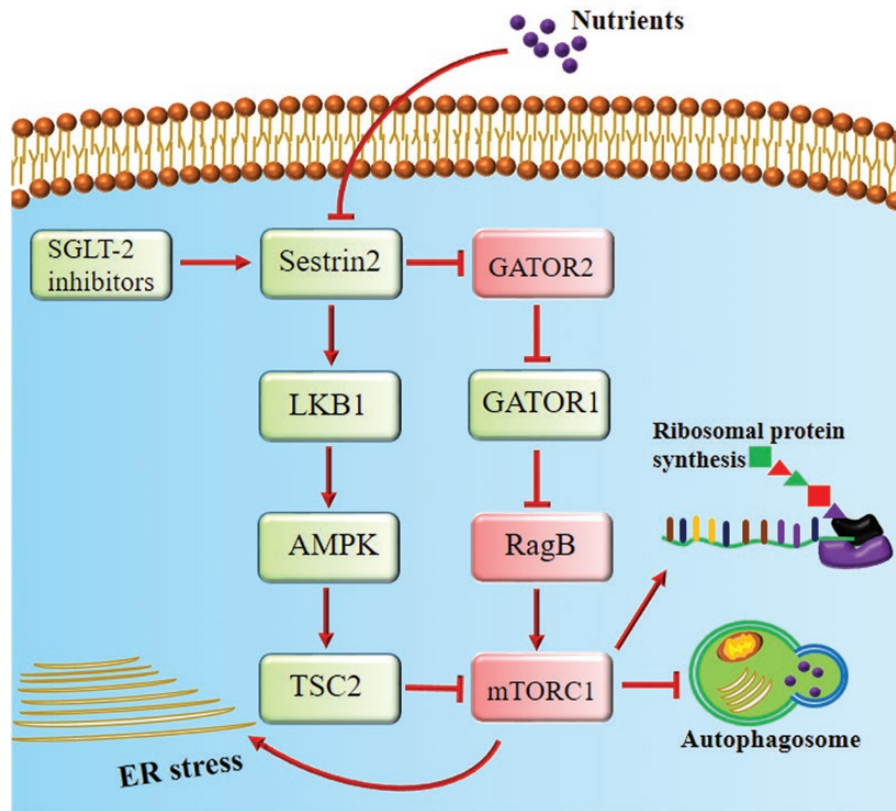
**Figure 1.** The effect of SGLT-2 inhibition and Sestrin2 on mTORC1. SGLT-2 inhibition upregulates Sestrin2. Subsequently, Sestrin2 activates LKB1/AMPK/tuberous sclerosis complex 2 signaling pathway or inhibits GATOR2/GATOR1/RagB signaling pathway to remove the deleterious effects of mTORC1 in damaged cardiovascular system. mTORC1 activates ribosomal protein synthesis, which can activate unfolded protein response and ER stress in inflammation. In addition, mTORC1 attenuates autophagy that helps to the removal of dysfunctional organelles and plays a crucial role in cardiovascular homeostasis. Contrary to SGLT-2 inhibition, nutrient sufficiency and overnutrition downregulates Sestrin2 and activates mTORC1.

Furthermore, autophagy confines myocardial injury and myocardial remodeling after myocardial infarction (71,72).

SGLT-2 inhibition also augments the Kruppel-like factor 9/vascular endothelial growth factor A pathway to improve autophagy in cardiomyocytes (73). Kruppel-like factor 9 is a transcription factor that promotes the gene expression of autophagy-related proteins and activates the cellular mechanisms of autophagy (74). Consistently, it was observed that SGLT-2 inhibition augments autophagy to ameliorate myocardial infarction in rats (75).

### SGLT-2 inhibition improves mitochondrial function and attenuates oxidative stress to ameliorate myocardial infarction, heart failure, and arrhythmia

The heart heavily relies on mitochondrial respiration for its energy metabolism (76). Ineffective and dysfunctional mitochondrial activity results in energy depletion, contractile failure, reactive oxygen species (ROS) production, inflammation, and apoptosis of cardiomyocytes (76). These alterations in cellular level progress to heart failure in the long term (76). In addition, mitochondrial dysfunction is a major contributor for myocardial injury during myocardial ischemia/reperfusion. Impaired calcium homeostasis and burst of oxidative stress due to mitochondrial dysfunction leads to severe myocardial injury during myocardial infarction (77).

Perturbation of mitochondrial calcium and energy homeostasis are major players in myocardial electrical and contractile dysfunction (78). Empagliflozin decreased the cytoplasmic concentration of $Ca^{2+}$ and $Na^+$ and increased the mitochondrial concentration of $Ca^{2+}$. This effect was mediated through inhibition of $Na^+/H^+$ exchanger (79). Previously, it was shown that increased activity of $Na^+/H^+$ exchanger and increased cytoplasmic concentration of $Ca^{2+}$ and $Na^+$ are responsible for deterioration of heart failure (80,81). Similarly, dual SGLT-1 and SGLT-2 inhibition by sotagliflozin significantly improved mitochondrial function of the myocardium, decreased oxidative stress, and improved left atrial dysfunction through modulation of $Ca^{2+}$ release into the cytoplasm (82). Interestingly, Ye et al revealed that SGLT-2 inhibition activates AMPK, thereby inhibiting $Na^+/H^+$ exchanger (83).

Sestrin2/AMPK pathway activates peroxisome proliferator-activated receptor-gamma coactivator (PGC)

1α expression to improve mitochondrial and myocardial function after myocardial infarction (84). PGC-1α interacts with peroxisome proliferator-activated receptor (PPAR) gamma, thereby regulating the function of several transcription factors, improving mitochondrial respiration, and decreasing ROS production (Fig. 2) (85,86). Higher PGC-1α expression predicts more efficient mitochondrial function, inhibits vascular calcification, and improves cardiac function (87,88). Because of its high energy demand, the heart strongly relies on proper mitochondrial function to provide its energy requirement. Dysfunctional mitochondrial activity not only leads to energy depletion but also causes accumulation of ROS and accelerates apoptosis (89). Herein, a subset of autophagy named mitophagy can remove the dysfunctional mitochondria and prevent the subsequent destructive events (89).

Sestrin2 can activate nuclear factor erythroid 2-related factor 2 (Nrf2) by liberating it from Kelch-like ECH-associated protein 1 sequestration (90). Nrf2 is a transcription factor for numerous antioxidant genes and promotes their expression by binding to antioxidant response element (90). This function of Sestrin2 can markedly attenuate oxidative stress, subsequent to SGLT-2 inhibition. The protective effect of empagliflozin on oxidative stress and mitochondria dysfunction has been associated with decreased mortality after myocardial ischemia in diabetic rats (75,91,92).

Empagliflozin enhanced the expression of BCL2-interacting protein 3 and led to downregulation of mitochondrial fission 1 protein in cardiomyocytes (75).

BCL2-interacting protein 3 augments mitophagy in myocytes and prevents cell death (93). Uncontrolled expression of fission 1 protein leads to mitochondrial fragmentation and results in the apoptosis of cardiomyocytes (Fig. 2) (94).

Dapagliflozin, another SGLT-2 inhibitor, successfully restricted infarct size and prevented ventricular arrhythmias and left ventricular dysfunction in a rat model of myocardial infarction. Dapagliflozin enhanced mitochondrial function and increased antiapoptotic proteins such as BCL2 to improve myocardial infarction (95). Shao et al indicated that empagliflozin improves mitochondrial function of cardiomyocytes and prevents atrial fibrillation via PGC-1α/nuclear respiratory factor-1/mitochondrial transcription factor A (TFAM) signaling pathway. Additionally, empagliflozin significantly attenuated oxidative stress, decreased the serum concentrations of highly sensitive C-reactive protein, and inhibited atrial fibrosis in diabetic rats (86). TFAM preserves the integrity of mitochondrial DNA. Besides, it was shown that increased expression of TFAM can profoundly mitigate cardiac dysfunction (Fig. 2) (96). According to these findings, amelioration of mitochondrial dysfunction accounts for a major proportion of cardioprotective effects of SGLT-2 inhibitors.

**SGLT-2 inhibition attenuates endoplasmic reticulum stress and endoplasmic reticulum stress–mediated apoptosis in the cardiovascular system**

Endoplasmic reticulum (ER) is heavily involved in $Ca^{2+}$ homeostasis in cardiomyocytes; hence, ER stress and the
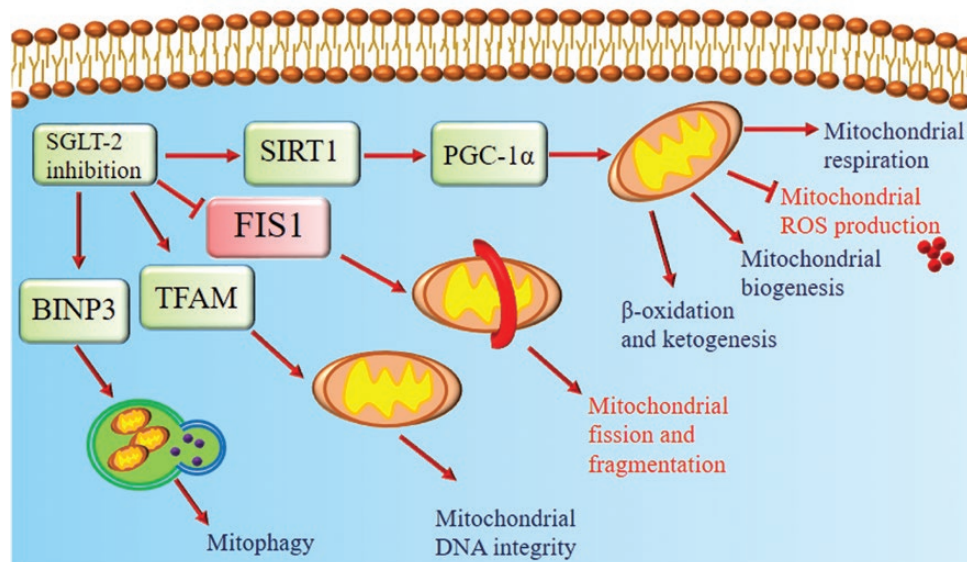


**Figure 2.** The effect of SGLT-2 inhibition on mitochondrial homeostasis. SGLT-2 inhibition activates SIRT1/PGC-1α signaling pathway, which can improve mitochondrial respiration, mitochondrial biogenesis, β-oxidation, and ketogenesis and confines mitochondrial ROS production. BCL2-interacting protein 3 and TFAM upregulation by SGLT-2 inhibitors can enhance mitophagy and maintain mitochondrial DNA integrity, respectively. SGLT-2 inhibitors downregulate fission 1 protein, thereby preventing mitochondrial fission and fragmentation.
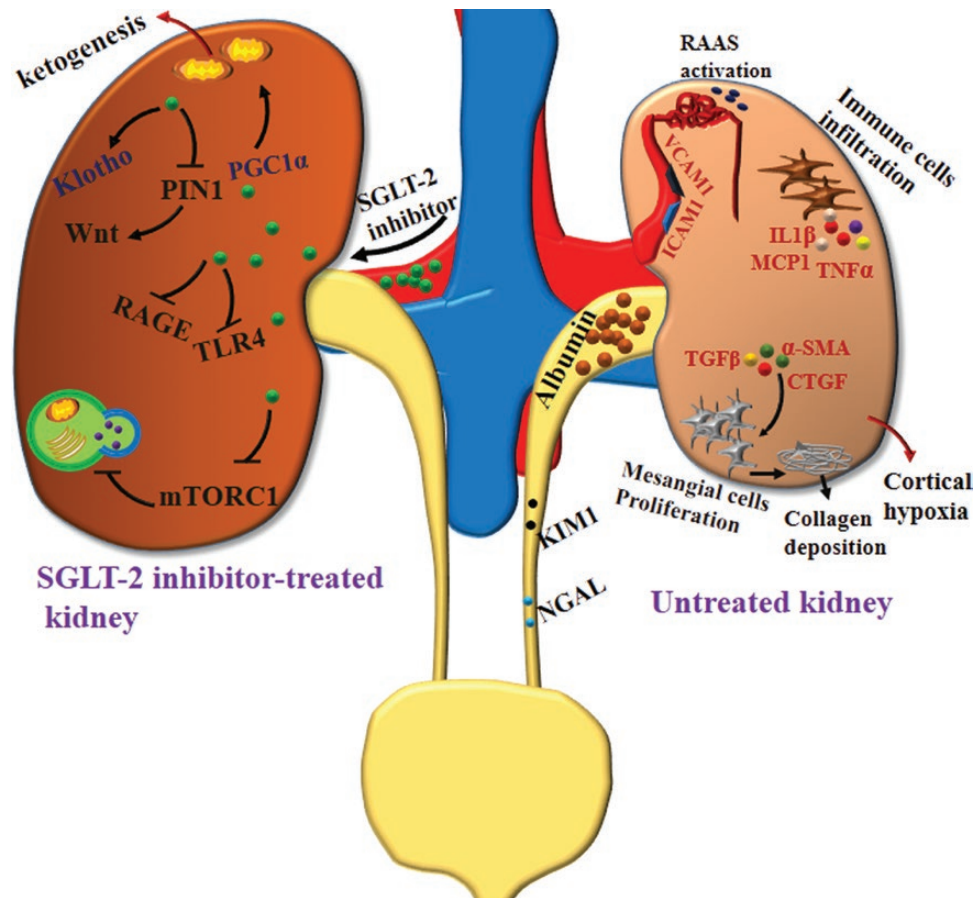
**Figure 3.** The protective effects of SGLT-2 inhibition on diabetic nephropathy. SGLT-2 inhibition improves mitochondrial function and expedites ketogenesis through PGC-1α. SGLT-2 inhibition suppresses TLR4 and RAGE signaling pathways and attenuates the inhibitory effect of mTORC1 on autophagy. SGLT-2 inhibitors downregulate peptidylprolyl cis/trans isomerase, peptidyl-prolyl cis/trans isomerase never in mitosis A-interacting 1/ Wnt pathway, upregulate Klotho, thereby decreasing TGF-β, α smooth muscle actin, and connective tissue growth factor and preventing mesangial cells activation. SGLT-2 inhibitors can reduce the expression of intercellular adhesion molecule 1, vascular cell adhesion molecule 1, and MCP1, which confine immune cells infiltration and alleviate inflammation. Further, SGLT-2 inhibition suppresses RAAS and ameliorate the detrimental effect of RAAS on kidney fibrosis and albuminuria.

following dysregulation of $Ca^{2+}$ homeostasis impair heart function [97]. ER stress plays a pivotal role in the development of heart failure [98]. Furthermore, ER stress is dramatically activated and involved in atherosclerotic plaque rupture and myocardial injury following myocardial infarction [97].

SGLT-2 inhibition vigorously attenuated the detrimental effects of ER stress on cardiomyopathy, mediated through downregulation of activating transcription factor 4 (ATF4), CCAAT/enhancer binding protein homologous protein (CHOP), X-box binding protein 1, tumor necrosis factor (TNF) receptor-associated factor 2, and caspase 12 [99]. Overactivation of ATF4/CHOP pathway results in the overexpression of proapoptotic proteins and activates ER stress-induced apoptosis [99,100]. X-box binding protein 1 and TNF receptor-associated factor 2 can also augment the inflammatory response after ER stress [101]. mTORC1 activation increases ribosomal protein synthesis during inflammation, which causes unfolded protein response, ER stress, and subsequently apoptosis [102]. SGLT-2 inhibitors can prevent the initiation of ER stress by inhibiting mTORC1 and also attenuate the progression of ER stress to apoptosis (Fig. 1).

## SGLT-2 inhibitors-mediated ketogenesis enormously benefits cardiovascular system

SGLT-2 inhibitors vigorously stimulate ketogenesis even they are associated with slightly increased risk of diabetic ketoacidosis among diabetic patients [28,103,104]. Ketogenesis and ketogenic diet can enormously protect against cardiovascular system. For instance, ketogenesis protects against myocardial ischemia, improves mitochondrial function, and prevents apoptosis and myocardial dysfunction [105,106]. Furthermore, ketogenesis promotes autophagy and prevents oxidative stress,
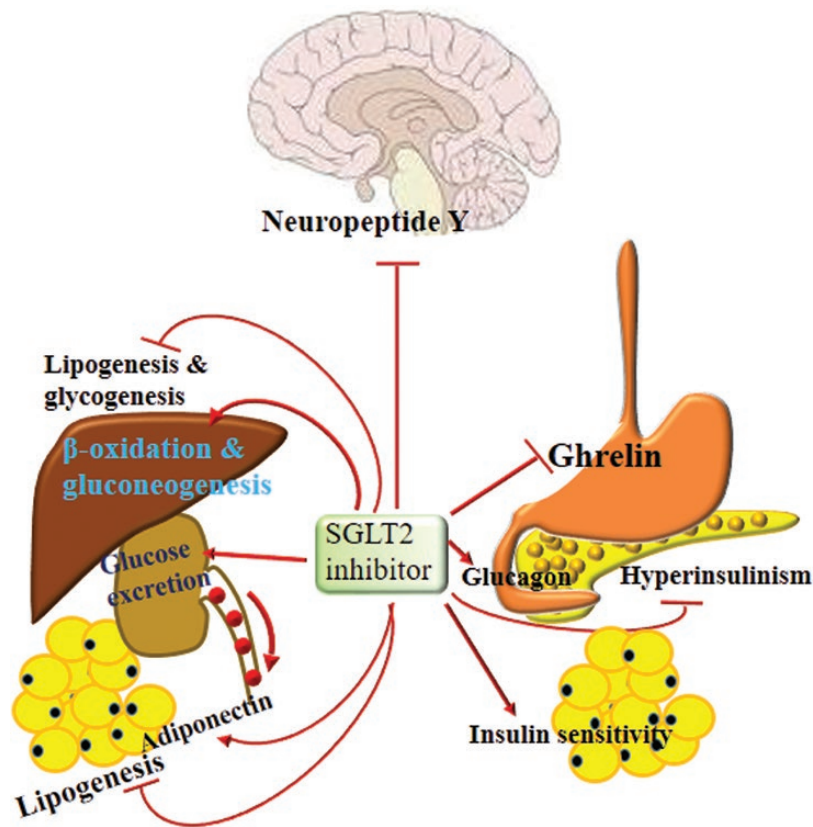
**Figure 4.** The protective effect of SGLT-2 inhibitors on obesity, lipid metabolism, and NAFLD. SGLT-2 inhibition leads to urinary excretion of glucose in the kidney and decreases insulin requirement and lipogenesis in the liver and adipose tissue. Further, SGLT-2 inhibition can suppress the appetite through downregulation of neuropeptide Y and ghrelin. SGLT-2 inhibition stimulates ketogenesis and gluconeogenesis and prevents fat and glycogen accumulation in the liver. SGLT-2 inhibition also increases adiponectin and glucagon that can mitigate NAFLD.

atherosclerosis, and myocardial remodeling ([107],[108]). Recent meta-analyses uncovered that ketogenic diet is associated with better body weight control, better glycemic control, and improvement in dyslipidemia among diabetic patients ([109],[110]). SGLT-2 inhibitors enhance sirtuin 1 (SIRT1) expression and activate SIRT1/PGC-1α/fibroblast growth factor 21 (FGF21) signaling pathway to promote ketogenesis. Furthermore, this pathway promotes autophagy and improves heart cells function and viability ([111],[112]). AMPK partly mediates the positive effect of SGLT-2 inhibitors on SIRT1/PGC-α/FGF21 axis ([113]). In addition, potentiation of ketogenesis by SGLT-2 inhibitors can protect the heart against energy depletion ([114]). Based on these findings, augmentation of ketogenesis can enormously support cardiovascular health during stress condition.

## SGLT-2 inhibition prevents atherosclerotic plaque formation and rupture by modulating endothelial dysfunction, inflammation, and macrophages activity

Empagliflozin enhances the expression of endothelial nitric oxide that results in vasodilation and protects against atherosclerosis, hypertension, and other cardiovascular

adverse events ([60]). It was observed that empagliflozin ameliorates endothelial dysfunction in diabetic rats ([115]). It upregulated Nrf2 and strongly attenuated oxidative burst. Moreover, empagliflozin inhibited advanced glycation end-products/receptor for advanced glycation end-products (RAGE) signaling pathway, which is a major contributor for vascular inflammation, oxidative stress, and macrophage recruitment in vascular complications of diabetes ([115]).

Dapagliflozin showed protective effect on the formation and stabilization of atherosclerotic plaques in a mice model of atherosclerosis. It suppressed oxidative stress, downregulated NLR family pyrin domain containing 3 (NLRP3), prevented macrophages infiltration, and decreased inflammatory cytokines such as interleukin (IL) 1β and IL18 ([116-118]). Indeed, SGLT-2 inhibition activated AMPK signaling, thereby suppressing NLRP3 inflammasome ([118]). Furthermore, SGLT-2 inhibition significantly reduced monocyte chemoattractant protein 1 (MCP-1) and vascular cell adhesion molecule 1 (VCAM-1) to prevent inflammatory cells infiltration into vessels' wall ([119]). Oxidized lipoproteins, ROS, and ER stress activate NLRP3, thereby stimulating macrophages response

in atherosclerosis (120). SGLT-2 inhibition vigorously modulates the deleterious effects of numerous harmful mechanisms.

Dapagliflozin also decreased inducible nitric oxide expression and attenuated Toll-like receptor 4 (TLR4)/nuclear factor kappa B (NF-κB)/tumor necrosis factor alpha (TNF-α) signaling pathway to prevent lipid accumulation and hinder atherosclerosis (121). The TLR4/NF-κB pathway promotes the expression of inflammatory and fibrogenic molecules such as MCP-1 and transforming growth factor β (TGF-β) that can aggravate atherosclerosis (122).

Sestrin2 knockout led to decreased AMPK phosphorylation and increased NF-κB phosphorylation in mouse aorta endothelial cells. In addition, Sestrin2 knockout led to ER stress and burst of oxidative stress in these cells (123). Hyperglycemia and oxidized low-density lipoprotein can downregulate Sestrin2/AMPK pathway in monocytes and accelerate mTORC1 signaling. Activation of mTORC1 signaling increases the expression of inflammatory mediators and differentiation of M1 macrophages (124). Genetically augmented Sestrin2/AMPK pathway reversed these effects and increased M2 macrophage differentiation (124). Sestrin2-mediated inhibition of mTORC1 also induces autophagy in macrophages and enhances their M2 polarization (125). Autophagy is crucial for atherosclerotic plaque stability. Attenuation of autophagy results in increased oxidative stress and apoptosis of lesional macrophages and leads to atherosclerotic plaque necrosis (126). Similarly, it has been demonstrated that higher proportions of M2 subtype of macrophages are associated with plaque stability, while increased abundance of M1 subtype predicts atherosclerotic plaque instability (127). Hence, SGLT-2 inhibition can protect against atherosclerotic plaque formation and increase plaque stability partly through upregulation of Sestrin2/AMPK/mTORC1 pathway and downregulation of NF-κB and NLRP3 signaling pathways in macrophages and endothelial cells.

### SGLT-2 inhibitors mitigate hypertension though several mechanisms

SGLT-2 inhibition decreased blood pressure in human and animal studies (128,129). SGLT-2 inhibition can augment the blood pressure lowering effect of angiotensin receptor blockers (130). Furthermore, luseogliflozin abrogated high-salt diet-induced high blood pressure in rats. This finding shows that SGLT-2 inhibition is useful to attenuate the salt sensitivity of blood pressure (131). Takeshige et al unveiled that SGLT-2 inhibition by empagliflozin can enhance urinary sodium excretion to lower blood pressure (132). It was also shown that SGLT-2 inhibition accelerates circadian fall of blood pressure and decreases nocturnal blood pressure in hypertensive rats with a nondipper

pattern of blood pressure (132). Indeed, SGLT-2 inhibition improves circadian rhythm of sympathetic nerve, thereby ameliorating nondipper hypertension (133). The inhibitory effect of SGLT-2 inhibitors on sympathetic nervous system accounts for a major proportion of their anti-hypertensive effects (134).

Interestingly, it has been reported that angiotensin II upregulates SGLT-2 expression in the kidney. Furthermore, canagliflozin reverted the deleterious effect of angiotensin on the kidney (135). Regarding the mutual link between renal dysfunction and hypertension and the beneficial effects of SGLT-2 inhibition on both of them, SGLT-2 inhibitors are a good therapeutic option for diabetic patients who are at higher risk of both hypertension and renal dysfunction (136,137). Schork et al observed that SGLT-2 inhibitors were associated with a transient decrease in extracellular fluid volume and activation of the renin-angiotensin-aldosterone system (RAAS) in the first days of use, but these changes returned to their baseline after 3 to 6 months of use (138). According to these results, there is no concern about RAAS activation during long-term use of SGLT-2 inhibitors, and they can decrease blood pressure without compensatory increase in RAAS.

As mentioned previously, SGLT-2 inhibitors can increase nitric oxide production, thereby decreasing vascular tonicity (60). Moreover, it was observed that empagliflozin prevents arterial remodeling by ameliorating mitochondrial dysfunction in rats, which helps to mitigate the effect of long-term hypertension on the vasculature (86).

SGLT-2 inhibition improves circadian rhythm of blood pressure, enhances urinary excretion of $Na^+$, contributes to vasorelaxation, and prevents arterial remodeling. These properties of SGLT-2 inhibitors heavily improves hypertension, itself, and hypertension-associated cardiovascular diseases such as heart failure, stroke, and myocardial infarction.

### SGLT-2 inhibition mitigates cardiomyopathy by upregulating reversion-inducing cysteine-rich protein with Kazal motif and attenuating NLRP3- and NF-κB-mediated cardiomyocytes apoptosis

SGLT-2 inhibition decreased myocardial content of inflammatory cytokines such as IL6 and increased the production of anti-inflammatory cytokines such as IL10. SGLT-2 inhibition also increased M2 subtype of macrophages and reduced their M1 subtype. Furthermore, SGLT-2 inhibitors hindered the activation of NF-κB in the mice model of cardiomyopathy, which is a major driver for inflammation and promotes the expression of inflammatory cytokines (58,139). Interestingly, NF-κB expression in patients with asymptomatic or mildly symptomatic hypertrophic cardiomyopathy predicts progression to heart failure in the long

term (140). Downregulation of NF-κB also alleviates myocardial ischemia/reperfusion injury and enhances atherosclerotic plaque stability (141,142).

Previous studies unveiled that NLRP3 inflammasome is involved in the pathogenesis of cardiomyopathy and mediates the production of several inflammatory cytokines (143). In addition, NLRP3 gene silencing has been associated with notable improvement in cardiomyopathy (144). Dapagliflozin, in an AMPK-dependent manner, could downregulate NLRP3/apoptosis-associated speck-like protein containing a C-terminal caspase recruitment domain (apoptosis-associated speck-like protein containing a C-terminal caspase recruitment domain) signaling pathway in the rat model of cardiomyopathy (118). NLRP3/apoptosis-associated speck-like protein containing a C-terminal caspase recruitment domain pathway activates caspase 1 and stimulates apoptosis; hence, SGLT-2 inhibition can prevent cardiomyocytes apoptosis in cardiomyopathy (118).

Empagliflozin significantly increased reversion-inducing cysteine-rich protein with Kazal motif (RECK) expression in the mice model of diabetic cardiomyopathy. RECK prevents fibroblast migration and negatively regulates cardiac fibrosis (58,145,146). Even so, the detrimental effect of angiotensin II on cardiac fibrosis and cardiac remodeling heavily depends on downregulation of RECK (145). Therefore, SGLT-2 inhibition can alleviate cardiomyopathy by preserving cardiomyocytes viability and enhancing the antifibrotic effects of RECK.

This section attempted to illuminate the complex and interwoven molecular mechanisms involved in the protective effects of SGLT-2 inhibitors on cardiovascular diseases. It has been clarified that SGLT-2 inhibition can improve cardiovascular diseases through diverse mechanisms, and it is worth expanding their clinical application in the management of cardiovascular diseases.

## The Effects of SGLT-2 Inhibitors on Kidney Diseases

### Clinical Findings

The meta-analysis performed by Tadashi et al revealed that SGLT-2 inhibitors ameliorated the annual decline in estimated glomerular filtration rate [placebo subtracted difference (95% CI) 1.35 mL/1.73 m$^2$/year (0.78-1.93)] in diabetic patients. They also improved the composite renal outcome [HR (95% CI) 0.71 (0.53-0.95)] (37). Similarly, Zelniker et al performed a meta-analysis, including 34 322 diabetic patients, and found that SGLT-2 inhibitors decreased the risk of progression of renal disease by 45% [HR (95% CI) 0.55 (0.48-0.64)]. Meanwhile, SGLT-2

inhibitors had the same effects on those with and without atherosclerotic cardiovascular diseases, but they were more effective in the early stages of CKD (15). Recent meta-analysis published in *JAMA Cardiology* showed that SGLT-2 inhibitors are associated with significant improvement in the kidney outcome [HR (95% CI) 0.62 (0.56-0.70)] among diabetic patients (147). SGLT-2 inhibitors lowered albumin/creatinine ratio (weight mean differences (95% CI) –14.64 mg/g (–25.5 to –4.12)] and significantly decreased the risk of microalbuminuria [relative risk (RR; 95% CI) 0.69 (0.49 to 0.97)], macroalbuminuria [RR (95% CI) 0.49 (0.33-0.73)], exacerbation of nephropathy [RR (95% CI) 0.73 (0.58-0.93)], and end-stage renal disease [RR (95% CI) 0.70 (0.57-0.87)] in diabetic patients (148). Furthermore, SGLT-2 inhibitors reduced the risk of acute kidney injury in both clinical trials [RR (95% CI) 0.64 (.53-0.78)] and observational studies [RR (95% CI) 0.40 (0.33-0.48)] (149).

The renoprotective effect of SGLT-2 inhibitors is greater than the renoprotective effect of GLP-1 receptor agonists and other antidiabetic medications (43). It seems that dapagliflozin and canagliflozin have slightly better impact on urine albumin-to-creatinine ratio, followed by empagliflozin and ipragliflozin, respectively (150-153). Furthermore, canagliflozin and empagliflozin are slightly superior in terms of glomerular filtration rate preservation, compared with dapagliflozin and ipragliflozin (148). However, these comparisons were not statistically approved and replicated by all clinical trials.

## Pathophysiological Mechanisms Involved in the Renoprotective Effects of SGLT-2 Inhibitors

Diabetes is associated with extensive molecular and cellular alterations in the kidney. Diabetes leads to mitochondrial dysfunction, oxidative burst, and increased activity of inflammatory molecules such as NF-κB in the kidney (154).

Diabetes and hyperglycemia significantly increase the expression of SGLT-2 in the kidney of rats (155). Animal models have shown that SGLT-2 inhibitors such as tofogliflozin and dapagliflozin can protect against renal tubular cells injury and prevent their apoptotic cell death (156,157). Besides, SGLT-2 inhibitors effectively mitigate diabetic tubulopathy by improving mitochondrial dysfunction (158,159). Empagliflozin consistently decreased the markers of tubular epithelial cells injury such as neutrophil gelatinase-associated lipocalin and kidney injury molecule 1, measured in the kidney tissue and urine of diabetic rats (160). SGLT-2 inhibition also augments autophagy in podocytes and renal tubular cells that improves their viability and prevents apoptotic cell death (158,161,162). Besides, SGLT-2 inhibitors effectively

mitigate diabetic tubulopathy by improving mitochondrial function (158,159).

Similar to the heart, activation of Sestrin2/AMPK pathway improved hyperglycemia-induced mitochondrial dysfunction in the kidney and hindered podocytes apoptosis (163). Mitochondrial dysfunction has been implicated in the pathogenesis of CKD, particularly in diabetic nephropathy (164). Suppression of Sestrin2 expression has been implicated in the pathogenesis of diabetic nephropathy (165). SGLT-2 inhibitors positively regulate Sestrin2 expression that can profoundly ameliorate oxidative stress, inflammation, mitochondrial dysfunction, ER stress, and fibrosis in the kidney (60,61,163,165).

SGLT-2 inhibition improves renal cortex hypoxia and simultaneously confines the deleterious effects of hypoxia such as oxidative stress, inflammation, apoptosis, and fibrosis in the kidney (166,167). As mentioned previously, SGLT-2 inhibitors stimulate ketogenesis (168). Using ketone bodies as the source of energy alleviates inflammation and protects against tubular cells apoptosis and renal fibrosis (169,170). Empagliflozin protected against diabetic nephropathy by attenuating mTORC1 signaling and enhancing ketogenesis. Inhibition of ketogenesis reverted the protective effects of empagliflozin on diabetic nephropathy (168). SGLT-2 inhibitors activate SIRT1/PGC-α/FGF21 pathway to promote ketogenesis in the kidney (Fig. 2) (171).

Empagliflozin was administered in a rat model of unilateral ureteric obstruction that leads to kidney injury. The results revealed that SGLT-2 inhibition could upregulate klotho and prevent TLR4/NF-κB and Wnt signaling pathways in the damaged kidney. Besides, empagliflozin decreased the expression of fibrogenic molecules such as TGF-β, connective tissue growth factor, α smooth muscle actin, and fibronectin and reduced renal fibrosis in histopathological measurement (172,173). Similarly, canagliflozin could decrease IL6, TNF-α receptor, fibronectin and matrix metalloproteinase 7, which are critically involved in renal inflammation and fibrosis (174). Klotho is a major molecule for preventing renal fibrosis. Consistently, decreased Klotho expression in human renal biopsy specimens has been associated with renal fibrosis (175). Furthermore, Klotho inhibits Wnt and NF-κB signaling pathways, decreases TGF-β expression and attenuates ER stress; hence, SGLT-2 inhibition can prevent renal fibrosis by enhancing the expression of klotho (176-179). Overactivation of Wnt signaling pathway is frequently observed in the kidney of diabetic patients and results in podocytes dysfunction, epithelial-mesenchymal transition, renal fibrosis, and progression of diabetic nephropathy (180,181).

Canagliflozin attenuated inflammation and fibrosis in the mice model of diabetic nephropathy. It suppressed the renal expression of TNF-α, connective tissue growth factor, collagen 1A1, and MCP-1 through activation of AMPK and downregulation of peptidyl-prolyl cis/trans isomerase never in mitosis A-interacting 1 (182). As a regulator of cell mitosis, Peptidylprolyl cis/trans isomerase never in mitosis-interacting 1 is essential for development of renal fibrosis. It stimulates the proliferation of mesangial cells to increase fibrotic lesions in the kidney (182-184).

In addition to attenuating NF-κB signaling, empagliflozin reduced the expression of high mobility group box 1 (HMGB1) and RAGE in the damaged kidney. Attenuation of HMGB1/RAGE signaling pathway prevents the release of several inflammatory cytokines such as TNF-α, IL6, and MCP-1 (185). Similarly, dapagliflozin ameliorated renal injury in a rat model of diabetic nephropathy via inhibition of HMGB1/RAGE/NF-κB signaling pathway. Attenuation of this pathway by dapagliflozin has been associated with decreased production of fibronectin, MCP-1, intercellular adhesion molecule 1, collagenase type 1, superoxide dismutase, and ROS (156). TLR4 and RAGE are major members of pattern recognition receptors (PRRs) and provoke innate immunity response (186,187). HMGB1 is a damage-associated molecular pattern and HMGB1/RAGE/TLR4/NF-κB/TNF-α axis plays a pivotal role in the activation of immune system and pathogenesis of kidney injury (188). Likewise, it was observed that blockade of HMGB1 can alleviate diabetic nephropathy in mice (189).

Shin et al showed that dapagliflozin attenuates RAAS to protect against kidney damage (190). Similarly, canagliflozin attenuated hyperglycemia-induced augmentation of RAAS and decreased renal proximal tubular angiotensinogen (191). Interestingly, a strong correlation was observed between the response of albuminuria to RAAS inhibitors and the response of albuminuria to SGLT-2 inhibitors. Patients' weak response to RAAS inhibitors predicted their weak response to SGLT-2 inhibitors (192). RAAS inhibition prevents renal fibrosis, improves albuminuria, and slows down the annual decline of renal function (193-195). Interestingly, it was observed that combination of an SGLT-2 inhibitor and an angiotensin converting enzyme inhibitor can more effectively hinder the development and progression of kidney injury in diabetic rats, compared with monotherapy with each one these drugs (196). Regarding their additive effect on the kidney, the combination of SGLT-2 inhibitors and RAAS inhibitors can be a good combination to restrict the progression of CKD in diabetic patients.

SGLT-2 inhibitors suppressed kidney inflammation and fibrosis in animal models and improved acute kidney injury and CKD among diabetic patients. The question remains whether these drugs can replicate the same results in nondiabetic population or not (Fig. 3).

## The Effects of SGLT-2 Inhibitors on NAFLD

### Clinical Findings

Recently, the meta-analysis of previous clinical trials showed that 24-week administration of SGLT-2 inhibitors for overweight or obese patients with NAFLD can effectively decrease alanine aminotransferase [weighted mean differences (WMD; 95% CI) –10.0 IU/L (–12.2 to –7.79)], gamma-glutamyl transferase [WMD (95% CI) –14.49 IU/L (–19.35 to –9.36)], as well as the absolute percentage of liver fat content on magnetic resonance imaging [WMB (95% CI) –2.05% (–2.61% to –1.48%)] (197). The promising results of previous studies revealed that SGLT-2 inhibitors can improve liver steatosis in their long-term use and contribute to the management of NAFLD (198,199). According to the results of clinical trials, dapagliflozin, and empagliflozin were slightly superior to other SGLT-2 inhibitors such as canagliflozin and ipragliflozin regarding their effect on alanine aminotransferase, gamma-glutamyl transferase, and liver fat content (197,200-204).

SGLT-2 inhibitors moderately decrease body weight in both diabetic [WMD (95% CI) –1.86 kg (–2.03 kg to –1.7 kg), $P < 0.01$] and nondiabetic patients [WMD (95% CI) –1.34 kg (–1.51 kg to –1.17 kg)] (205-207). Adding SGLT-2 inhibitors to GLP-1 receptor agonists or metformin resulted in much more improvement in body weight, blood pressure, and HbA1c, compared with monotherapy with each one of them (208,209). Weight loss can profoundly help to alleviate liver steatosis and improve NAFLD (210,211). Moreover, SGLT-2 inhibition decreases plasma triglyceride and increases high-density lipoprotein to improve dyslipidemia (212). Dyslipidemia is a major coexisting condition of NAFLD and increases the risk of cardiovascular events in patients with NAFLD (213).

### Pathophysiological Mechanisms Involved in the Protective Effects of SGLT-2 Inhibitors on NAFLD

Dapagliflozin decreased liver steatosis and fibrosis in high-carbohydrate, high-fat–induced NAFLD. It attenuated inflammation and decreased TNF-α, IL1β, and IL18 in the liver homogenate (214,215). Similarly, empagliflozin decreased the production of several inflammatory cytokines such as IL1β, IL6, and IL8 to improve hepatic steatosis (216-218). Similarly, ipragliflozin attenuated oxidative stress and inhibited the production of IL6, TNF-α, and MCP-1 to mitigate liver injury and improve hepatic steatosis (219). Likewise, canagliflozin increased BCL2 and decreased caspase 3 to prevent hepatocytes apoptosis (220).

Empagliflozin increased the decreased expression of SIRT1 to expedite fatty acid oxidation. Meanwhile, empagliflozin inhibited hepatic lipogenesis, which is markedly involved in the pathogenesis of NAFLD (216-218).

In addition, empagliflozin suppressed the gene expression of CHOP, ATF4, and growth arrest and DNA damage-inducible protein (Gadd45) to prevent the deleterious effects of ER stress on hepatocytes (221). As mentioned previously, CHOP mediates ER stress-induced apoptotic cell death (222,223). Hence, SGLT-2 inhibition can effectively alleviate ER stress and prevent ER stress-mediated apoptosis in the liver.

Empagliflozin increased the decreased expression of SIRT1 to expedite fatty acid oxidation. Meanwhile, empagliflozin inhibited hepatic lipogenesis, which is markedly involved in the pathogenesis of NAFLD (216-218). Activation of SIRT-1/PGC-α/PPAR-α pathway by SGLT-2 inhibitors promotes fatty acid oxidation (224). Consistently, empagliflozin augmented β-oxidation to decrease the lipid content of liver. In addition, it increased the expression of PPAR-α and decreased the expression of PPAR-γ, sterol regulatory element-binding transcription factor 1c and fatty acid synthase to hinder hepatic lipogenesis (221). PPAR-α promotes β-oxidation and enhances lipid catabolism while sterol regulatory element-binding transcription factor 1c/PPAR-γ/fatty acid synthase pathway is a major driver for free fatty acid synthesis (225,226). Furthermore, it was shown that the beneficial effects of canagliflozin on NAFLD is associated with increased expression of zinc alpha-2 glycoprotein (220). Zinc alpha-2 glycoprotein activates extracellular signal-regulated kinase (ERK). Subsequently, ERK activates β3-adrenergic receptors to promote lipolysis (227-230). Based on these findings, SGLT-2 inhibition can expedite the conversion of triglycerides into free fatty acids and simultaneously accelerate free fatty acids catabolism.

SGLT-2 inhibition decreases insulin levels (219). SGLT-2 inhibition accelerates hepatic gluconeogenesis and reduces hepatic glycogenesis (231,232). Excessive glycogenesis and lipogenesis leads to hepatic steatosis and attenuation of these pathways contributes to the treatment of NAFLD (221,233-235). The increase in hepatic gluconeogenesis cannot impair glycemic control because SGLT-2 inhibitors increase the urinary excretion of glucose and finally decrease blood glucose level.

SGLT-2 inhibition by empagliflozin attenuated NLRP3 inflammasome activation in the liver of rats (236). NLRP3 inflammasome has a key role in the liver inflammation. Additionally, activation of NLRP3 inflammasome is essential for development of liver fibrosis and possesses a pivotal role in the progression of NAFLD to nonalcoholic steatohepatitis (NASH) (237,238). As mentioned previously, SGLT-2 inhibition significantly downregulates α smooth muscle actin, TGF-β, and collagen 1A1 to improve liver fibrosis in the rat model of NAFLD (239,240). TGF-β activates janus kinase 1/signal transducer and activator of transcription 3 signaling pathway, which leads
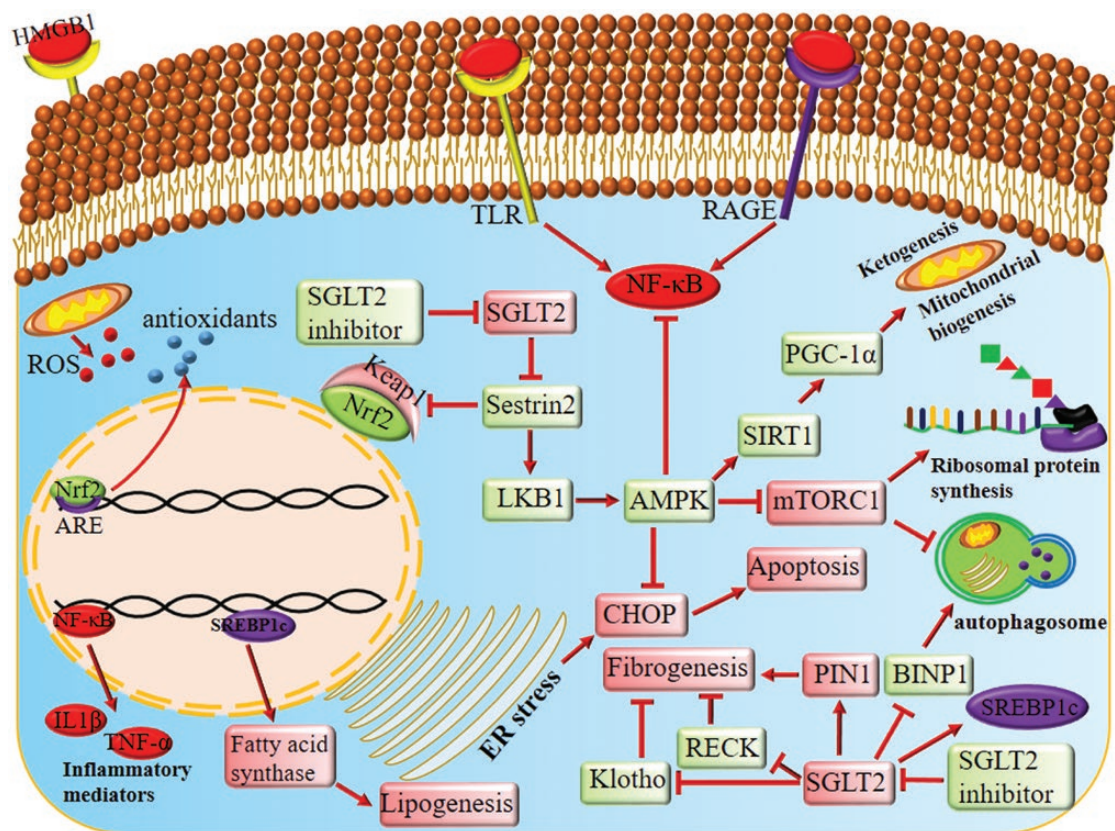
**Figure 5**. The effect of SGLT-2 inhibitors on several intracellular signaling pathways. SGLT-2 inhibitors activate Sestrin2/LKB1/AMPK signaling pathway, thereby regulating several cellular events. AMPK upregulates SIRT1/PGC-1α to enhance mitochondrial biogenesis. SGLT-2 inhibitors can also downregulate NF-κB, mTORC1 and CHOP. Accordingly, SGLT-2 inhibitors negatively regulate ribosomal protein synthesis, inflammatory cytokines production and ER stress-mediated apoptosis. In addition, SGLT-2 inhibitors increase autophagy by inhibiting mTORC1 and enhancing BINP1 function. These drugs prevent lipogenesis by decreasing SREBP1c. SGLT-2 inhibitors, in a Sestrin2-dependent manner, liberate Nrf2 from Keap1 anchoring and potentiate the production of numerous endogenous antioxidants. Finally, SGLT-2 inhibitors effectively confine fibrogenesis in the damaged organ by upregulating klotho and RECK and suppressing PIN1 expression.

to expression of a group of genes, contributing to liver fibrosis (241).

Twenty-four-week treatment with dapagliflozin reduced the serum levels of soluble DPP-4 in patients with diabetes and NAFLD (242). DPP-4 inhibitors activate AMPK and suppress hepatic lipogenesis to improve NAFLD (243-245). DPP-4 degrades GLP-1 and prevents its beneficial effects on NAFLD (246). Recent meta-analysis performed by Mantovani et al revealed that 26-week treatment with GLP-1 receptor agonists markedly improved liver fat content on magnetic resonance imaging, decreased liver fibrosis in histopathology, and reduced serum aminotransferases in patients with or without diabetes (247).

Ipragliflozin increased the plasma concentration of adiponectin, while it decreased the plasma concentration of leptin and FGF21. It significantly improved oxidative stress, inflammation, and fibrosis in the mice model of NAFLD (248,249). Lower adiponectin/leptin ratio is associated with metabolic syndrome, presence of NAFLD, and severity of NAFLD and liver fibrosis (250,251). Likewise, higher levels of FGF21 are detected in patients with NAFLD (252). Dapagliflozin decreased liver fat content, suppressed liver inflammation, alleviated hepatocellular injury, and, consequently, reduced the plasma levels of FGF21 and hepatic enzymes in diabetic patients after 8 and 12 weeks of treatment (201,253). However, SGLT-2 inhibitors typically increase FGF21 level (254,255). FGF21 enhances fatty acid oxidation and ketogenesis, attempts to alleviate liver injury, and, as a compensatory mechanism, increases during liver injury (256,257). Decreased levels of FGF21 following administration of dapagliflozin may be due to decreased hepatocellular injury after 8 to 12 weeks, similar to what happened for hepatic enzymes (253).

SGLT-2 inhibitors can slightly increase glucagon secretion and also improve insulin resistance (258,259). It was shown that stimulation of glucagon receptor and GLP-1 receptor can inhibit intrahepatic lipogenesis and mitigate NAFLD (260,261). Similar to SGLT-2 inhibitors, glucagon promotes ketogenesis (103,262). Ketogenic diet decreases body weight, intrahepatic triglyceride accumulation, hepatic insulin resistance, and plasma leptin. In addition, ketogenic diet significantly enhances hepatic mitochondrial redox state (263,264).

Accumulating evidence shows that SGLT-2 inhibitors can partly improve NAFLD. SGLT-2 inhibitors decrease

intrahepatic lipid accumulation. They also prevent the progression of NAFLD to NASH and liver fibrosis by ameliorating liver inflammation and apoptosis of hepatocytes. These effects can be helpful in diabetic patients who are complicated with NAFLD. Future studies should answer whether SGLT-2 inhibitors can improve NAFLD in nondiabetic patients (Fig. 4).

## Conclusion and Future Research Direction

SGLT-2 inhibitors are a new class of antidiabetic drugs that can effectively improve the coexisting conditions of diabetes such as cardiovascular diseases, kidney diseases and NAFLD in diabetic patients. This review article attempted to explain how these drugs can interact with numerous signaling pathways and molecular mechanisms to improve these diseases (Fig. 5). Now, the question is whether we should use SGLT-2 inhibitors for nondiabetic patients who are suffering from these conditions. Another question is whether these drugs effectively improve other diseases that were not addressed or measured in previous human studies. Future studies will answer these questions and expand our knowledge of the biological function of SGLT-2.

## Additional Information

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