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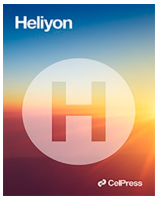

Review article

SGLT-2 inhibitors as novel treatments of multiple organ fibrosis

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ABSTRACT

Fibrosis, a significant health issue linked to chronic inflammatory diseases, affects various organs and can lead to serious damage and loss of function. Despite the availability of some treatments, their limitations necessitate the development of new therapeutic options. Sodium-glucose cotransporter 2 inhibitors (SGLT2i), known for their glucose-lowering ability, have shown promise in offering protective effects against fibrosis in multiple organs through glucose-independent mechanisms. This review explores the anti-fibrotic potential of SGLT2i across different tissues, providing insights into their underlying mechanisms and highlighting recent research advancements. The evidence positions SGLT2i as a potential future treatments for fibrotic diseases.

1. Introduction

Fibrosis is a widespread pathological condition that transforms healthy cells and tissues in organs into fibrous tissue under certain diseases, leading to structural and functional disruptions and potentially complete organ failure [1–3]. This process is not limited to a single organ but affects multiple ones, including the heart, liver, kidneys, lungs, and peritoneum [4–8]. Though the pathogenic triggers differ by organ, common factors like chronic infections, autoimmune reactions, oxidative stress, and cellular death are frequently involved in fibrogenesis [2,9,10] (Fig. 1). The impact of fibrosis on clinical outcomes is profound, contributing to organ dysfunction and significantly increasing mortality [11], with nearly 45 % of disease-related deaths in developed nations linked to fibrotic conditions. This prevalence is likely even higher in developing countries, exacerbated by aging populations, environmental pollutants, and widespread epidemics, making fibrosis an increasingly common issue [12,13].

Despite advances in understanding fibrosis mechanisms and treatments, only a few therapies are available that marginally decelerate fibrosis progression [14,15]. The adverse effects (such as nausea and gastrointestinal discomfort) and the high cost of these treatments often hinder patient compliance, underscoring the urgent need for new therapeutic strategies targeting novel mechanisms and pathways in fibrosis [16]. Within the realm of anti-fibrotic research, sodium-glucose cotransporter 2 inhibitors (SGLT2i) have emerged as effective, affordable, and widely used in treating hyperglycemia, with a growing body of evidence supporting their potential as antifibrotic agents, marking them as a promising class for future fibrosis therapies.

2. SGLT-2 inhibitor

SGLT2 inhibitors (SGLT2i), which are taken orally and have been the focus of significant interest in recent years, have their roots in

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research dating back to the 1930s, beginning with the discovery of non-specific SGLT inhibition effects from extracts of apple tree root bark. With progress in medical technology, the original compound, phlorizin, has been chemically altered to create a variety of new compounds, collectively known as SGLT2i [3]. The key players in renal glucose reabsorption, Sodium-glucose cotransporter 1 (SGLT-1) and Sodium-glucose cotransporter 2 (SGLT-2) are located in the epithelial cells of the renal tubules. Typically, glucose that has been filtered through the glomerulus is reabsorbed in the renal tubules via SGLT-1 and SGLT-2, with SGLT-2 playing a dominant role in the S1 and S2 segments of the tubules, accounting for 90 % of glucose reabsorption. SGLT-1, while primarily found in the kidneys and gastrointestinal tract, plays a smaller role in glucose reabsorption in the gastrointestinal tract [17]. By competitively binding to glucose-binding sites on SGLT-2 proteins in the renal tubules, SGLT2i reduce the reabsorption of glucose by these tubules, leading to an increase in the excretion of glucose, sodium, and water in the urine, thus lowering blood glucose levels and reducing volume load [18–20]. The FDA has approved four specific SGLT2i for use: empagliflozin (EMPA), canagliflozin (CANA), dapagliflozin (DAPA), and ertugliflozin, all of which are highly selective for SGLT-2 inhibition, while sotagliflozin inhibits both SGLT-1 and SGLT-2 transport proteins (Table 1).

SGLT-2 inhibitors also offer organ-protective benefits beyond glucose management, including benefits for the cardiovascular system and kidneys [21–23]. These benefits stem from their ability to promote glucose excretion, reduce glucose toxicity, delay the onset of diabetic complications, aid in weight loss, decrease the risk of hypertension, enhance glucose metabolism, and improve insulin sensitivity [24]. The non-glucose-lowering protective effects of SGLT-2i, including antioxidant stress [25,26], anti-inflammatory actions [27], anti-aging [28], enhancement of mitochondrial function [29,30], metabolic regulation [31] and anti-fibrotic properties (Fig. 2), have become increasingly acknowledged. While extensive research has been conducted on the role of SGLT2i in organ fibrosis, particularly in the heart and kidneys, a comprehensive summary and synthesis of these mechanisms remain outstanding. Thus, our objective is to methodically review the actions of SGLT2i in fibrosis across various organs, assess their future therapeutic potential, and offer insights and guidance for the development of novel antifibrotic medications.

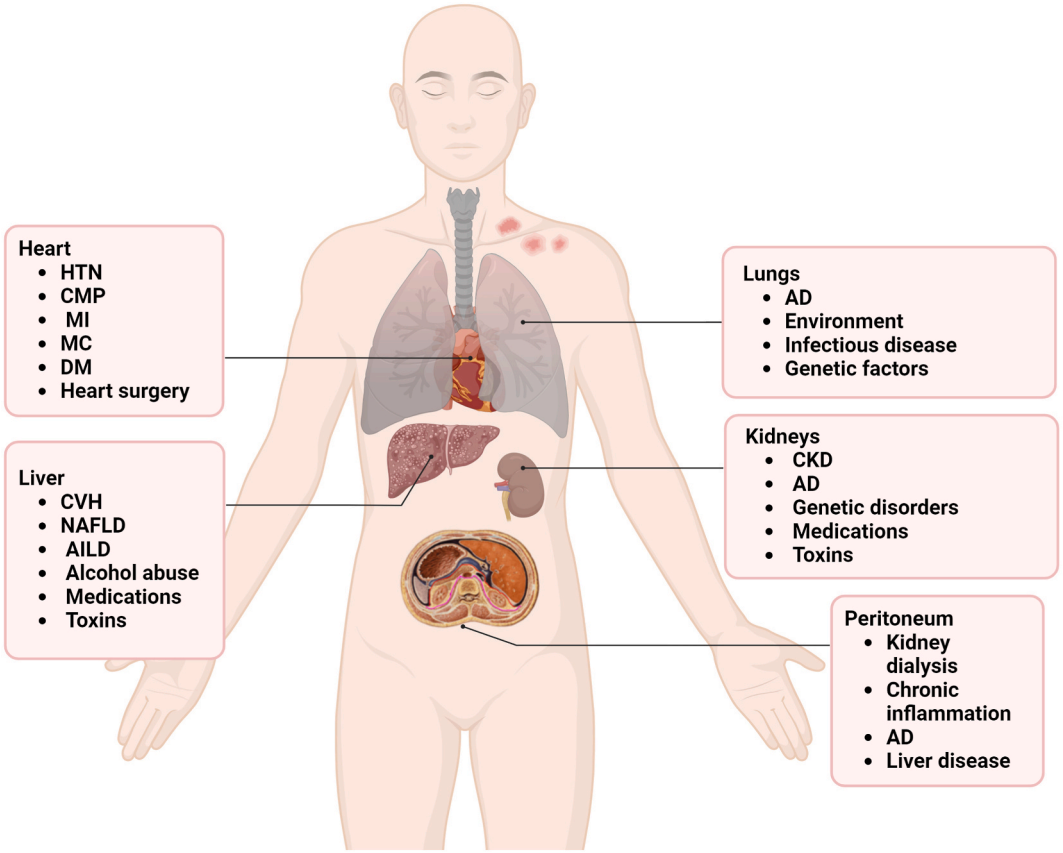

Fig. 1. The primary causes of organ fibrosis. Various factors can lead to the occurrence and progression of fibrosis in different organs.
Abbreviation: CVH,Chronic viral hepatitis; NAFLD,Non-alcoholic fatty liver disease; AILD, Autoimmune liver disease; HTN,Hypertension; CMP, Cardiomyopathy; MI,Myocardial infarction; MC,Myocarditis; DM,Diabetes; CKD, Chronic kidney disease; AD,Autoimmune diseases; (Created with bioRender.com) .

Table 1
SGLT2 inhibitors.

Agent	SGLT2 selectivity	Company	Brand	Dose mg/day	Route of excretion
Dapagliflozin	High	AstraZeneca*	Farxiga	5, 10	Urine
Canagliflozin	moderate	Janssen, Napp	Ilnvokana	100,300	Urine, feces
Empagliflozin	High	Boehringer	Jardiance	10,25	Urine, feces
Ertugliflozin	High	Merck Sharp & Dohme, Pfizer	Steglatro	5, 15	Urine, feces
Sotagliflozin	low	Lexicon	Zynquista	200	Urine, feces
Ipragliflozin	High	Astellas	Suglat	25,50	Urine, feces
Luseogliflozin	High	Taisho	Lusefi	2.5,5	Urine, feces
Tofogliflozin	High	Chugai, Kowa	Apleway	20,40	Urine, feces

SGLT2i is a sodium-glucose cotransporter 2 inhibitor; SGLT stands for sodium-glucose cotransporter. High selectivity is defined as SGLT2/SGLT1 > 1,000, moderate selectivity as 250 < SGLT2/SGLT1 < 500, and low selectivity as SGLT2/SGLT1 < 20.

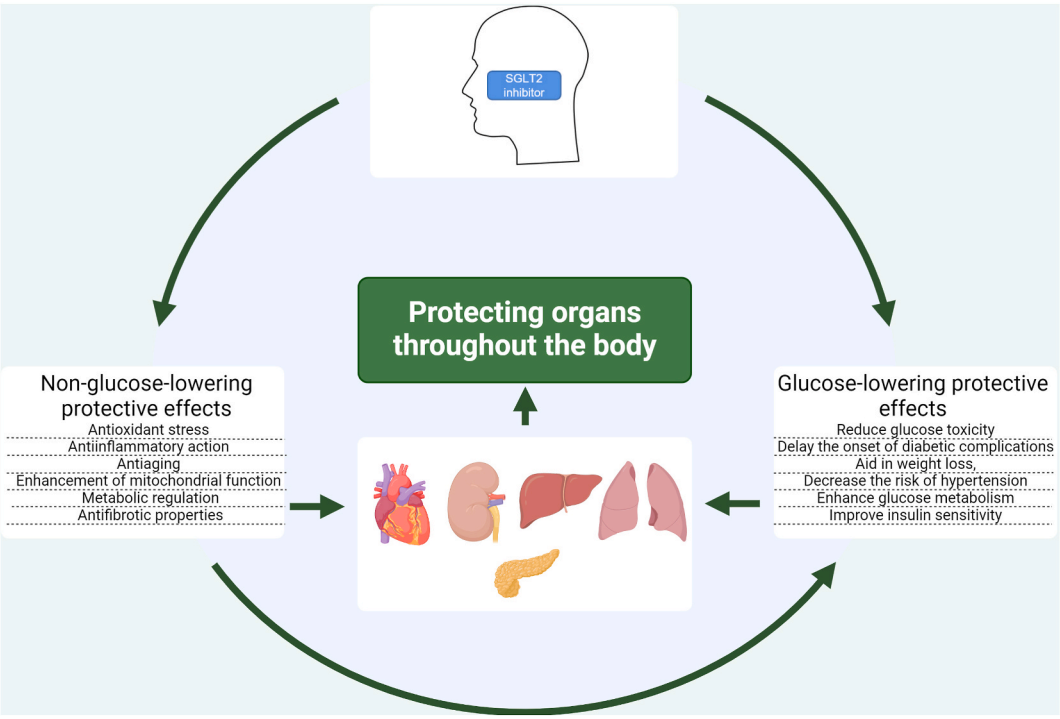

Fig. 2. SGLT2 inhibitor exerts pleiotropic effects on multiple organ systems.
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3. SGLT-2 inhibitors and organ fibrosis

3.1. Liver fibrosis

Liver fibrosis represents a pathological and physiological response involving the excessive growth of connective tissue within the liver, triggered by a variety of harmful factors [32]. It stands as the common endpoint of all chronic liver diseases, marked by the overproduction of extracellular matrix (ECM) proteins. This overproduction results in damage to liver cells and the creation of fibrotic scars [33,34]. Without the removal of these causative factors, fibrosis can progress to cirrhosis, the most advanced stage of liver disease. Cirrhosis is among the leading causes of morbidity and mortality worldwide [35]. Consequently, the prevention and reversal of liver fibrosis are critical objectives in the management of chronic liver conditions and the fight against cirrhosis. Despite its significance, current therapeutic options for liver fibrosis are limited to the elimination of causative factors or liver transplantation, with no other effective treatments available.

3.1.1. The effects of SGLT-2 inhibitors on liver fibrosis

SGLT2i have been identified as highly promising agents in combating liver fibrosis, according to various studies [36]. Research led by Professor Goto demonstrated that SGLT2i could decelerate the progression of liver fibrosis in bluegill fish through the reduction of blood glucose levels [37]. Similarly, studies in rat models have shown that SGLT2i may mitigate the development of liver fibrosis by

enhancing insulin sensitivity (IR) [38]. Beyond their glucose-lowering capabilities, SGLT2i also exert beneficial effects on liver fibrosis via glycemic-independent mechanisms, including the modulation of liver metabolism, protection against hepatocyte apoptosis, the suppression of autophagy, and anti-inflammatory and antioxidant actions. For instance, in rats on a choline-deficient L-amino acid (CDAA) diet, SGLT2i demonstrated an ability to ameliorate liver fibrosis by altering hepatic metabolism [39]. These drugs also counteract liver fibrosis by preventing hepatocyte death [40] and by inhibiting the activation of autophagy-related to O-GlcNAcylation processes in the liver [41]. Through their hypoglycemic, antioxidative, and anti-inflammatory properties, SGLT2i lower the levels of inflammatory cytokines like Tumor Necrosis Factor-alpha (TNF-α), Interleukin 6 (IL-6), and C–C Motif Ligand 2 (CCL2), and reduce oxidative stress, contributing to their anti-fibrotic effects in the liver [40,42–44].

Clinical research further supports the efficacy of SGLT2i against liver fibrosis. Liver stiffness measurement (LSM), Fibrosis-4 (FIB-4) index and Non-alcoholic fatty liver disease (NAFLD) fibrosis scores are crucial tools in evaluating the severity of liver fibrosis and have been widely used to assess the impact of treatment in patients. Clinical trials focusing on individuals with NAFLD have evidenced that SGLT2i significantly lowers LSM, FIB-4, and NAFLD fibrosis scores [44–50] (Table 3). Additionally, a clinical investigation by Professor Takeshita and his team on the effects of SGLT-2i on NAFLD in patients with type 2 diabetes (T2DM) reported improvements in liver fibrosis, as measured by pathological scores [51,52](Table 3).

3.2. Renal fibrosis

Chronic kidney disease (CKD) represents a significant worldwide public health challenge, impacting approximately 15 % of the adult population globally. The issue is becoming more acute with the rise in the aging population, positioning it as a growing global concern [53]. Renal fibrosis is identified as the universal concluding pathway for the progression of CKD from various origins, including ischemic events, infections, autoimmune conditions, toxicity or drug-related injuries, diabetes, and genetic disorders. It is established as the most reliable indicator for the advancement of CKD to end-stage renal disease, which necessitates interventions such as dialysis or kidney transplantation [54]. Despite its critical importance, effective treatments to halt the progression of renal fibrosis remain elusive [55].

3.2.1. The effects of SGLT-2 inhibitors on renal fibrosis

SGLT-2i have been recognized for their renal protective effects in chronic kidney disease (CKD), particularly in environments of high glucose that contribute to renal fibrosis through mechanisms like enhanced matrix protein synthesis, activation of fibrosis-related pathways, and alterations in extracellular matrix management [56,57]. SGLT-2i are known to alleviate renal fibrosis by lowering blood glucose levels [19,58,59]. Beyond glucose reduction, evidence from preclinical studies suggests SGLT-2i addresses renal fibrosis through various mechanisms, including ameliorating hypoxia and oxidative stress, reducing inflammatory responses, promoting autophagy, regulating metabolism, and capillary protection.

Hypoxia is a well-established catalyst for renal fibrosis [60]. Research led by Professor Judit Hodrea demonstrated that DAPA could modify the renal tubules' response to hypoxia, thus diminishing tubulointerstitial fibrosis [61]. In experiments with human proximal tubular (HK-2) cells, EMPA was found to reduce renal fibrosis by decreasing the expression of hypoxia-inducible factor-1α (HIF-1α) [62]. Oxidative stress, another key player in renal fibrosis, is mitigated by SGLT-2i, as several studies have shown their capacity to manage oxidative stress to lessen renal fibrosis [63–65]. The anti-inflammatory properties of SGLT-2i also contribute to their renal benefits, where, for example, dapagliflozin inhibits the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome in ischemia-reperfusion injury (IRI) models, protecting against fibrosis [66]. Additionally, SGLT-2i reduces the infiltration of inflammatory cells, such as macrophages [67–69], and regulates autophagy, which is another path through which these drugs combat renal fibrosis. CANA modulates autophagy via the signal transducer and activator of the transcription 6 (STAT6) pathway [70], while EMPA affects mitochondrial autophagy to improve renal function [68]. Addressing metabolism and lipid toxicity, SGLT-2i has been found to reduce renal fibrosis by minimizing lipid buildup in renal tubular cells, as shown in studies by Professor Zhang and colleagues [71]. Their ability to protect capillaries, preventing endothelial loss and subsequent fibrosis after kidney injury via a glucose transporter 2 (GLUT2)-dependent mechanism, further underscores the comprehensive anti-fibrotic actions of SGLT-2i [72].

Transforming growth factor β-1(TGF-β1) is a crucial fibrotic cytokine. A clinical study by Professor Tian and colleagues demonstrated that SGLT2i enhances the secretion of TGF-β1 via renal pathways and improves the progression of renal fibrosis [73]. Despite promising preclinical data indicating the potential of SGLT2i to lessen renal fibrosis, the clinical evidence remains sparse, partly due to the challenges of direct fibrosis measurement, such as requiring kidney biopsies. Hence, there's a call for more comprehensive clinical trials to confirm the ability of SGLT2i to reduce renal fibrosis, offering hope for a new avenue in the treatment of CKD.

3.3. Cardiac fibrosis

Myocardial fibrosis involves the development of a collagen network within the heart's interstitial space, a condition often triggered by inadequate blood flow, systemic illnesses, medication effects, or other detrimental factors impacting the cardiovascular system or the heart directly. This alteration in the heart muscle not only changes its structural integrity but also exacerbates cardiac dysfunction, potentially leading to arrhythmias and significantly influencing the progression and outcomes of heart failure in patients [74,75]. Despite considerable research efforts, the precise processes underlying cardiac fibrosis remain incompletely understood. There is a pressing need for more effective, evidence-based treatment options to address cardiac fibrosis [76].

3.3.1. The effects of SGLT-2 inhibitors on cardiac fibrosis

SGLT2i has shown significant benefits in managing heart failure and lowering the risk of cardiovascular mortality [77,78]. Recent findings highlight that SGLT-2i can ameliorate cardiac fibrosis through diverse mechanisms, offering cardioprotective benefits. The toxic effects of prolonged high blood sugar levels can lead to the overproduction of cytokines, activation, and growth of cardiac fibroblasts, increased extracellular matrix synthesis, and accumulation in the myocardial interstitium and around blood vessels. This results in reduced elasticity of the heart muscle and compromised cardiac function. SGLT-2i addresses myocardial fibrosis caused by hyperglycemia by improving blood sugar control [79,80]. Moreover, SGLT-2i combats myocardial fibrosis through non-glycemic pathways, including anti-inflammatory actions, reduction of oxidative stress, suppression of autophagy, and metabolic adjustments. Specifically, SGLT-2i mitigate myocardial fibrosis and inflammation by affecting signaling pathways such as Hypoxia-inducible factor 2α (HIF-2α) [81], Signal transducer and activator of transcription 3 (STAT3) [82], Nlrp3/Apoptosis-associated speck-like protein (ASC) inflammasome [83], Serum and glucocorticoid regulated kinase 1 (SGK1) signaling [84], NLRP3, and Myeloid differentiation primary response 88 (MyD88)-related pathways [85]. Additionally, these inhibitors curb myocardial fibrosis and oxidative stress via mechanisms including the Nuclear factor erythroid 2-related factor 2 (Nrf2)/Antioxidant response elements (ARE) [86], Janus kinase/Activator of transcription (Jak/STAT) [87], and Phosphoinositide 3-kinase (PI3K)/Protein kinase B (AKT)/Nrf2 signaling pathways [88]. SGLT-2i also affects fibroblast activation and autophagy regulation to improve myocardial fibrosis through pathways like TGF-β/Smad [86,89,90] and Sodium-hydrogen exchangers (NHE) signaling [91–94]. A 2022 study demonstrated that SGLT-2i reduced ventricular fibrosis in mice by targeting the mTOR pathway, suggesting a new avenue for addressing myocardial fibrosis [95].

Clinical investigations have also underscored the noteworthy contribution of SGLT-2 inhibitors (SGLT-2i) in addressing myocardial fibrosis. The extracellular volume fraction (ECV) emerges as a pivotal clinical indicator for identifying myocardial fibrosis (MF). In Professor Mason's recent study, the influence of empagliflozin on cardiac ECV among patients with type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD) came to light. This examination, encompassing 97 participants, revealed that following a 6-month observation period, the ECV measurement decreased in the empagliflozin cohort compared to the placebo cohort, signifying the beneficial impact of EMPA in diminishing cardiac fibrosis and enhancing ventricular remodeling [96]. MF, serving as a prevalent endpoint across various cardiac ailments like heart failure, myocardial infarction, and cardiomyopathy, has been consistently demonstrated in multiple clinical inquiries to be pivotal in the effectiveness of SGLT-2i against heart failure, myocardial infarction, and cardiomyopathy. Nonetheless, the accurate assessment of cardiac fibrosis necessitates meticulous techniques and methodologies, encompassing histopathology, imaging modalities, and biomarkers. These techniques might pose implementation challenges or entail significant costs, thus impeding the progress of associated research.

3.4. Pulmonary fibrosis

Pulmonary fibrosis (PF) represents a persistent and progressive respiratory ailment characterized by widespread fibrosis of bronchial connective tissue and alveolar walls, resulting in impairment of ion transfer and oxygen/carbon dioxide exchange within normal lung tissue [97]. Furthermore, PF may induce complications such as heart and pulmonary arterial hypertension [98,99]. The predominant variant is idiopathic pulmonary fibrosis (IPF) [100]. Presently, only pirfenidone and Nintedanib have exhibited evidence of slowing the progression of IPF, albeit accompanied by associated toxicities and limited capacity to reverse fibrosis [101]. Consequently, lung transplantation stands as the sole viable treatment avenue at present.

In mice subjected to bleomycin-induced PF, markers of PF in Bronchoalveolar Lavage Fluid (BALF), including TGF, were observed in the group treated with SGLT-2 inhibitors. Notably, the hydroxyproline content displayed a significant reduction, accompanied by substantial enhancements in histopathological, immunohistochemical, and electron microscope findings [98]. This phenomenon may be linked to the mechanism by which SGLT-2 inhibitors ameliorate oxidative stress, elicit anti-inflammatory responses, and regulate cellular apoptosis [102]. This may be related to the mechanism of SGLT-2i improving the body's oxidative stress, anti-inflammatory response, and regulating cell apoptosis [102]. Nonetheless, research regarding the effects of SGLT-2 inhibitors on PF remains limited, necessitating further exploration into the specific mechanisms involved.

3.5. Other Forms of fibrosis

Peritoneal dialysis (PD), serving as a renal replacement therapy, ensures efficacy, safety, and a heightened quality of life [103,104]. Nonetheless, owing to the extended utilization of the patient's peritoneum as a filtration dialyzer over time, peritoneal fibrosis emerges as the primary contributor to technology failure and disease progression, potentially necessitating a transition to alternative dialysis modalities and even resulting in patient mortality [105]. Despite these challenges, effective clinical interventions for addressing peritoneal fibrosis remain scarce [106].

In mice subjected to chronic infusion of peritoneal dialysis solution, SGLT-2 inhibitors have demonstrated the ability to inhibit TGF via β/Smad signaling, thereby significantly shielding against high glucose peritoneal dialysis-induced peritoneal fibrosis, effectively impeding its progression [2]. This phenomenon may be attributed to the mechanism wherein SGLT-2 inhibitors enhance the peritoneal microenvironment by mitigating damage to the kidney and peritoneum induced by hyperglycemia, hyperinsulinemia, cellular stress, and other factors, alongside inhibiting inflammation, reducing oxidative stress, and augmenting free fatty acid utilization [107]. Despite limited reports on the anti-fibrotic effects of SGLT-2 inhibitors on peritoneal fibrosis, further elucidation of their anti-fibrotic properties in peritoneal tissue is warranted.

4. Conclusion and future Prospects

This review provides an overview of the research advancements concerning SGLT2 inhibitors (SGLT2i) in fibrosis studies and therapies, encompassing insights from both basic experiments and clinical trials. Accumulating evidence from in vitro and in vivo investigations suggests that SGLT2 inhibitors possess anti-fibrotic properties across diverse tissues and organs, including the liver, kidneys, heart, peritoneum, and lungs. These effects potentially involve pathways associated with glycemic control as well as non-glycemic pathways, such as anti-inflammatory responses, antioxidant stress mitigation, downregulation of autophagy, metabolic regulation, and anti-apoptosis mechanisms (Fig. 3) (Table 2). Ongoing research on the anti-fibrotic effects of SGLT2 inhibitors in various organs is continuously evolving towards more comprehensive and updated directions. Recent studies indicate that SGLT2 inhibitors may offer preventive and therapeutic benefits against pulmonary fibrosis (PF) through multiple mechanisms, including inhibition of various inflammatory signaling molecules and reduction of pathways leading to oxidative lung damage. Furthermore, several other investigations suggest that SGLT2 inhibitors may exhibit specific preventive and therapeutic effects on fibrosis in organs like the pancreas [108,109].

However, the evaluation of fibrosis clinically is constrained by limited and less widely available methods, hence current evidence regarding the anti-fibrotic effects of SGLT2 inhibitors primarily stems from animal studies and fibrosis cell models, with clinical trial data being relatively scarce. Moreover, despite having undergone numerous clinical trials, the long-term safety profile of SGLT2 inhibitors necessitates further research and monitoring, particularly regarding their potential to increase the risks of hypoglycemia, ketoacidosis, infections, and osteoporosis, among others [110–112]. Additionally, while SGLT2 inhibitors can ameliorate the pathological status of diabetes and multi-organ fibrosis, there may be instances where their use in combination with other therapeutic agents is warranted to achieve optimal clinical outcomes. The complete elucidation of the anti-fibrotic mechanisms of SGLT2 inhibitors remains elusive, emphasizing the need for further investigation into their safety and efficacy in human subjects. In summary, although more rigorous research is warranted to validate the potential of SGLT2 inhibitors in treating multi-organ fibrosis, the preliminary evidence has garnered significant attention from the scientific community, heralding a promising new avenue in fibrosis management.

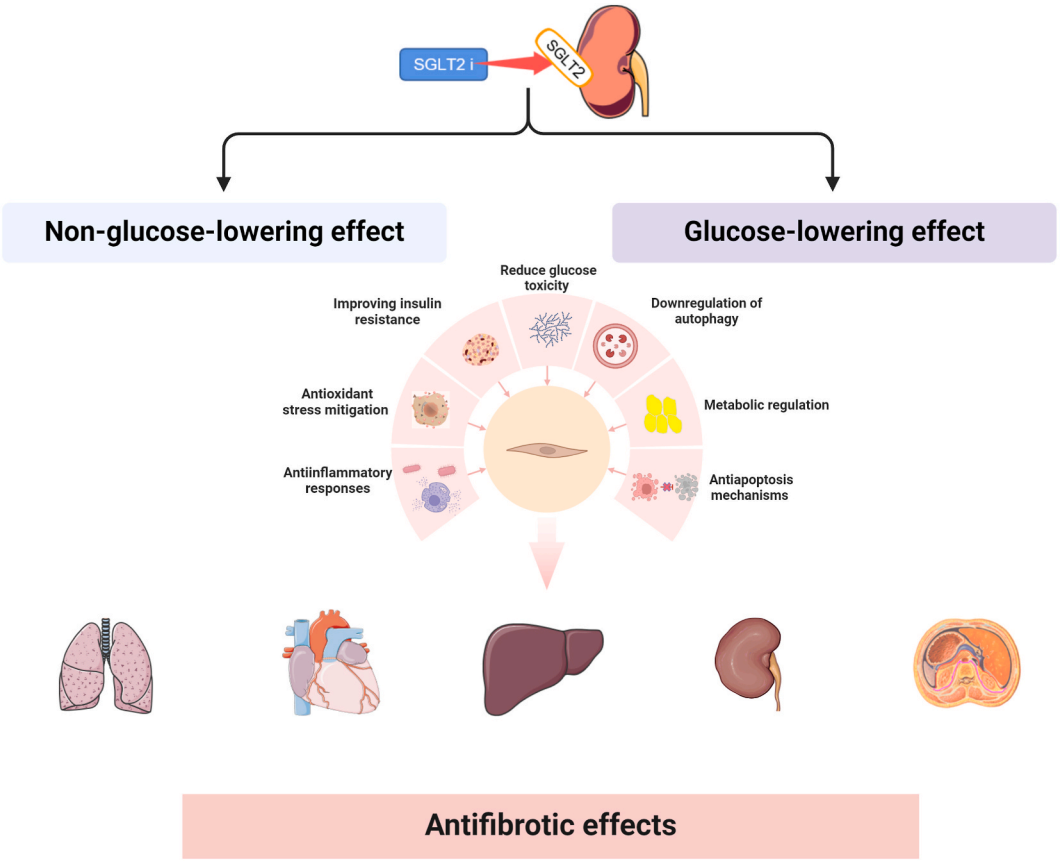

Fig. 3. The effects of SGLT-2 inhibitors on Organ fibrosis
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Table 2
Summary of preclinical anti-fibrotic effects and underlying mechanisms of SGLT2 inhibitors.

Fibrotic disease	Models	In vitro/in vivo	Effects and related mechanisms	Reference
Liver fibrosis	NASH liver tissue using medaka	In vitro	To suppress the accumulation and fibrosis of fat tissue by regulating hepatic metabolism	[37]
	OLETF rats and their littermate non-diabetic LETO rats	In vitro	Alleviate the development of liver fibrosis by improving IR	[38]
	Rat model of diet-induced NAFLD	In vitro	Via anti-inflammatory, anti-fibrotic, antioxidant, and anti-apoptotic mechanisms	[40]
	human normal hepatocytes and hepatoma cells	In vivo	Alleviating fibrosis through autophagy activation associated with SGLT2 expression and O-GlcNAcylation in the liver	[41]
	NASH rat model of nondiabetes	In vitro	Mitigating liver fibrosis through the attenuation of hepatic lipid peroxidation and inflammatory responses	[42]
	NAFLD in rats fed a CDAA diet	In vitro	Prevented hepatic TG accumulation and fibrosis in CDAA-diet rats	[39]
	Mouse model of NASH	In vitro	Anti-steatotic, anti-inflammatory, and anti-fibrotic effects.	[43]
Renal fibrosis	T1DM was induced by streptozotocin in adult male Wistar rats	In vitro	Diminished high glucose-induced protein O-GlcNAcylation and moderated the tubular response to hypoxia through the hypoxia-inducible factor pathway	[61]
	Dall salt-sensitive rats with hypertensive kidney damage caused by a high salt diet.	Both in vitro and vivo	Acts as a renoprotective agent by suppressing EMT in the pathology of renal fibrosis via interaction with the SIRT3-FOXO3a pathway	[63]
	Mouse model of renal fibrosis caused by unilateral ureteral obstruction	Both in vitro and vivo	Antagonizes renal fibrosis by regulating signals related to inflammation and oxidative stress and is associated with Glutamate ionotropic receptor, NMDA type subunit 1	[64]
	The I/R fibrosis mice model	Both in vitro and vivo	Prevented activation of NLRP3 inflammasome and protected the kidney against fibrosis development	[66]
	Ang II-induced renal fibrosis in rats	In vitro	Caused by reduced inflammatory infiltration and unrelated to the regulation of elevated blood pressure	[67]
	5/6 nephrectomy-induced CKD in rats	Both in vitro and vivo	This outcome is attributable to the targeted modulation of the mTOR and mitophagy pathways, leading to the inhibition of CD206CD68 M2 macrophage polarization and the attenuation of inflammatory signals from CD8 effector T cells.	[68]
	Intraperitoneal injection of CsA induces renal fibrosis in rats	In vitro	Empagliflozin administration caused a reduction in blood pressure in CsA-treated rats. It showed a protective effect on CsA nephropathy by decreasing renal fibrosis, type I and type IV collagen expression, macrophage infiltration, and tyrosine hydroxylase expression.	[69]
	Unilateral ureteral occlusion and ischemia-reperfusion renal fibrosis mouse models	Both in vitro and vivo	Acts to counter abnormal renal fatty acid metabolism and interstitial fibrosis through the m6A-modified SQSTM1/autophagy/STAT6 axis	[70]
	Non-diabetic mice	In vitro	Through a VEGF-dependent pathway induced by the dysfunction of proximal tubular glucose uptake in tubules with injury-induced GLUT2 downregulation	[72]
	Streptozotocin-induced renal fibrosis in mice	Both in vitro and vivo	Via inhibition of EMT and aberrant glycolysis in proximal tubules	[59]
Cardiac fibrosis	Cardiomyocyte-specific Dsg 2 exon-11 knockout mice	Both in vitro and vivo	Suppressing cardiac fibrosis and inflammation via reverting the HIF-2α signaling pathway	[81]
	Coronary artery ligation induced myocardial infarction in mice	Both in vitro and vivo	Attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts	[82]
	Myocardial fibrosis induced by intravenous Alloxan in rabbits with diabetes.	Both in vitro and vivo	Attenuated left ventricular diastolic dysfunction and cardiac fibrosis via regulation of SGK1 signaling	[84]
	Doxorubicin-induced myocardial cell fibrosis in mice	Both in vitro and vivo	Reduced ferroptosis, fibrosis, apoptosis, and inflammation in doxorubicin-treated mice through the involvement of NLRP3 and MyD88-related pathways, resulting in significant improvements in cardiac functions	[85]
	KK-Ay mice (genetic type 2 diabetes model)	In vitro	Suppressed oxidative stress and fibrosis through inhibition of the transforming growth factor β/Smad pathway and activation of Nrf2/ARE signaling	[86]
	Contraction of the left circumflex artery induces chronic myocardial ischemia in Yorkshire swine.	Both in vitro and vivo	Attenuation of fibrosis via reduced Jak/STAT signaling, activation of adenosine monophosphate-activated protein kinase, and antioxidant signaling	[87]
	Doxorubicin-induced cardiac fibrosis in rats	Both in vitro and vivo	The administration of DAPA could mitigate the Dox-elicited cardiotoxicity by reducing oxidative stress, mitochondrial	[88]

(*continued on next page*)

Table 2 (*continued*)

Fibrotic disease	Models	In vitro/in vivo	Effects and related mechanisms	Reference
			dysfunction, fibrosis, hypertrophy, and inflammation via PI3K/AKT/Nrf2 signaling.	
	Rabbit model of congestive heart failure induced by contraction of the aorta	In vitro	By inhibiting the TGF-β1/Smad signaling pathway	[89]
	Angiotensin II induces myocardial fibrosis in rats	Both in vitro and vivo	By regulating the TGF-β1/Smad signaling in a non-glucose-lowering dependent manner	[90]
	High-fat-fed induced myocardial hypertrophy and fibrosis in mice	Both in vitro and vivo	By reducing TGF-β2 expression in cardiomyocytes via the suppression of NHE-1 activity	[91]
	Human atrial fibroblasts	Both in vitro and vivo	Inhibiting NHE decreases the expression of phosphorylated PLC and IP3 production, thereby reducing ER Ca2+ release, extracellular Ca2+ entry, and the profibrotic activities of atrial fibroblasts.	[92]
	Coronary artery ligation induced myocardial infarction in rats	Both in vitro and vivo	Regulating excessive autophagy by inhibiting the activity of NHE1 in myocardial cells	[93]
	Aortic constriction surgery to induce cardiac hypertrophy in rats	In vivo	The downstream mechanistic target of the mTOR pathway, relevant for protein synthesis, cardiac hypertrophy, and adverse cardiac remodeling, was reduced by SGLT2 inhibition, alleviating ER stress and UPR providing a mechanism for abundant reduced left ventricular fibrosis.	[95]
	Human cardiac fibroblasts	In vivo	By weakening myofibroblast activity and cell-mediated collagen remodeling	[94]
Pulmonary fibrosis	Bleomycin-induced pulmonary fibrosis in mice	In vitro	Targeting oxidative stress, proinflammatory cytokines, apoptosis, and toll-like receptor 4 to ameliorate bleomycin-induced lung fibrosis	[102]
Peritoneal fibrosis	High-glucose dialysate treatment causes peritoneal fibrosis in mice	Both in vitro and vivo	Beneficial effects on the health of peritoneal and mesothelial cells in vivo and in vitro by inhibiting the expression of SGLT2 in the peritoneum	[107]

Abbreviation: NASH, Non-alcoholic steatohepatitis; OLETF, Obese diabetic Otsuka Long-Evans Tokushima fatty; LETO, Long-Evans Tokushima Otsuka; NAFLD, Non-alcoholic fatty liver disease; SGLT2, Sodium glucose cotransporter 2; CDAA, Choline-deficient L-amino acid; TG, Total triglyceride; T1DM, Type 1 diabetes; EMT, Epithelial-mesenchymal transition; SIRT3-FOXO3a, Sirtuin 3 - Forkhead box class O 3a; NMDA, N-methyl-D-aspartatic acid; I/R, Ischemia-reperfusion-induced; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; Ang II, Angiotensin II; CKD, Chronic kidney disease; mTOR, Mammalian target of rapamycin; CsA, Cyclosporine A; VEGF, vascular endothelial-derived growth factor; GLUT2, Glucose transporters 2; HIF-2α, Hypoxia-inducible factor 2α; STAT3, signal transducer and activator of transcription 3; SGK1, Serum and glucocorticoid regulated kinase 1; MyD88, Myeloid differentiation primary response 88; Nrf2/ARE, Nuclear factor E2-related factor 2/Antioxidant response elements; Jak/STAT, Janus kinase-Activator of transcription; PI3K/AKT/Nrf2, Phosphoinositide 3-kinase/Protein kinase B/Nuclear factor erythroid 2-related factor 2; TGF-β, transforming growth factor β; NHE, Sodium-hydrogen exchangers; PLC, Phospholipase C; IP3, Inositol 1,4,5-trisphosphate; IP3, Inositol 1,4,5-trisphosphate; ER, Endoplasmic reticulum; UPR, unfolded protein response.

Ethics approval and consent to participate Ethics approval and consent to participate

Not applicable.

Availability of data and material

The data and materials used in this review are publicly available.

Consent for publication

All the authors have read and approved the final version of the manuscript and given consent.

Data availability statement

Data included in article/supplementary material/referenced in article.

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Table 3
Summary of clinical anti-fibrotic effects of SGLT2 inhibitors.

Study	Disease	Country	Sample size (E/C)	Male, %	Age, year	Treatment	Duration	Primary outcomes
Shimizu et al. [113]	T2DM + NAFLD	Japan	33/24	60	E: 56.2 ± 11.5 C: 57.1 ± 13.8	E: dapagliflozin 5 mg qd C: standard treatment	24w	LSM, FIB-4 index, NAFLD fibrosis score
Taheri et al. [114].	NAFLD in the absence of T2DM	Iran	43/47	56	E: 43.8 ± 9.7 C: 44.1 ± 9.3	E: empagliflozin 10 mg qd C: placebo	24w	LSM,
Lee et al. [115]	T2DM	China	30/30	60	E: 56.9 ± 10.7 C: 60.6 ± 7.03	E: dapagliflozin 10 mg qd + insulin C: sitagliptin 100 mg qd + insulin	24w	LSM,
Chehrehgosha a 2021 [116]	T2DM + NAFLD	Iran	17/34	49	E: 50.5 ± 8.4 C: 52.5 ± 7.9	E: empagliflozin 10 mg qd C: pioglitazone 30 mg qd	24w	LSM,
Chehrehgosha b 2021 [116]	T2DM + NAFLD	Iran	18/37	43	E: 50.5 ± 8.4 C: 51.8 ± 7.8	E: empagliflozin 10 mg qd C: placebo	24w	LSM,
Takeshita. et al. [117]	T2DM + NAFLD	Japan	20/20	53	E: 59.0 (43.0–64.8) C: 50.5 (38.3–65.0)	E: tofogliflozin 20 mg qd C: glimepiride(1w 0.5 mg qd; 2-48w 6.0 mg qd)	48w	Hepatic histological scores、FIB-4 index
Takahashi. et al. [118]	T2DM + NAFLD	Japan	24/26	58	E: 59.0 (46.8–64.3) C: 50.0 (48.0–68.8)	E: Ipragliflozin 50 mg qd C: Enhanced lifestyle modification, including Antidiabetic agents except for SGLT2i, pioglitazone, and GLP-1 analog	72w	Hepatic histological scores
Hu et al. [119]	T2DM + NAFLD	China	30/30	78	E: 48.9 ± 10.6 C: 52.1 ± 10.2	E: dapagliflozin 50 mg qd C: metformin 0.5 g tid	12w	LSM,
Bellanti et al. [120]	T2DM	Italy	26/26	58	E: 60.6 ± 6.78 C: 63.4 ± 10.4	NA	6 m	FIB-4 index, NAFLD fibrosis score
Arai et al. [121]	T2DM + NAFLD	Japan	202/202	59	E: 56.0 (48.0–66.0) C: 56.0 (48.0–66.0)	NA	48w	FIB-4 index
Mason et al. [122]	T2DM	Canada	39/35	92	E: 62.0 ± 8.0 C: 64.0 ± 10.0	E:empagliflozin 10 mg qd C: placebo 10 mg qd	6 m	ECV
Tian et al. [123]	T2DM	China	68/68	60	NA	na	12w	UTGFβ1

Abbreviation: E, experimental group; C, control group; w, week; m, month; qd, once daily; tid, three times a day; qw, once a week; T2DM, type 2 diabetes mellitus; NAFLD, non-alcoholic fatty liver disease; LSM, liver stiffness measurement; CAP, controlled attenuation parameter; FIB-4, Fibrosis-4; ECV, Myocardial extracellular volume; UTGFβ1,urine transforming-growth-factor-beta 1.

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CRediT authorship contribution statement

Junpei Hu: Writing – review & editing, Writing – original draft. **Jianhui Teng:** Writing – original draft. **Shan Hui:** Writing – review & editing, Formal analysis. **Lihui Liang:** Writing – review & editing, Investigation, Funding acquisition.

Declaration of competing interest

The authors, Junpei Hu, Shan Hui, Jianhui Teng and Lihui Liang, declare that there are no conflicts of interest pertaining to the research conducted and the publication of the study titled "SGLT-2 Inhibitors as Novel Treatments of Multiple Organ Fibrosis" The authors have no financial or personal relationships with individuals or organizations that could influence the interpretation of the research findings. This statement attests that the research was conducted impartially and with scientific integrity.

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Abbreviation

SGLT-1: Sodium-glucose cotransporter 1
SGLT-2: Sodium-glucose cotransporter 2
SGLT2i: Sodium-glucose cotransporter 2 inhibitors
EMPA: Empagliflozin
CANA: Canagliflozin
DAPA: Dapagliflozin
FDA: Food and Drug Administration
ECM: Extracellular matrix
IR: Insulin resistance
CDAA: Choline-deficient L-amino acid
TNF-α:: Tumor necrosis factor alpha
IL-6: Interleukin 6
CCL2: C–C motif ligand 2
FIB-4: Fibrosis-4
NAFLD: Non-alcoholic fatty liver disease
T2DM: Type 2 diabetes
CKD: Chronic kidney disease
HK-2: Human proximal tubular
HIF-1α: Hypoxia-inducible factor-1α
IRI: Ischemia-reperfusion injury
NLRP3: NOD-, LRR- and pyrin domain-containing protein 3
STAT6: Transcription 6
GLUT2: Glucose transporters 2
TGF-β1: Transforming growth factor β-1
HIF-2α: Hypoxia-inducible factor 2α
STAT3: Signal transducer and activator of transcription 3
ASC: Apoptosis-associated speck-Like protein
SGK1: Serum and glucocorticoid regulated kinase 1
MyD88: Myeloid differentiation primary response 88
Nrf2: Nuclear factor erythroid 2-related factor 2
ARE: Antioxidant response elements
Jak: Janus kinase-Activator of transcription
PI3K: Phosphoinositide 3-kinase
AKT: Protein kinase B
TGF-β:: Transforming growth factor β
NHE: Sodium-hydrogen exchangers
ECV: Extracellular volume fraction
MF: Myocardial fibrosis
CAD: Coronary artery disease
PF: Pulmonary fibrosis
IPF: Idiopathic pulmonary fibrosis
BALF: Bronchoalveolar Lavage Fluid