INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Paper

SGLT2 Inhibitors as Antifibrotic Agents: Molecular Mechanisms and Therapeutic Potential in Cardiac and Renal Fibrosis Review article

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ARTICLE INFO

Published: 08 Sept 2026

Keywords:
SGLT2 inhibitors; Fibrosis; TGF-β/Smad signaling; PI3K/AKT/mTOR pathway; Oxidative stress; Myofibroblast; Renal fibrosis; Myocardial fibrosis; Extracellular matrix; Antifibrotic therapy

DOI:
10.5281/zenodo.22655398

ABSTRACT

Excessive extracellular matrix accumulation and increasing tissue dysfunction are the key features of fibrosis, a significant disease load in several organ systems. Even though it contributes to death worldwide, there are still few and poorly accepted treatment alternatives. Sodium-glucose cotransporter-2 (SGLT2) inhibitors which were initially designed as antidiabetic agents, have emerged as intriguing antifibrotic prospects. With a focus on TGF-β/Smad signalling, PI3K/AKT/mTOR activation, and oxidative stress, this review investigates the molecular mechanisms underlying fibrosis and how SGLT2 inhibitors modify these pathways to slow the progression of fibrosis in cardiac and renal tissues. Based on the evidence that is now available, SGLT2 inhibitors are a family of antifibrotic medicines that are therapeutically accessible, mechanistically versatile, and deserving of more research

INTRODUCTION

Extracellular matrix (ECM) components, particularly collagen, build up excessively in fibrosis, a pathological process that causes organ failure and tissue scarring. It typically arises as a result of oxidative stress, prolonged damage, chronic inflammation, or abnormal wound healing. After an injury, tissue repair typically returns the structure to normal. However, persistent fibroblast and myofibroblast activation in fibrosis leads to excessive deposition of collagen and other extracellular matrix proteins, resulting in stiffness and disruption of normal tissue architecture.The heart, liver, kidneys, lungs, and peritoneum are among the many organs that are impacted by this process. Fibrogenesis is often caused by common mechanisms such as autoimmune reactions, oxidative stress, cellular death, and chronic infections, although the pathogenic triggers vary by organ. Fibrosis has a dramatic effect on clinical outcomes, increasing

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

mortality and causing organ dysfunction, fibrotic diseases are responsible for roughly 45% of disease-related deaths. Due to ageing populations, environmental contaminants, and widespread epidemics, this frequency is probably even higher in poorer nations, making fibrosis a more prevalent problem. Only a few medications are available that only slightly slow the course of fibrosis, despite breakthroughs in our understanding of fibrosis processes and treatments. Patient compliance is frequently hampered by the side effects (such as nausea and gastrointestinal pain) and high cost of current medications, highlighting the critical need for innovative therapeutic approaches that target novel fibrosis mechanisms and pathways. In the field of anti-fibrotic research, sodium-glucose cotransporter 2 inhibitors (SGLT2i) have demonstrated to be effective and widespread use in the treatment of hyperglycemia. An increasing amount of evidence supports their potential as antifibrotic agents, making them a promising class for future fibrosis therapies 1.

Extracellular matrix (ECM) homeostasis and tissue structure are preserved by fibroblasts, which are diverse mesenchymal cells. Following tissue injury, they become activated into myofibroblasts, characterized by increased ECM production, stress fiber formation, and contractile activity. Persistent myofibroblast activation causes pathological fibrosis by excessive collagen deposition and tissue stiffening, whereas transitory stimulation promotes normal wound healing and tissue repair. Fibroblast–myofibroblast transition and fibrotic development are primarily regulated by mechanical variables like ECM stiffness and signalling pathways like transforming growth factor-β (TGF-β) 2.

By controlling fibroblast activation, ECM production, EMT, and several interrelated signalling pathways, TGF-β plays a critical role in the development and progression of fibrosis. Organ fibrosis and excessive tissue remodelling are caused by persistent stimulation of TGF-β signalling. The PI3K/AKT/mTOR pathway is a crucial molecular regulator of fibrosis and contributes to fibroblast activation, ECM accumulation, inflammation, and aberrant tissue remodelling. Therefore, targeting TGF-β-mediated pathways, particularly the Smad3/Smad7 balance, represents a promising therapeutic strategy for the management of fibrotic diseases3.

Fibrosis in the liver, kidney, lung and heart is linked to dysregulation of this signalling cascade. Thus, one intriguing therapeutic approach for preventing or treating fibrotic disorders is to target PI3K/AKT/mTOR signaling4.

One important pathogenic component in the growth and fibrosis of uterine fibroids is oxidative stress. Oxidative stress increases smooth muscle proliferation, inflammation, collagen production, and extracellular matrix buildup through ROS-mediated activation of PI3K/AKT/mTOR and TGF-β signalling pathways. Thus, focusing on oxidative stress and associated signalling pathways may offer promising treatment approaches to stop fibroid growth and lessen fibrosis5

A class of oral antidiabetic medications known as sodium-glucose cotransporter-2 (SGLT2) inhibitors was first created to treat type 2 diabetes mellitus by preventing renal glucose reabsorption and increasing urine glucose excretion. Empagliflozin, Dapagliflozin, and Canagliflozin are common agents. Because of its pleiotropic protective effects that go beyond glycaemic management, SGLT2 inhibitors have become a novel therapeutic approach for fibrosis in recent years. Their positive function in decreasing fibrosis in several organs, including as the heart, kidneys, liver, and lungs, has been shown in both experimental and clinical investigations. Both glucose-dependent and glucose-independent mechanisms, such as suppression of inflammatory

cytokines like TNF-α and IL-6, inhibition of NLRP3 inflammasome activation, reduction of oxidative stress through activation of antioxidant pathways like Nrf2, and attenuation of profibrotic TGF-β/Smad signalling, are responsible for the antifibrotic effects of SGLT2 inhibitors. These substances also enhance mitochondrial function, lower tissue hypoxia, control autophagy and cellular metabolism, and prevent the epithelial-mesenchymal transition (EMT), which limits collagen formation, fibroblast activation, and extracellular matrix deposition. When taken as a whole, these processes reduce the development of organ fibrosis and demonstrate the potential of SGLT2 inhibitors as antifibrotic drugs 6.

2. Cellular and Molecular Mechanisms of Fibrosis

2.1 Fibroblast Activation and the Myofibroblast Transition

Fibroblasts are diverse mesenchymal cells found in almost every connective tissue, where they carry out vital homeostatic functions like ECM component creation, remodelling, and destruction. Fibroblasts exhibit a non-activated state in the undamaged condition, preserving structural support without producing an excessive amount of matrix. However, fibroblasts experience a crucial phenotypic change into myofibroblasts after tissue damage, which is fuelled by a mix of soluble mediators, mechanical signals, and cell-cell interactions.Myofibroblasts differ from their precursor fibroblasts in a number of ways: they produce significantly more extracellular matrix (ECM) proteins, especially type I and type III collagen; they form prominent cytoplasmic stress fibres made of alpha-smooth muscle actin (α-SMA); and they acquire contractile activity that allows for physical remodelling of the surrounding matrix. These characteristics are ideal for the requirements of acute wound healing, where temporary myofibroblast activation promotes wound closure and temporary matrix deposition before the cells eventually suffer apoptosis as the healing process comes to an end.When activation turns from transient to permanent, the pathogenic aspect of myofibroblast biology becomes apparent.

Myofibroblasts in fibrotic illness remain in a chronically active state that sustains excessive collagen deposition, progressive matrix stiffness, and disruption of normal tissue architecture instead of going through planned cell death after the lesion has healed. The ECM's mechanical characteristics take part in a self-reinforcing cycle: fibroblasts pathways intensify profibrotic signalling as matrix stiffness rises, further promoting myofibroblast activation and collagen synthesis. A key aspect of fibrotic growth is the reciprocal interaction between matrix mechanics and cellular behaviour, which makes it a crucial target for therapeutic intervention 2.

2.2 TGF-β Signaling in Fibrogenesis

In almost every organ system, transforming growth factor-beta (TGF-β) plays a crucial role in the development and maintenance of fibrosis. It is the most powerful and well-studied profibrotic cytokine discovered to date. It can coordinate fibroblast activation, extracellular matrix (ECM) synthesis, epithelial-to-mesenchymal transition (EMT), and the inhibition of ECM-degrading enzymes, all of which simultaneously promote matrix production and prevent its clearance. Receptor-regulated Smad proteins, primarily Smad2 and Smad3, undergo nuclear translocation and phosphorylation as part of the classical signalling cascade that is started by TGF-β. The type I receptor is phosphorylated upon ligand attachment to the TGF-β type II receptor, which in turn phosphorylates Smad2 and Smad3. Together with the common mediator Smad4, these activated Smads form heteromeric complexes that

translocate to the nucleus and control the transcription of profibrotic target genes, such as those that encode collagen, fibronectin, and tissue inhibitor of metalloproteinases (TIMPs).The balance between Smad3, which drives profibrotic transcription, and Smad7, an inhibitory Smad that acts as a negative feedback regulator by targeting the TGF-β receptor complex for degradation, is a critical determinant of fibrotic outcome. Persistent TGF-β signaling is associated with suppression of Smad7 expression, shifting the Smad3/Smad7 balance in favour of sustained profibrotic gene activation.In addition to the canonical Smad pathway, TGF-β activates a number of non-Smad signalling cascades that promote fibrogenesis, such as the PI3K/AKT/mTOR axis, Rho-GTPase signalling and mitogen-activated protein kinase (MAPK) pathways. Beyond the direct transcriptional effects on ECM genes, these non-canonical pathways also amplify and diversify the profibrotic response, with TGF-β also impacting cell survival, proliferation, cytoskeletal architecture and metabolic reprogramming. The large number of downstream effectors of TGF-β explains the central role of this cytokine in fibrosis and the difficulty of targeting it therapeutically, since a broad inhibition of TGF-β activity risks compromising its essential functions in immune regulation and tissue homeostasis.Apart from the canonical Smad pathway, TGF-β also activates several non-Smad signalling cascades promoting fibrogenesis, such as the PI3K/AKT/mTOR axis, Rho-GTPase signalling and mitogen-activated protein kinase (MAPK) pathways. Besides direct transcriptional effects on ECM genes, TGF-β can also regulate cell survival, proliferation, cytoskeletal architecture and metabolic reprogramming. These non-canonical pathways contribute to, and diversify, the profibrotic response. TGF-β is important in fibrosis and hard to target therapeutically because of the many downstream effectors. This is due to the possible disruption of the essential role of TGF-β in immune modulation and tissue homeostasis via general TGF-β activity inhibition 3.

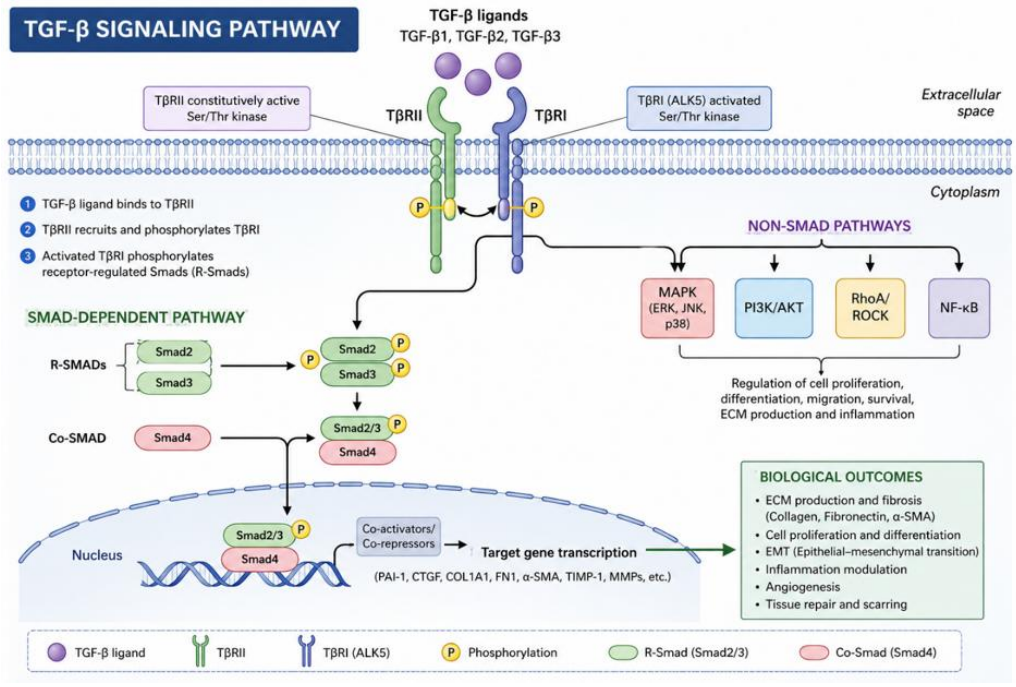

Figure 1 : Schematic Representation of the TGF-β Signalling Pathway and Its Role in Fibrosis

2.3 PI3K/AKT/mTOR Pathway Dysregulation

The phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) signalling pathway is another important molecular axis in the pathophysiology of fibrosis. This pathway combines diverse upstream signals such as growth factors, cytokines and mechanical cues to modulate fundamental cellular processes including survival, proliferation, protein synthesis and metabolism. Dysregulation of PI3K/AKT/mTOR signalling has been shown to be involved in fibroblast activation, ECM accumulation, inflammatory cytokine production and abnormal tissue remodelling in fibrotic disease of the liver, kidneys, lungs and heart.

Activated PI3K phosphorylates phosphatidylinositol-4,5-bisphosphate (PIP2) into phosphatidylinositol-3,4,5-trisphosphate (PIP3), which attracts AKT to the plasma membrane for phosphorylation and activation. Activated AKT phosphorylates and activates mTOR complex, which regulates protein synthesis via its downstream effectors S6 kinase 1 (S6K1) and eukaryotic initiation factor 4E-binding protein 1 (4EBP1). In the context of fibrosis, mTOR C1 activation promotes the translational machinery required for high-level collagen and extracellular matrix protein synthesis, and AKT activation promotes fibroblast survival and resistance to apoptosis, thus maintaining the myofibroblast population.

The PI3K/AKT/mTOR pathway and TGF-β signalling are not parallel but closely related. TGF-β can activate PI3K/AKT signalling through both Smad-dependent and Smad-independent pathways, and AKT can reciprocally modulate Smad activity, leading to complex cross-regulatory networks that enhance profibrotic outcomes. mTOR signalling also participates in the regulation of autophagy, a cellular degradation pathway that exerts a double, context-dependent function in fibrosis: autophagy may support myofibroblast differentiation under some conditions, whereas dysregulation of autophagy results in the accumulation of damaged organelles and the maintenance of cellular stress responses that sustain fibrogenesis4.

2.4 Oxidative Stress and Reactive Oxygen Species in Fibrosis

A common aspect of fibrotic disease in all organ systems is oxidative stress, which is defined as an imbalance between the generation of reactive oxygen species (ROS) and the ability of cellular antioxidant defence systems. NADPH oxidases, mitochondrial electron transport chain malfunction, and inflammatory cell activation are the main sources of ROS, which accumulate and cause fibrogenesis by a variety of convergent pathways.

At the molecular level, ROS serve as second messengers that intensify profibrotic cascades started by upstream stimuli by activating the TGF-β/Smad and PI3K/AKT/mTOR signalling pathways.

ROS simultaneously increase latent TGF-β activation and TGF-β expression, creating a positive feedback loop where profibrotic signalling and oxidative stress support each other. In addition to these pathway-level effects, ROS directly harm lipids, proteins, and DNA in cells, resulting in inflammatory reactions and cellular death that further promote matrix deposition and fibroblast activation. Because ROS-mediated activation of PI3K/AKT/mTOR and TGF-β signalling enhances smooth muscle cell proliferation, inflammatory mediator production, collagen synthesis, and ECM buildup, the involvement of oxidative stress in uterine fibroids has been particularly extensively characterised. Antioxidant pathways, especially the nuclear factor erythroid 2-related factor 2 (Nrf2) antioxidant response element system, are crucial

targets for antifibrotic intervention because the underlying role of oxidative stress in fibrogenesis is conserved throughout organ systems. Heme oxygenase-1 (HO-1), superoxide dismutase, and glutathione peroxidase are just a few of the cytoprotective and antioxidant enzymes that Nrf2, a transcription factor, activates to fight ROS buildup and the fibrogenic signals it produces5.

3. SGLT2 inhibitors: Pharmacology and Mechanisms of Action

3.1 Primary Pharmacological Mechanism

During the past few years there has been a lot of scientific and medical interest in a class of oral drugs called SGLT2 inhibitors (SGLT2i). Their origins lie in the research of the 1930's when it was found that phlorizin isolated from the bark of the roots of the apple tree had non-selective SGLT inhibitory activity. Later advances in medicinal chemistry allowed the modification of phlorizin, leading to development of several newer compounds collectively called SGLT2 inhibitors6. Sodium-glucose cotransporter 1 (SGLT-1) and sodium-glucose cotransporter 2 (SGLT-2) are expressed in the epithelial cells of the renal tubules and are mainly responsible for glucose reabsorption in the kidneys. These transporters mediate the reabsorption of the filtered glucose by the glomerulus, and SGLT-2 is mainly involved in the S1 and S2 segments of the proximal tubules and is responsible for approximately 90% of this reabsorption. On the other hand, SGLT-1 is mostly found in the kidneys and gastrointestinal tract and contributes a relatively small amount 7. The SGLT2 inhibitors competitively interact with the glucose-binding sites on the SGLT-2 proteins in the renal tubules, resulting in decreased reabsorption of glucose and increased excretion of glucose, salt and water in the urine. These results help to lower blood sugar levels and decrease fluid overload 8. Sotagliflozin inhibits both SGLT-1 and SGLT-2 transporters. Four highly selective SGLT-2 inhibitors have received FDA approval namely empagliflozin, canagliflozin, dapagliflozin and ertugliflozin9.

3.2 Pleiotropic Effects Beyond Glycemic Control

The identification of benefits of SGLT2 inhibitors beyond blood glucose lowering has changed their clinical profile and has led to a great deal of research into their mechanisms of action in non-diabetic settings. Investigation into the broader biological effects of these agents was prompted by large cardiovascular outcome trials, such as EMPA-REG OUTCOME, CANVAS, and DAPA-HF, which showed reductions in cardiovascular mortality, heart failure hospitalisation, and renal disease progression that could not be explained solely by improved glycaemic control.Pleiotropic effects of SGLT2 inhibitors on fibrosis include a variety of inter-related pathways. They inhibit activation of the NLRP3 inflammasome, a multi-protein complex that activates and releases the potent inflammatory mediators IL-1β and IL-18, and inhibit the production of pro-inflammatory cytokines like tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) thus decreasing systemic and tissue inflammation. They achieve this by activating the Nrf2 antioxidant pathway, which reduces ROS production and enhances cellular antioxidant capacity, thus reducing oxidative stress. They change mitochondrial function via increasing energy efficiency and decreasing mitochondrial ROS generation that contributes to oxidative stress and inflammatory signalling.They regulate autophagy and cellular metabolism in ways that may influence fibroblast survival and activation. In addition to this they reduce the transcriptional drive toward ECM synthesis and myofibroblast persistence by directly attenuating the TGF-β/Smad signalling pathway. Furthermore, SGLT2 inhibitors prevent

epithelial cells from undergoing epithelial-mesenchymal transition (EMT), which can result in activated fibroblasts in fibrotic tissue 10-19.

4. Antifibrotic Effects of SGLT2 inhibitors Across Organ Systems

4.1 Renal fibrosis

Most chronic kidney diseases (CKDs) lead to renal fibrosis, which is characterised by an increase in interstitial space due to myofibroblast proliferation and excessive production of extracellular matrix (ECM). Renal function, specifically glomerular filtration rate (GFR) is negatively correlated with the degree of interstitial fibrosis20.

Adult polycystic kidney disease is one of the many hereditary disorders that cause renal fibrosis, but mutations in podocyte- or glomerular-associated genes like APOL1, WT1, NPHS1 and COL4A3 also cause it. Additionally, genetic association studies have revealed polymorphisms in genes regulating the renin-angiotensin-aldosterone system, DNA repair, TGFβ and reactive oxygen species (ROS) signalling, endocytosis, autophagy, apoptosis, and WNT signalling pathways 21-23.

Tubular epithelial injury is a common mechanism among various kidney disorders, highlighting the significance of epithelial damage in the onset of fibrosis. Proteinuria can be caused by glomerular filtration barrier dysfunction, direct medication nephrotoxicity, hypoxia, diabetes, or genetic disorders. When damaged tubular epithelial cells dedifferentiate, adopt a flattened morphology, and express injury markers such as mesenchymal markers such as vimentin, a phenomenon known as partial epithelial–mesenchymal transition (EMT) occurs. Experimental and clinical studies have demonstrated that injured proximal tubular epithelial cells play a central role in promoting kidney fibrosis. These cells activate immune cells that further enhance fibrotic responses and stimulate fibroblasts and pericytes through epithelial–mesenchymal transition24.

In mouse models local fibroblasts and pericytes are the main source of renal myofibroblasts and endothelial cells and epithelial cells and immune cells contribute little to the myofibroblast population 25. The interaction of mesenchymal cells, immunological cells such as macrophages, and damaged proximal tubular epithelial cells are the primary cause of renal fibrosis 26. All the various experimental models of kidney fibrosis developed to explore possible treatment strategies are unable to mimic the complexity of renal fibrotic disease in humans.

4.1.1 Effects of SGLT-2 Inhibitors on Renal Fibrosis

In chronic kidney disease (CKD), SGLT-2 inhibitors (SGLT-2i) have shown renoprotective effects in hyperglycaemic states that result in renal fibrosis by elevating matrix protein synthesis, pro-fibrotic signalling and impairing extracellular matrix turnover 27,28. SGLT-2i decreases blood glucose and slows renal fibrosis progression29,30. In addition to their glucose-lowering properties, there is a growing body of pre-clinical evidence suggesting antifibrotic effects of SGLT-2i through different mechanisms including reduction of hypoxia and oxidative stress, inhibition of inflammatory responses, stimulation of autophagy, correction of metabolic derangements and maintenance of capillary integrity .

Renal fibrosis is thought to be mostly caused by hypoxia31. Research by Professor Judit Hodrea and associates shown that dapagliflozin (DAPA) can reduce tubulointerstitial fibrosis by changing the hypoxic response of renal tubular cells 32. Empagliflozin (EMPA) has been shown to inhibit renal fibrosis in human proximal tubular HK-2 cells by downregulating the expression of hypoxia-inducible factor-1α (HIF-1α)33. Oxidative stress also plays a crucial role in fibrotic

kidney injury, and several investigations have demonstrated that SGLT-2i reduce renal fibrosis by reducing oxidative stress levels 34-36.

Besides to this SGLT-2i exert anti-inflammatory effects that play a part in their protective role within the kidneys. For example, dapagliflozin inhibits the activation of the NOD-, LRR- and pyrin domain containing protein 3 (NLRP3) inflammasome in ischemia-reperfusion injury (IRI) models and thereby limits the development of fibrosis 37. In addition, SGLT-2i reduces the infiltration of inflammatory cells into renal tissue, particularly macrophages 38–40. Regulation of autophagy is another critical mechanism for their antifibrotic effects. Canagliflozin (CANA) has been shown to control autophagy through the signal transducer and activator of transcription 6 (STAT6) pathway41, while EMPA enhances renal function by modulating mitochondrial autophagy42.

Renal fibrosis is closely related to lipid toxicity and metabolic imbalance. Professor Zhang and colleagues discovered that SGLT-2i decreases the accumulation of lipids in renal tubular cells, which in turn slows the progression of fibrosis. These agents also prevent loss of the renal capillary network via a glucose transporter 2 (GLUT2)-dependent mechanism that inhibits endothelial cell loss and subsequent fibrosis following kidney injury. These results together highlight the different antifibrotic potential of SGLT-2 inhibitors in renal disease.

Transforming growth factor-β1 (TGF-β1) is a key cytokine in the pathogenesis of fibrosis. In a clinical study from Professor Tian and colleagues, SGLT2 inhibitors control renal TGF-β1 production and delay the progression of renal fibrosis. There are currently no clinical data, but several pre-clinical studies have shown the potential antifibrotic effects of SGLT2 inhibitors in kidney disease. A major drawback is the challenge of directly assessing renal fibrosis, because accurate measurement typically requires invasive procedures such as kidney biopsy.

Table 1 summarises the antifibrotic effects of SGLT2 inhibitors in models of renal fibrosis, emphasising the study types, experimental models, and key molecular pathways that contribute to the renoprotective effects of SGLT2 inhibitors.

Experimental models	Study type	Key findings	Reference
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	32
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	34
The I/R fibrosis mice model	Both in vitro and vivo	Prevented activation of NLRP3 inflammasome and protected the kidney against fibrosis development	36
Ang II-induced renal fibrosis in rats	In vitro	Caused by reduced inflammatory infiltration and unrelated to the regulation of elevated blood pressure	37

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.	38

4.2 Myocardial fibrosis

Myocardial fibrosis, defined as excessive accumulation of ECM proteins in the cardiac interstitium, is often associated with cardiac diseases. In the case of MI, fibrosis is reparative, replacing dead cardiomyocytes with collagen-rich scar tissue, to maintain structural integrity and prevent sequelae such as heart rupture. On the other hand, hypertension, ageing, obesity and diabetes are the main causes of interstitial fibrosis, increased myocardial stiffness, decreased ventricular compliance, diastolic dysfunction and heart failure with intact ejection fraction.

4.2.1 Mechanism of myocardial fibrosis

Diffuse myocardial fibrosis is characterised by the activation of cardiac fibroblasts which release collagen-processing enzymes, growth factors, cytokines and extracellular matrix proteins leading to over deposition of collagen and myocardial stiffening 47,48. Resident cardiac fibroblasts, key regulators of this process 49, have been hard to identify due to the absence of very specific markers. Lineage tracing and single cell transcriptomic studies have shown that fibroblasts are a heterogenous population with distinct embryological origins, anatomical locations and functional properties50-53. Differences in proliferation capacity and profibrotic signalling have been reported between atrial and ventricular fibroblasts and between left and right ventricular fibroblast populations 54,55.

Single-cell studies identified multiple fibroblast and myofibroblast subpopulations with differential expression of classical markers such as Col1a1, indicating functional diversity during cardiac injury and repair56-58. Activated fibroblasts proliferate, express more periostin, expand the endoplasmic reticulum and differentiate to myofibroblasts that express α-smooth muscle actin 59. The stimulated ECM-producing fibroblasts can contribute to fibrosis without full myofibroblast transition 59,60. Other sources of myofibroblasts have been suggested, including fibrocytes and endothelium or epicardial-derived mesenchymal cells; experimental data suggest that local fibroblasts are the predominant donors after pressure overload or myocardial infarction61.

The type of heart damage and the surrounding microenvironment determine the fibroblasts phenotypic and function62. While ischaemic injury causes dynamic inflammatory and reparative responses, pressure overload primarily generates an ECM-synthesizing program63. Fibroblasts identify DAMPs and release cytokines, chemokines, and MMPs during the inflammatory phase following myocardial infarction. Fibroblasts grow and actively produce extracellular matrix (ECM) during the proliferative phase, and they express collagen-crosslinking enzymes such LOXs during scar maturation. Following damage, both profibrotic and antifibrotic fibroblast subgroups were found by single-cell transcriptome analyses64,65. Fibroblasts may have protective functions in addition to their profibrotic activity by preventing cardiomyocyte damage, maintaining ECM structure, and reducing inflammation via the TGFβ–SMAD3 pathway66.

4.2.2 Role other cardiac cells

By producing cytokines, growth factors, and profibrotic mediators that activate cardiac fibroblasts and control ECM turnover, other cardiac cell types, such as cardiomyocytes, immune cells, endothelial cells, and lymphatic cells, contribute to widespread myocardial fibrosis67,68. A significant part is played by inflammation, with T cells and macrophages encouraging collagen deposition and fibroblast activation via mediators such TGFβ, IFNγ.Following damage, cardiac fibroblasts also react to DAMPs and inflammasome activation, especially NLRP3, which increases the production of IL-1β 69. By secreting TGFβ, LOXs, galectin 3-related factors, and MMP-containing exosomes70-82, stressed cardiomyocytes further promote fibrosis. By secreting TGFβ and endothelin 1, encouraging leukocyte recruitment via ICAM1, and causing hypoxia by capillary rarefaction83-89, endothelial cells make an indirect contribution.Lymphatic failure exacerbates diffuse myocardial fibrosis by causing oedema, mechanical stress, and chronic inflammation.

Inflammatory cytokines, growth factors, neurohumoral mediators, and mechanical stress all activate cardiac fibroblasts via pathways including integrins, MAPK90-95. Aldosterone and angiotensin II stimulate collagen synthesis, fibroblast proliferation, and myofibroblast differentiation96-101. TGFβ1 is a key profibrotic mediator that increases the expression of fibrogenic genes by activating conventional SMAD-dependent and non-canonical signalling pathways, including as MAPK, TAK1, and RHOA102-109. Fibroblast activation and ECM synthesis are further increased by non-coding RNAs, metabolic reprogramming, mitochondrial malfunction, and oxidative stress110-126. Age linked to diabetes and ageing increase profibrotic signalling and collagen crosslinking via RAGE127.

Procollagens, LOXs, MMPs, TIMPs, and other ECM-regulating substances that regulate collagen synthesis, maturation, and degradation are secreted by activated fibroblasts128-130. Myocardial stiffness and chronic fibrosis are caused by excess collagen deposition and crosslinking, which are mediated by elevated PCPs, PCPE1, LOXs. Collagen turnover and ventricular remodelling are similarly impacted by altered MMP–TIMP balance; in HFrEF, increased MMP activity is associated with myocardial dilatation and systolic dysfunction.

4.2.3 Effects of SGLT-2 Inhibitors on Cardiac Fibrosis

SGLT-2 inhibitors (SGLT2i) have shown significant therapeutic effects in lowering cardiovascular mortality and managing heart failure131,132. A growing body of research indicates that these substances have cardioprotective benefits by reducing heart fibrosis via a variety of mechanisms. Excessive cytokine production, cardiac fibroblast activation and proliferation, increased extracellular matrix deposition, and the buildup of fibrotic material in the myocardial interstitium and perivascular areas are all facilitated by persistent hyperglycemia. Heart function is hampered by these pathological alterations, which decrease myocardial flexibility. SGLT2i helps reduce cardiac fibrosis caused by hyperglycemia by enhancing glycaemic regulation 132,133.

Apart from their glucose-lowering activity, SGLT2i also reduce myocardial fibrosis through several glucose-independent mechanisms, including anti-inflammatory effects, attenuation of oxidative stress, modulation of autophagy, and metabolic regulation. These agents suppress myocardial inflammation and fibrosis through regulation of signaling pathways involving

Hypoxia-inducible factor-2α (HIF-2α)134, Signal transducer and activator of transcription 3 (STAT3)135, the NLRP3/Apoptosis-associated speck-like protein (ASC) inflammasome 136, Serum and glucocorticoid-regulated kinase 1 (SGK1) signaling 137, and NLRP3/Myeloid differentiation response related pathways138. In addition, SGLT2i alleviate oxidative stress and fibrotic remodeling through pathways such as nuclear factor erythroid 2-related factor 2 (Nrf2)/Antioxidant response element (ARE) signaling139, Janus kinase/Signal transducer and activator of transcription (JAK/STAT) signaling140, and the Phosphoinositide 3-kinase (PI3K)/Protein kinase B (AKT)/Nrf2 pathway 141.

By controlling fibroblast activation and autophagic processes through mechanisms linked to TGF-β/Smad signalling and sodium-hydrogen exchanger (NHE) pathways, SGLT2i further reduces myocardial fibrosis. Additionally, a 2022 study showed that SGLT2i decreased ventricular fibrosis in experimental animals via modifying the mTOR signalling system, indicating a new treatment approach to myocardial fibrosis142-148. The role of SGLT-2 inhibitors in reducing myocardial fibrosis has also been confirmed by clinical research. When evaluating cardiac fibrosis, extracellular volume fraction (ECV) is considered a crucial clinical indicator. Empagliflozin's effects on cardiac ECV were assessed in patients with type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD) in a recent study by Professor Mason and colleagues. After six months of treatment, the empagliflozin group showed a decrease in ECV compared to the placebo group, indicating improvement in cardiac fibrosis and ventricular remodelling 149.

A prevalent pathological outcome in many cardiovascular conditions, such as heart failure, myocardial infarction, and cardiomyopathy, is myocardial fibrosis. Reduction of cardiac fibrosis is a major factor in the therapeutic success of SGLT2i in these circumstances, as numerous clinical investigations have consistently demonstrated. However, because it requires sophisticated methods, including histological investigation, imaging techniques, and biomarker analysis, accurate diagnosis of cardiac fibrosis remains difficult. The development of relevant clinical research is nevertheless hampered by these methods complexity and expensive expense150-161.

Table 2: Experimental Models and Molecular Mechanisms of Emerging Therapeutic Targets in Myocardial Fibrosis.

Experimental models	Study type	Key findings	Reference
Coronary artery ligation-induced myocardial infarction in mice	Both in vitro and in vivo	Decreased cardiac fibrosis by modulating macrophage polarization through STAT3 signaling	149
Alloxan-induced diabetic myocardial fibrosis in rabbits	Both in vitro and in vivo	Improved left ventricular diastolic dysfunction and reduced fibrosis through regulation of SGK1 signaling	151
Doxorubicin-induced myocardial fibrosis in mice	Both in vitro and in vivo	Suppressed ferroptosis, fibrosis, apoptosis, and inflammation through NLRP3 and MyD88-related pathways, resulting in improved cardiac function	152

KK-Ay mice (genetic type 2 diabetes model)	In vitro	Reduced oxidative stress and fibrosis by inhibiting the TGF-β/Smad pathway and activating Nrf2/ARE signaling	153
Chronic myocardial ischemia induced by left circumflex artery constriction in Yorkshire swine	Both in vitro and in vivo	Attenuated fibrosis through suppression of Jak/STAT signaling, activation of AMPK, and enhancement of antioxidant signaling	154
Doxorubicin-induced cardiac fibrosis in rats	Both in vitro and in vivo	Reduced oxidative stress, mitochondrial dysfunction, fibrosis, hypertrophy, and inflammation through PI3K/AKT/Nrf2 signaling	155
Aortic constriction-induced congestive heart failure in rabbits	In vitro	Improved myocardial fibrosis by suppressing the TGF-β1/Smad signaling pathway	156
High-fat diet-induced myocardial hypertrophy and fibrosis in mice	Both in vitro and in vivo	Lowered TGF-β2 expression in cardiomyocytes through inhibition of NHE-1 activity	157
Human atrial fibroblasts	Both in vitro and in vivo	Inhibition of NHE reduced phosphorylated PLC expression and IP3 production, thereby decreasing ER Ca^{2+} release, extracellular Ca^{2+} influx, and profibrotic fibroblast activity	158
Coronary artery ligation-induced myocardial infarction in rats	Both in vitro and in vivo	Regulated excessive autophagy through inhibition of NHE1 activity in myocardial cells	159
Aortic constriction-induced cardiac hypertrophy in rats	In vivo	Reduced mTOR pathway activation, alleviated ER stress and unfolded protein response (UPR), and subsequently decreased left ventricular fibrosis and adverse cardiac remodelling	161

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HOW TO CITE: Shabna Rasheed, Dr. Rajalakshmi, SGLT2 Inhibitors as Antifibrotic Agents: Molecular Mechanisms and Therapeutic Potential in Cardiac and Renal Fibrosis Review article, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 9, 836-859, https://doi.org/10.5281/zenodo.22655398