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STATE-OF-THE-ART REVIEW

The Cardioprotective and Anticancer Effects of SGLT2 Inhibitors

JACC: CardioOncology State-of-the-Art Review

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ABSTRACT

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, originally approved for type 2 diabetes mellitus, have demonstrated efficacy in reducing cardiovascular events, particularly heart failure, in patients with and without diabetes. An intriguing research area involves exploring the potential application of SGLT2 inhibitors in cardio-oncology, aiming to mitigate the cardiovascular adverse events associated with anticancer treatments. These inhibitors present a unique dual nature, offering both cardioprotective effects and anticancer properties, conferring a double benefit for cardio-oncology patients. In this review, the authors first examine the established cardioprotective effects of SGLT2 inhibitors in heart failure and subsequently explore the existing body of evidence, including both preclinical and clinical studies, that supports the use of SGLT2 inhibitors in the context of cardio-oncology. The authors further discuss the mechanisms through which SGLT2 inhibitors protect against cardiovascular toxicity secondary to cancer treatment. Finally, they explore the potential anticancer effects of SGLT2 inhibitors along with their proposed mechanisms. (J Am Coll Cardiol CardioOnc 2024;6:159–182)

Sodium-glucose cotransporter-2 (SGLT2) inhibitors were originally developed to address type 2 diabetes mellitus (T2DM) by inhibiting glucose reabsorption in the renal proximal tubules.[1] Beyond SGLT2 inhibitors' glucose-lowering effects, extensive studies have highlighted their remarkable cardioprotective properties in patients, regardless of diabetes status.[2-6] Currently, 2 SGLT2 inhibitors, empagliflozin and dapagliflozin, have gained approval for treating heart failure (HF) with reduced ejection fraction and HF with preserved ejection fraction.[7-10] Emerging evidence suggests that SGLT2 inhibitors exert direct protective effects on the cardiovascular system, independently of glycemic control.[11] These effects encompass improved cardiac metabolism, reduced oxidative stress, modulation of neurohormonal pathways, attenuation of myocardial inflammation, and preservation of endothelial function.[12-14] Such multifaceted mechanisms underscore their potential as therapeutic agents in various cardiac conditions.

One area of particular interest involves exploring the potential protective effects of SGLT2 inhibitors in mitigating cancer treatment-related cardiotoxicity

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ABBREVIATIONS AND ACRONYMS

AKT = protein kinase B

AMPK = adenosine monophosphate-activated protein kinase

DOX = doxorubicin

ER = endoplasmic reticulum

ET = endothelin

HF = heart failure

LV = left ventricle/ventricular

mTOR = mammalian target of rapamycin

NLRP3 = nod-like receptor pyrin domain containing 3

NSCLC = non-small-cell lung cancer

PD-L1 = programmed cell death-ligand 1

SGLT2 = sodium-glucose cotransporter-2

T2DM = type 2 diabetes mellitus

and their role in cardio-oncology. Cardio-oncology is a clinical and scientific discipline that focuses on diagnosing, preventing, treating, and monitoring the cardiovascular consequences of cancer and its therapies.[15] With the growing number of cancer survivors and the ongoing use of cardiotoxic cancer therapies, such as anthracyclines, proteasome inhibitors, and tyrosine kinase inhibitors, there is a pressing need for cardioprotective strategies. A plethora of preclinical studies, along with a growing number of observational clinical studies, have suggested promising cardioprotective roles for SGLT2 inhibitors in mitigating cancer treatment-related cardiotoxicity.[16-21]

In the pursuit of improving the cardiovascular health of patients with cancer, it is crucial to develop cardioprotective agents that can effectively protect the heart without compromising the anticancer effects of cancer treatments. In this regard, several preclinical studies have demonstrated potential anticancer effects of SGLT2 inhibitors in various types of cancer, including breast, prostate, colorectal, and bladder cancer.[22-25] This growing preclinical evidence, highlighting the anticancer properties of SGLT2 inhibitors, further underscores their significance as promising cardioprotective agents against cancer therapy-related cardiotoxicity.

In this state-of-the-art review, we aim to underscore the potential role of SGLT2 inhibitors in cardio-oncology (**Central Illustration**). We begin with a discussion of the cardioprotective effects of SGLT2 inhibitors in HF. Next, we provide a comprehensive overview of the current preclinical research landscape and emerging clinical evidence pertaining to the use of SGLT2 inhibitors in cardio-oncology. We also discuss the mechanisms by which SGLT2 inhibitors may protect the cardiovascular system against the toxicity induced by cancer treatments. Finally, we explore the preclinical studies that demonstrate the potential anticancer effects of SGLT2 inhibitors, both as stand-alone therapies and in combination with other cancer treatments.

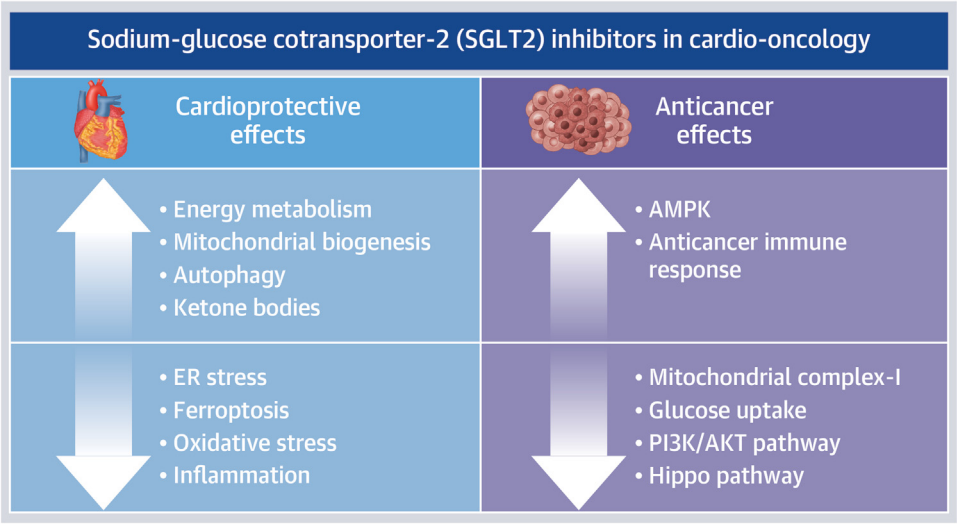
HIGHLIGHTS

- Observational studies suggest sodium-glucose cotransporter-2 (SGLT2) inhibitors protect from cardiotoxic chemotherapy.
- Preclinical studies show cardioprotective and anticancer effects of SGLT2 inhibitors.
- Randomized clinical trials are warranted to test SGLT2 inhibitors in cardio-oncology.

SGLT2 INHIBITORS IN HF

The serendipitous discovery of the cardioprotective effects of SGLT2 inhibitors originated from the EMPA-REG OUTCOME (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial. In this study, an unexpected 35% relative risk reduction in hospitalization for HF was observed in patients with T2DM and established cardiovascular disease treated with empagliflozin.[2] Further insights into the cardiovascular benefits of 2 more SGLT2 inhibitors, canagliflozin and dapagliflozin, were gained from comprehensive cardiovascular outcome trials: the CANVAS (Canagliflozin Cardiovascular Assessment Study) program, which focused on patients with T2DM and established cardiovascular disease, and DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events-Thrombolysis In Myocardial Infarction 58), which focused on patients with T2DM at risk for cardiovascular disease.[4,6] Both trials affirmed the benefits of SGLT2 inhibitors on hospitalization for HF, the composite of HF hospitalization or cardiovascular death, and renal composite outcomes. The clinical assessment of these agents extended to patients with HF as well as those with chronic kidney disease, regardless of their diabetic status. Both empagliflozin and dapagliflozin demonstrated efficacy in HF with reduced ejection fraction, as evidenced by reductions in the composite of HF hospitalization and cardiovascular death in the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction) and DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure) trials, respectively.[3,5] Finally, the use of empagliflozin and dapagliflozin, supported by the findings of the EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction)[26] and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure)[27] trials, respectively, was expanded to encompass the treatment of patients with HF with preserved ejection fraction. SGLT2 inhibitors also slowed the rate of kidney function deterioration while improving HF outcomes in patients with chronic kidney disease.[28-30]

CENTRAL ILLUSTRATION **The Role of SGLT2 Inhibitors in Cardio-Oncology**



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This illustration summarizes both the cardioprotective and the anticancer mechanisms of sodium-glucose cotransporter-2 (SGLT2) inhibitors. AMPK = adenosine monophosphate-activated protein kinase; ER = endoplasmic reticulum; PI3K = phosphoinositide 3-kinase.

These renal-protective effects may contribute to the overall effectiveness of SGLT2 inhibitors in patients with HF.

HIGHLIGHTS

- SGLT2 inhibitors, initially developed for diabetes, have emerged as a therapy for HF and chronic kidney disease.

SGLT2 INHIBITORS IN CARDIO-ONCOLOGY

CARDIO-ONCOLOGY. SGLT2 inhibitors, as previously discussed, have demonstrated improvement in cardiac outcomes in patients with HF, irrespective of diabetes. This suggests their potential role in cardio-oncology by improving cardiac outcomes in patients with cancer treated with cardiotoxic cancer therapies.

After recurrence of the primary cancer, cardiovascular disease emerges as the second leading cause of morbidity and mortality in cancer survivors.[31] Anticancer treatments are associated with serious cardiovascular adverse events, including HF, hypertension, arrhythmias, and coronary artery disease. Among these treatments, anthracyclines, widely used in the treatment of patients with various cancer types, posed the highest risk for cardiotoxicity.[32] Radiotherapy was associated with dose-dependent cardiac injury, potentially resulting in premature death because of ischemia, valvular disorders, or pericardial injury.[33] Trastuzumab caused cardiotoxicity of varying severity, ranging from asymptomatic decline in left ventricular (LV) ejection fraction to symptomatic HF, an effect that can worsen when combined with anthracyclines.[34] Patients undergoing cancer treatment with tyrosine kinase inhibitors such as sunitinib[35] and immune checkpoint inhibitors such as nivolumab and ipilimumab also experienced cardiovascular adverse effects, including hypertension and HF.[36] Similarly, carfilzomib was associated with hypertension, HF, and ischemia in more than 18% of patients.[37] Therefore, it is critical to discover new therapeutic agents capable of preventing and/or reversing the cardiovascular complications arising from cancer treatments, all while preserving the essential therapeutic benefits against cancer. SGLT2 inhibitors have demonstrated promising potential in this regard; this is further detailed in subsequent discussion.

CLINICAL STUDIES SUPPORTING THE USE OF SGLT2 INHIBITORS IN CARDIO-ONCOLOGY. Emerging clinical evidence from retrospective observational studies supports the use of SGLT2 inhibitors in patients with cancer undergoing potentially cardiotoxic therapies, especially doxorubicin (DOX) (Table 1). A recent observational retrospective cohort study

JACC: CARDIOONCOLOGY, VOL. 6, NO. 2, 2024
APRIL 2024:159–182

TABLE 1 Clinical Studies Supporting the Use of SGLT2 Inhibitors in Cardio-Oncology

First Author (Year)	Study Type	Population	Study Groups	Treatments	Key Findings
Gongora et al (2022)[16]	Observational retrospective cohort study	Patients with DM and cancer treated with anthracyclines, aged >18 y, and patients with prior HF	Cases (n = 32): patients with DM and cancer on SGLT2 inhibitors during anthracycline treatment Control (n = 96): patients with DM cancer on anthracycline treatment without SGLT2 inhibitors	CANA (34% [n = 11]), DAPA (16% [n = 5]), EMPA (50% [n = 16])	Patients on SGLT2 inhibitors had ↓ cardiac events after anthracycline therapy, including ↓ HF admissions and a ↓ rate of cardiac dysfunction No new cases of anthracycline-induced cardiac dysfunction were observed in patients taking SGLT2 inhibitors
Abdel-Qadir et al (2023)[18]	Observational population-based cohort study using medical records data sets	Patients aged ≥65 y with treated diabetes, no prior HF, receiving anthracycline-based chemotherapy for cancer	SGLT2 inhibitor–treated patients (n = 99) SGLT2 inhibitor–unexposed patients (n = 834)	CANA, DAPA, EMPA	SGLT2 inhibitor exposure ↓ risk of HF hospitalization, but no significant difference in incident HF diagnosis SGLT2 inhibitor use was associated with a statistically nonsignificant ↓ rate of mortality
Avula et al (2024)[38]	Retrospective cohort analysis of deidentified, aggregated patient data	Patients aged ≥18 y with histories of T2DM, cancer, and exposure to potentially cardiotoxic antineoplastic therapies, with subsequent diagnoses of cardiomyopathy or HF	Patients on SGLT2 inhibitors (n = 640) SGLT2 inhibitor–unexposed patients (n = 640), after propensity score matching	CANA, DAPA, EMPA	Patients on SGLT2 inhibitors had ↓ risk of acute HF exacerbation and all-cause mortality Less frequent all-cause hospitalizations or emergency department visits, atrial fibrillation/flutter, acute kidney injury, and need for renal replacement therapy in patients on SGLT2 inhibitors

CANA = canagliflozin; DAPA = dapagliflozin; DM = diabetes mellitus; EMPA = empagliflozin; HF = heart failure; SGLT2 = sodium-glucose cotransporter-2; T2DM = type 2 diabetes mellitus; ↑ = increase; ↓ = decrease.

investigated the effectiveness and safety of SGLT2 inhibitors in patients with cancer and diabetes mellitus who were treated with anthracyclines.[16] This study included 32 case patients on SGLT2 inhibitors during anthracycline treatment and 96 control patients treated with anthracyclines without SGLT2 inhibitors. The most common cancer type in both groups was lymphoma, followed by breast cancer. Over a median follow-up period of 1.5 years, SGLT2 inhibitors were associated with a lower rate of cardiac events, such as HF admissions and cardiomyopathy, compared with patients who did not receive SGLT2 inhibitors. Additionally, SGLT2 inhibitors appeared to be safe in this population, demonstrating improved overall mortality and lower rates of sepsis and neutropenic fever.

Similarly, a retrospective cohort study based on population data used administrative data sets encompassing individuals ≥65 years of age, treated for diabetes, and undergoing anthracycline treatment between 2016 and 2019.[18] During a median follow-up period of 1.6 years, the study included 933 patients, with 99 receiving SGLT2 inhibitors and 834 without SGLT2 inhibitors. The predominant cancer types in both groups were breast cancer and lymphoma. This study revealed that the use of SGLT2 inhibitors was associated with a lower rate of hospitalization for HF, but not incident HF, after anthracycline chemotherapy in older patients with cancer.

A recent retrospective study assessed the efficacy of SGLT2 inhibitors in patients experiencing cardiac dysfunction due to cancer therapy, including anthracyclines, alkylating agents, antimetabolites, monoclonal antibodies, tyrosine kinase inhibitors, proteasome inhibitors, and radiation therapy.[38] The study focused on patients ≥18 years of age with histories of T2DM, cancer, and exposure to potentially cardiotoxic antineoplastic therapies, with subsequent diagnoses of cardiomyopathy or HF between 2013 and 2020. The study cohort included 1,280 patients experiencing cardiac dysfunction or HF related to cancer therapy (640 in each group, categorized on the basis of SGLT2 inhibitor use). Hematologic cancer was the most common, followed by gastrointestinal cancer, breast cancer, and lymphoma. Over a 2-year follow-up period, patients on SGLT2 inhibitors exhibited a lower risk for acute HF exacerbation and all-cause mortality, along with fewer all-cause hospitalizations or emergency department visits, incidences of atrial fibrillation or flutter, acute kidney injury, and the need for renal replacement therapy.

These findings suggest that SGLT2 inhibitors may be beneficial in reducing the risk for cardiotoxicity in patients with cancer. Nevertheless, randomized clinical trials are needed to determine the efficacy and risks of SGLT2 inhibitors in mitigating cardiotoxicity for patients undergoing cardiotoxic therapies. To this end, the EMPACT (Empagliflozin in the Prevention of

TABLE 2 In Vivo Studies Demonstrating the Cardioprotective Effects of SGLT2 Inhibitors Against Cancer Treatment–Related Cardiotoxicity

First Author (Year)	Species/Strain	Anticancer Treatment	SGLT2 Inhibitor Treatment	Key Findings	Proposed Mechanisms
Oh et al (2019)[39]	Male C57BL/6J mice	DOX (15 mg/kg, single dose, i.p.) DOX (2.5 mg/kg every other day for 12 d, i.p.)	EMPA (0.03% in NCD)	↑ FS ↓ Hypertrophic pathologic changes Preserved LV mass ↓ Perivascular and interstitial fibrosis	↑ βOHB levels
Yang et al (2019)[40]	Male Sprague-Dawley rats with subtotal nephrectomy	DOX, CRS (7 mg/kg, once every 5 d for 20 d, i.p.)	EMPA (20 mg/kg/d, i.p., from day 24 after CRS induction)	↑ EF ↓ LV remodeling ↓ BNP	↓ NOX-1, NOX-2, and oxidized protein ↓ TNF-α, NF-κB, IL-1β, and MMP-9 ↓ Mitochondrial-Bax, cleaved caspase-3, and cleaved PARP ↓ TGF-β and Smad3 ↓ γ-H2AX, cytosolic cytochrome *c* ↑ Mitochondrial cytochrome *c*
Wang et al (2020)[41]	Male C57BL/6 mice	DOX (5 mg/kg, once per week for 4 wk, i.v. and i.p.)	EMPA (50 mg/kg/d in NCD for 5 wk, 1 wk before DOX)	↑ FS ↓ cTnT ↓ BNP ↑ Contractility, ↓ DNA damage ↓ Cardiac fibrosis	↑ Autophagic flux with ↑ in autophagosomes ↓ Accumulation of autolysosomes ↑ Beclin 1 in the heart ↑ TLR9 and SIRT3 in the heart ↑ Formation of beclin 1-TLR9-SIRT3 complex
Sabatino et al (2020)[17]	Male C57BL/6 mice	DOX (5 mg/kg per week for 5 wk, i.p.)	EMPA (10 mg/kg, daily for 5 wk, oral gavage)	Improved SBP and DBP ↑ FS, EF ↓ Myocardial fibrosis and remodeling ↓ cTnT	↓ ERK activity
Baris et al (2021)[42]	Male Sprague-Dawley rats	DOX (2.5 mg/kg every other day for 14 d, i.p.)	EMPA (10 mg/kg daily for 14 d, oral gavage)	↓ Prolongation of QT and QTc intervals ↑ EF, FS Preserved LVEDD and LVESD ↓ Myofibril loss	↑ Mitochondrial biogenesis probably by PGC-1α up-regulation
Quagliariello et al (2021)[43]	Female C57BL/6 mice	DOX (2.17 mg/kg/d for 7 d, i.p.)	EMPA (10 mg/kg/d, 3 d before DOX, oral gavage)	↑ EF, FS ↓ Cardiac fibrosis	↓ Ferroptosis and MDA content in the heart ↓ XO ↓ IL-1β, IL-6, and IL-8 cardiac expression ↓ MyD88 and NLRP3 ↓ Cardiac procollagen 1α1, MMP-9 ↓ Apoptosis
Chen (2023)[49]	Male Sprague-Dawley rats	DOX (2.5 mg/kg twice a week for 4 wk, i.p.)	EMPA (30 mg/kg/d for 4 wk, intragastric)	↓ LVEDD and LVESD, ↑ EF and FS ↓ CK-MB and NT-proBNP	↓ Oxidative stress (↑ SOD and CAT) ↑ Energy metabolism (↑ serum ATP/ADP) ↑ AMPK/SIRT1/PGC-1α pathway
Chang et al (2021)[44]	Male Sprague-Dawley diabetic rats	DOX (5 mg/kg/wk for 4 wk, i.p.)	DAPA (10 mg/kg/d for 6 wk, oral) followed by DOX	↑ EF, FS ↑ Survival ↓ Hemodynamic declines (+dP/dt) and (−dP/dt) ↓ Fibrosis	↓ ER stress (GRP78, PERK, eIF-2α, ATF-4, and CHOP) ↓ Apoptosis (Bax and cleaved caspase-3, ↑ Bcl-2)
Chang et al (2022)[46]	Male Sprague-Dawley rats	DOX (5 mg/kg/wk for 4 wk i.p.)	DAPA (10 mg/kg/d for 6 wk oral)	↑ Survival, ↑ EF, FS, ↓ myocardial fibrosis ↓ Hemodynamic changes (Ves, Ved ESPVR, +dP/dt, −dP/dt, and tau)	↓ Apoptosis (mechanisms in vitro)
Hsieh et al (2022)[47]	Male Sprague-Dawley rats	DOX (3 mg/kg for 4 wk, i.p.)	DAPA (0.1 mg/kg/d for 5 d for 4 wk, oral gavage)	↑ EF, FS	↓ Smad3, BNP, α-SMA, and phosphorylated p38 (mechanisms in vitro)

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Cardiotoxicity in Cancer Patients Undergoing Chemotherapy Based on Anthracyclines) trial, a randomized, multicenter, placebo-controlled, double-blind clinical trial (NCT05271162), is currently underway. This trial aims to determine the efficacy of empagliflozin in preventing LV systolic dysfunction in patients with cancer exposed to high cumulative doses of anthracyclines.

TABLE 2 Continued

First Author (Year)	Species/Strain	Anticancer Treatment	SGLT2 Inhibitor Treatment	Key Findings	Proposed Mechanisms
Belen et al (2022)[45]	Male Sprague-Dawley albino rats	DOX (2.5 mg/kg/d every other day, 6 doses, i.p.)	DAPA (1 mg/kg/d, oral gavage)		↓ cTnT, pro-BNP, TNF-α, FGF-21 levels
Kim et al (2022)[48]	C57BL/6J mice	DOX (15 mg/kg single dose, i.p.) DOX (2.5 mg/kg every 4 d for 24 d, cumulative dose, 15 mg/kg, i.p.)	DAPA (1 mg/kg/d, oral) + high ARNI (sacubitril/valsartan 68 mg/kg/d) or low ARNI (34 mg/kg/d) 1 d after DOX	DAPA + low ARNI was the best regarding improved survival rate, cardiac function, hemodynamic change, and kidney function ↑ EF, FS ↑ β-MHC and MyBPC3 ↓ NT-proANP ↓ ANP and BNP	Improved metabolic flexibility in DOX-injected heart through PPAR signaling pathway ↑ Genes related to fatty acid transport, fatty acid oxidation, ketogenesis, and gluconeogenesis-modulating metabolic pathway, including glucose, ketone bodies, and fatty acids
Hu et al (2023)[50]	Male C57BL/6 mice	DOX (5 mg/kg, once a week for 4 wk, i.p.)	DAPA (1.5 mg/kg/d for 4 wk, oral gavage)	↓ LVIDd and LVIDs, ↑ EF and FS ↓ Remodeling	↓ NLRP3 inflammasome ↓ Inflammatory markers (IL-6, IL-1β, and IL-18)
Satyam et al (2023)[51]	Female Wistar rats	DOX (20 mg/kg, single dose, i.p.)	DAPA (0.9 mg/kg/d for 8 d, oral gavage)	Reversed DOX ECG changes ↓ CK-MB, AST	
Quagliariello et al (2023)[52]	Female C57BL/6 mice	DOX (2.17 mg/kg for 10 d, i.p.)	DAPA (12 mg/kg/d, oral gavage)	↑ EF	↓ Cardiac NLRP3, MyD88, DAMPs, and NF-κB ↓ Inflammatory markers (IL-1β, IL-6, TNF-α, G-CSF, and GM-CSF) ↑ Phosphorylated AMPK ↓ Calgranulin S100 and galectine-3 ↓ Myocardial and renal NF-κB
Ulusan et al (2023)[53]	Male Wistar albino rats	DOX (2.15 mg/kg, every 3 d for 21 d, i.p.)	DAPA (10 mg/kg/d, oral gavage)	↑ EF ↓ Prolongation of QRS, QT	
Ren et al (2021)[20]	Male C57BL/6J	Sunitinib (40 mg/kg/d for 28 consecutive days, oral gavage)	EMPA (10 mg/kg/d for 28 consecutive days, oral gavage)	↓ HTN ↑ EF, FS Reversed left ventricular systolic and diastolic dysfunction ↑ CFR	↓ cTnT, pro-BNP levels Autophagy restoration ↑ AMPK-mTOR signaling pathway
Min et al (2023)[21]	Male C57BL/6J mice	Trastuzumab (10 mg/kg, once a week for 6 wk, i.p.)	EMPA (10 mg/kg twice per week for 6 wk, i.p.)	↑ EF, FS, ↓ LVESD Improved cardiomyocyte mechanical and intracellular dysfunction Preserved mitochondrial integrity and function	↓ Apoptosis, ferroptosis, DNA damage ↓ Oxidative stress ↓ Intracellular Ca^{2+} decay rate ↑ Mitochondrial biogenesis (PGC-1α)
Ali et al (2023)[19]	Wistar albino rats	Cisplatin (7 mg/kg, single dose, i.p.)	CANA (10 mg/kg/d, oral)	↓ AST, ALP, CK-MB, LDH	↑ Nrf2 ↓ NO, MPO ↓ iNOS, NF-κB, TNF-a, IL-1β ↑ PI3K/AKT pathway ↓ Bax, Bcl-2, cytochrome *c*

AKT = protein kinase B; ALP = alkaline phosphatase; α-SMA = α-smooth muscle actin; AMPK = adenosine monophosphate-activated protein kinase; ANP = atrial natriuretic peptide; ARN = angiotensin receptor neprilysin inhibitor; AST = aspartate aminotransferase; ATF-4 = activating transcription factor 4; Bax = Bcl-2-associated X protein; β-MHC = β-myosin heavy chain; βOHB = β-hydroxy butyrate; BNP = B-type natriuretic peptide; CAT = catalase; CFR = coronary flow reserve; CK-MB = creatine kinase MB; CRS = cardiorenal syndrome; cTnT = cardiac troponin T; DAMP = damage-associated molecular pattern; DOX = doxorubicin; ECG = electrocardiographic; EF = ejection fraction; eIF-2α = eukaryotic initiation factor 2α; ER = endoplasmic reticulum; ERK = extracellular signal-regulated kinase; FGF = fibroblast growth factor; FS = fractional shortening; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; GRP78 = glucose-regulated protein 78; HTN = hypertension; i.p. = intraperitoneally; IL = interleukin; IL = interleukin; IL = interleukin; iNOS = inducible nitric oxide synthase; LDH = lactate dehydrogenase; LV = left ventricle; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; LVIDd = left ventricular internal diameter at end-diastole; LVIDs = left ventricular internal diameter at end-systole; MDA = malondialdehyde; MMP = matrix metallopeptidase; MPO = myeloperoxidase; mTOR = mammalian target of rapamycin; MyBPC3 = myosin-binding protein C3; MyD88 = myeloid differentiation primary response 88; NCD = normal chow diet; NF-κB = nuclear factor kappa-B; NLRP3 = nod-like receptor protein 3; NO = nitric oxide; NOX-1 = NADPH oxidase 1; NOX-2 = NADPH oxidase 2; Nrf2 = nuclear factor erythroid 2-related factor 2; NT-proANP = N-terminal pro-atrial natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide; p38 = p38 mitogen-activated protein kinase; PARP = poly(adenosine diphosphate-ribose) polymerase; PERK = protein kinase R-like endoplasmic reticulum kinase; PGC = peroxisome proliferator-activated receptor-γ coactivator; PI3K = phosphoinositide 3-kinase; PPAR = peroxisome proliferator-activated receptor; QTc = corrected QT; SIRT1 = sirtuin 1; SIRT3 = sirtuin 3; Smad3 = mothers against decapentaplegic homolog 3; SOD = superoxide dismutase; TGF = transforming growth factor; TLR9 = Toll-like receptor 9; TNF = tumor necrosis factor; XO = xanthine oxidase; other abbreviations as in Table 1.

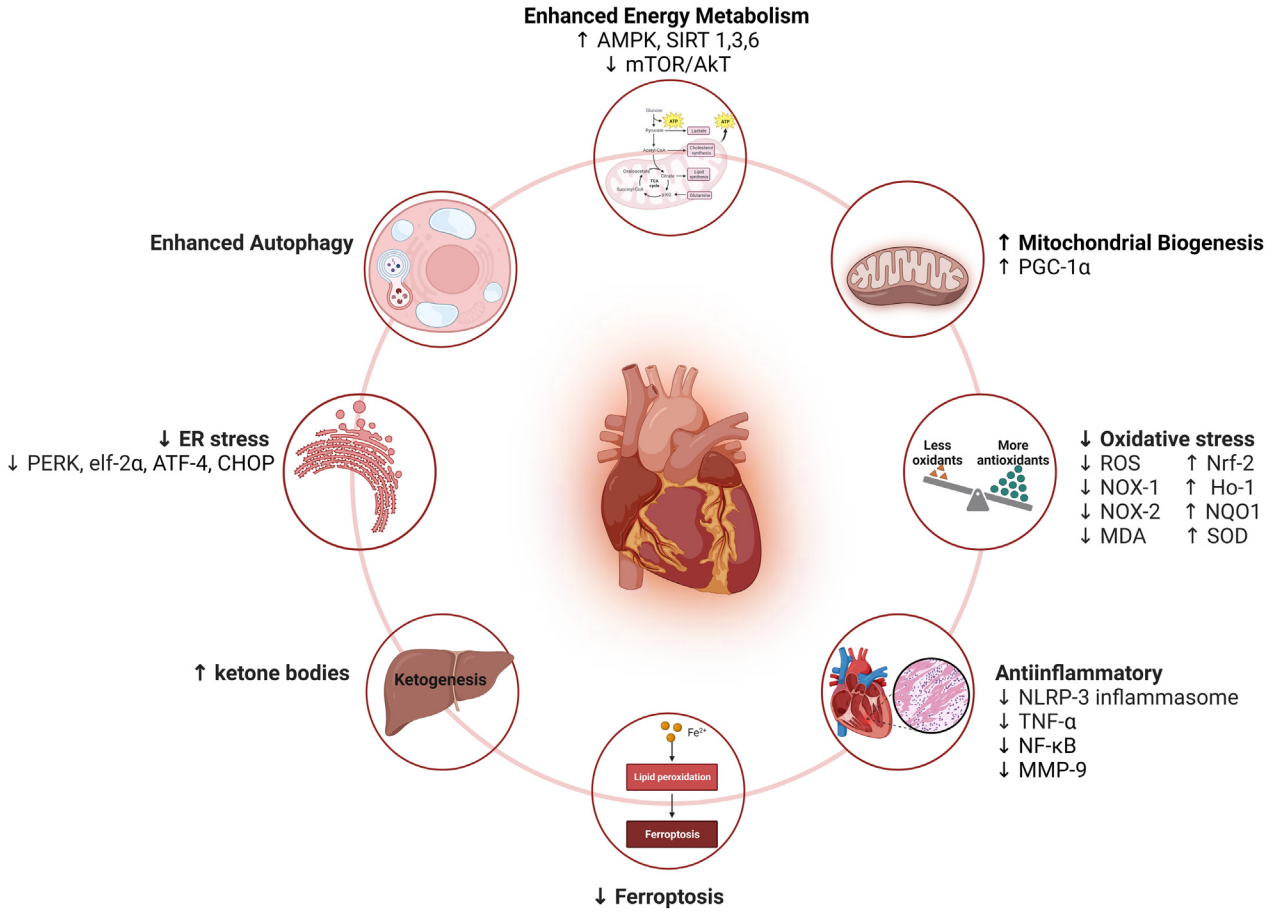
TABLE 3 In Vitro Studies Demonstrating the Cardioprotective Effects of SGLT2 Inhibitors Against Cancer Treatment–Related Cardiotoxicity

First Author (Year)	Cell Type	Anticancer Treatment	SGLT2 Inhibitor Treatment	Key Findings	Results and Proposed Mechanisms
Wang et al (2020)[41]	Isolated neonatal rat ventricular cardiomyocytes and AC16 human cardiomyocytes	DOX (1 μM for 24 h)	EMPA (200 nM)	EMPA protected cells from DOX-induced apoptosis	↑ Autophagic flux (↑ the LC3-II/LC3-I ratio) ↑ Binding of SIRT3 to the beclin 1-TLR9 complex through TLR9 ↓ ROS levels and DNA damage
Quagliariello et al (2021)[43]	HL-1 adult mouse cardiomyocytes	DOX (0.1-50 μM for 24 h) DOX (100 nM for 12 h)	EMPA (10, 50, 100, and 500 nM)	↑ Viability ↓ Apoptosis	↓ $[Ca^{2+}]i$ ↓ iROS, MDA 4-HNA, NO ↓ IL-8, IL-6, IL1-β ↓ Leukotrienes B4 ↓ p65/NF-κB ↓ MyD88 and NLRP3
Lin et al (2023)[82]	Isolated ventricular myocytes	DOX (1 μM for 120 min)	EMPA (1 μM 30 min before DOX)	↓ Contraction malfunction	↓ Mitochondrial ROS production ↓ Ca^{2+}-handling disorders by ↑ Ca^{2+} transients, ↓ Ca^{2+} transient decay time, ↓ frequency of Ca^{2+} sparks, and ↑ Ca^{2+} content in the sarcoplasmic reticulum ↓ Oxidation of Ca^{2+}/calmodulin-dependent protein kinase II (ox-CaMKII) and CaMKII-dependent phosphorylation of RyR2
Chang et al (2021)[44]	H9c2 rat cardiac myoblast	DOX (1 μM for 24 h) with high glucose	DAPA (10 μM 1 h before DOX)	↓ Apoptosis	↓ ROS generation ↓ ER stress
Chang et al (2022)[46]	H9c2 rat cardiac myoblast	DOX (1 μM for 24 h)	DAPA (10 μM 1 h before DOX)	↓ Apoptosis	↓ ROS ↑ STAT3 expression
Hsieh et al (2022)[47]	H9c2 rat cardiac myoblast	DOX (10 μM for 24 h)	DAPA (0-20 μM)	↓ Apoptosis ↑ Viability	↑ AKT/PI3K signaling ↑ Nrf2 nuclear translocation and activation ↑ Antioxidant HO-1, NQO1, and SOD activity ↓ Oxidative stress and mitochondrial dysfunction ↓ Smad3 activation ↓ ANP, BNP, collagen I, fibronectin, and α-SMA ↓ Fibrosis, inflammation ↓ p38 activation, nuclear NF-κB p65, IL-8
Hu et al (2023)[50]	H9c2 rat cardiac myoblast	DOX (5 μM for 24 h)	DAPA (5 μM)		↓ NLRP3 inflammasome ↓ Inflammatory markers (IL-6, IL-1β, and TNF-α) ↓ Phosphorylated p38, phosphorylated ERK, and TLR4
Quagliariello et al (2020)[55]	AC16 human cardiomyocytes	Ipilimumab (50-500 nM for 72 h) for cell viability, then 100 nM for 12 h	EMPA (500 nM)	EMPA under hyperglycemic conditions ↓ cardiotoxicity of ipilimumab with ↑ responsiveness to ipilimumab in breast cancer cell lines	↓ Leukotrienes type B4 production ↓ ROS production, MDA ↓ p65-NF-κB expression ↓ NLRP3 and MyD88 ↓ Cytokines and growth factors (IL-1β, IL-6, PDGF, VEGF, TGF-β)
Maurea et al (2021)[54]	Coculture model of hPBMCs and cardiomyocytes	Ipilimumab (200 nM for 72 h)	DAPA	↑ Viability	↓ $[Ca^{2+}]i$ ↓ Lipid peroxidation ↓ p65/NF-κB ↓ IL-8, IL-6, IL1-β ↓ NLRP3 inflammasome
Ren et al (2021)[20]	H9c2 rat cardiac myoblast	Sunitinib (1-20 μM for 48 h)	EMPA (50-1,000 nM for 48 h)	↑ Viability	Autophagy restoration Restored the AMPK/mTOR signaling pathway Inhibition of AMPK or autophagy abolished EMPA effects
Madonna et al (2022)[56]	HAECs	Ponatinib (1.7 nM) for 0-48 h	EMPA (100 or 500 nM) or DAPA (100 nM) for 0-48 h	EMPA ↑ the viability of cells exposed to ponatinib EMPA and DAPA ↓ the senescence of ponatinib-treated cells	EMPA ↑ autophagic flux EMPA and DAPA ↑ proangiogenic function of endothelial cells EMPA and DAPA ↓ senescence of cells exposed to ponatinib
Min et al (2023)[21]	Isolated neonatal mouse cardiomyocytes	Trastuzumab (2 μM for 8 h)	EMPA (1 μM)		↓ Lipid peroxidation ↓ Ferroptosis, DNA damage, cytosolic DNA accumulation
Dabour et al (2023)[57]	HUVECs and EA.hy926 cells	Carfilzomib (0.5 μM for 24 h)	CANA, DAPA, EMPA (1-20 μM) 2 h before carfilzomib	Only CANA protected endothelial cells	AMPK restoration

CaMKII = Ca^{2+}/calmodulin-dependent protein kinase II; $[Ca^{2+}]i$ = intracellular calcium; HAEC = human aortic endothelial cell; hPBMC = human peripheral blood mononuclear cell; HUVEC = human umbilical vein endothelial cell; iROS = intracellular reactive oxygen species; NQO1 = NAD(P)H quinone dehydrogenase 1; PDGF = platelet-derived growth factor; STAT3 = signal transducer and activator of transcription 3; TLR4 = Toll-like receptor 4; VEGF = vascular endothelial growth factor; other abbreviations as in Tables 1 and 2.

JACC: CARDIOONCOLOGY, VOL. 6, NO. 2, 2024
APRIL 2024:159–182

FIGURE 1 **Cardioprotective Mechanisms of SGLT2 Inhibitors Against Cancer Treatment–Induced Cardiotoxicity**



Sodium-glucose cotransporter-2 (SGLT2) inhibitors protect against cardiovascular toxicity induced by anticancer drugs via multiple mechanisms. They enhance energy metabolism by increasing the activation of nutrient deprivation pathways (adenosine monophosphate-activated protein kinase [AMPK] and sirtuin [SIRT] 1, SIRT3, and SIRT6) while inhibiting the nutrient surplus pathways (AKT/mammalian target of rapamycin [mTOR]), resulting in enhanced autophagy and increased mitochondrial biogenesis (peroxisome proliferator–activated receptor-γ coactivator-1α [PGC-1α]). Additionally, SGLT2 inhibitors mitigate oxidative and endoplasmic reticulum (ER) stress, block inflammatory pathways, inhibit ferroptosis, and enhance ketogenesis. Created using BioRender.com. ATF-4 = activating transcription factor 4; CHOP = C/EBP homologous protein; eIF-2α = eukaryotic initiation factor 2α; Ho-1 = heme oxygenase 1; MDA = malondialdehyde; MMP = matrix metalloproteinase; NLRP-3 = nod-like receptor pyrin domain containing 3; NF-κB = nuclear factor κB; NOX-1 = NADPH oxidase 1; NOX-2 = NADPH oxidase 2; Nrf-2 = nuclear factor erythroid 2–related factor 2; NQO1 = NAD(P)H quinone dehydrogenase 1; PERK = protein kinase R-like endoplasmic reticulum kinase; ROS = reactive oxygen species; SOD = superoxide dismutase; TNF = tumor necrosis factor.

HIGHLIGHTS

- Retrospective observational clinical studies suggest that SGLT2 inhibitors are associated with lower cardiac events and improved survival in patients with cancer receiving potentially cardiotoxic therapies.
- There is an important need for prospective randomized clinical trials to determine the safety and efficacy of leveraging SGLT2 inhibitors in cardio-oncology.

PRECLINICAL STUDIES SUPPORTING THE USE OF SGLT2 INHIBITORS IN CARDIO-ONCOLOGY. Subsequent to landmark studies demonstrating the cardioprotective effects of SGLT2 inhibitors in HF, numerous in vivo (**Table 2**) and in vitro (**Table 3**) studies, starting in 2019, have underscored the cardioprotective roles of SGLT2 inhibitors in mitigating cardiotoxicity induced by various cancer treatments, including DOX,[17,39-53] sunitinib,[20] trastuzumab,[21] cisplatin,[19] ipilmumab,[54,55] ponatinib,[56] and carfilzomib.[57] DOX has received particular

attention because of its status as the most cardiotoxic cancer treatment and its widespread use.[32] Researchers have investigated several models of DOX cardiotoxicity, including acute[39,42,43,48,51] and chronic[17,39,41,46-48] cardiotoxicity, cardiorenal syndrome,[40] and conditions involving diabetic[44] and nondiabetic rodents. Empagliflozin[17,20,21,39-43,49,55,56] and dapagliflozin[44-46,48,50-54,56] have emerged as the most commonly used SGLT2 inhibitors, followed by canagliflozin.[19,57] Notably, no in vivo studies have reported the protective effects of canagliflozin against DOX, with only 1 in vivo study reporting the cardioprotective effects of canagliflozin against cisplatin[19] and an in vitro study demonstrating its efficacy against carfilzomib.[57] In vitro studies involved different types of cardiomyocytes,[21,47] as well as human aortic[56] and human umbilical vein endothelial cells.[57]

Empagliflozin has demonstrated multifaceted cardioprotective effects against DOX cardiotoxicity,[39-43,49] preserving cardiac function and inhibiting LV remodeling.[40] This is evident through improvements in LV ejection fraction, fractional shortening,[39,41,43,49,50] and the preservation of LV end-diastolic dimension and LV end-systolic dimension.[49] Additionally, empagliflozin improved myocardial strain, and it reduced cardiac fibrosis in mice treated with DOX.[17] Empagliflozin effectively prevented DOX-induced hypertrophic pathologic changes and perivascular and interstitial fibrosis, preserving LV mass.[39] This protection was further strengthened by the prevention of DOX-induced prolongation of QT and corrected QT intervals.[42] Similarly, empagliflozin ameliorated sunitinib-induced hypertension and cardiac dysfunction, reversing LV systolic and diastolic dysfunction while restoring coronary flow reserve.[20] Administered alongside trastuzumab, empagliflozin preserved ejection fraction and fractional shortening and improved cardiomyocyte mechanical and intracellular function.[21]

Dapagliflozin also exhibited substantial cardioprotective effects against DOX cardiotoxicity.[44-48,50-53] Dapagliflozin improved ejection fraction and fractional shortening,[44,46-48,50,52,53] mitigated DOX-induced hemodynamic declines (+dP/dt and −dP/dt), and reduced LV internal dimensions at end-diastole and end-systole.[44,50] Additionally, it successfully reversed DOX-induced electrocardiographic changes.[51] Furthermore, both empagliflozin and dapagliflozin demonstrated the ability to decrease the senescence of human aortic endothelial cells exposed to ponatinib.[56] Intriguingly, only canagliflozin, not empagliflozin or dapagliflozin, protected endothelial cells from carfilzomib-induced apoptosis.[57]

The observed effects of SGLT2 inhibitors in reversing LV remodeling in animals treated with DOX align with recent clinical trials investigating the impact of SGLT2 inhibitors on LV remodeling, in which empagliflozin, in particular, led to favorable reverse LV remodeling in patients with HF with reduced ejection fraction, both with and without diabetes.[58-60] These particular effects of SGLT2 inhibitors may partially explain their beneficial impact on clinical outcomes in patients with HF. In addition, a systematic review of 5 randomized controlled trials showed that SGLT2 inhibitors were associated with LV mass regression compared with placebo.[61]

HIGHLIGHTS

- An extensive body of preclinical studies demonstrate the cardioprotective effects of SGLT2 inhibitors in preventing cardiotoxicity secondary to various cancer treatments.

THE MOLECULAR MECHANISMS OF THE CARDIOPROTECTIVE EFFECTS OF SGLT2 INHIBITORS AGAINST CANCER TREATMENT–RELATED CARDIOTOXICITY

The molecular mechanisms underlying the protective effects of SGLT2 inhibitors against cancer treatment-related cardiotoxicity are multifactorial. In this section, we summarize the mechanisms that may contribute to the benefits of SGLT2 inhibitors in mitigating cardiotoxicity secondary to cancer treatment, emphasizing both direct and indirect myocardial effects related to inflammation, energetics, autophagic flux, oxidative and endoplasmic reticulum (ER) stress, ferroptosis, and endothelin-1 (ET-1) (**Figure 1**).

ANTI-INFLAMMATORY EFFECTS OF SGLT2 INHIBITORS. Inflammation played a central role in the onset and progression of HF, perpetuating a chronic and vicious cycle between inflammation and cardiac dysfunction.[62] This inflammatory process has been implicated in the mechanisms that underlie cardiotoxicity secondary to cancer therapy and radiotherapy.[63,64] Specifically, in DOX-induced HF, inflammation played a central role in both its onset and progression.[65] DOX triggered inflammatory responses by upregulating the levels of various inflammatory mediators, including interleukin-1 and tumor necrosis factor-α in the heart, activating immune responses, subsequently leading to cardiomyocyte damage.[66] In addition, DOX activated the nod-like receptor pyrin

domain containing 3 (NLRP3) inflammasome in cardiomyocytes, promoting cardiomyocyte apoptosis and cardiac remodeling and ultimately contributing to the development of HF.[67]

SGLT2 inhibitors exhibited considerable potential as anti-inflammatory agents, using indirect mechanisms that involve metabolic improvement, stress reduction, and direct modulation of inflammatory signaling pathways. These effects, which are largely independent of glucose levels, have established their clinical role in patients with HF, regardless of the presence of diabetes.[12] SGLT2 inhibitors have been shown to mitigate cardiac inflammation and fibrosis by modulating the activation of nuclear factor κB and the NLRP3 inflammasome, thereby attenuating the synthesis of proinflammatory cytokines.[12] Several studies have demonstrated the protective effects of SGLT2 inhibitors against DOX-induced myocardial inflammation.[40,43,45,47,50,52] In these studies, SGLT2 inhibitors effectively attenuated the inflammatory response, as indicated by reduced levels of cytokines, including tumor necrosis factor-α and interleukins. For example, early administration of empagliflozin resulted in reduced myocardial inflammatory mediators (tumor necrosis factor-α, nuclear factor κB, interleukin-1β, and matrix metalloproteinase 9) in a model of DOX-induced cardiorenal syndrome.[40] Additionally, empagliflozin[43] and dapagliflozin[45,50,52] consistently mitigated the expression of NLRP3 inflammasome and proinflammatory cytokines, demonstrated in both in vivo and in vitro settings across acute and chronic models of DOX cardiotoxicity. Furthermore, dapagliflozin protected H9c2 rat cardiomyoblasts from DOX-induced cytotoxicity by inhibiting the Toll-like receptor 4/NLRP3/nuclear factor κB inflammatory circuit.[50]

Similarly, empagliflozin attenuated the activation of NLRP3 inflammasome and proinflammatory cytokines in response to ipilimumab cardiotoxicity in AC16 human cardiomyocytes.[55] Dapagliflozin showed similar attenuation in vitro in response to trastuzumab and ipilimumab cardiotoxicity.[54] Recently, canagliflozin counteracted cisplatin-induced cardiotoxicity by reducing levels of nuclear factor κB, myeloperoxidase, inducible nitric oxide synthase, tumor necrosis factor-α, and interleukin-1β.[19]

The reported anti-inflammatory effects against cancer therapy–related cardiotoxicity are consistent with similar effects observed in other models of cardiometabolic diseases. Empagliflozin inhibited the expression and activation of nuclear factor κB in human cardiomyocytes exposed to high glucose concentrations.[68] Additionally, both empagliflozin and dapagliflozin attenuated cardiac dysfunction in mice with HF, irrespective of the presence or absence of diabetes, by mitigating the activity of the NLRP3 inflammasome.[69,70] Moreover, canagliflozin ameliorated the NLRP3 inflammasome-mediated release of cytokines in an experimental model of autoimmune myocarditis in mice.[71]

Although empagliflozin inhibited the activation of the NLRP3 inflammasome in macrophages of patients with T2DM,[72] it did not exhibit significant alterations in inflammatory biomarkers, including plasma high-sensitivity C-reactive protein and midregional proadrenomedullin, as observed in some human studies involving patients with HF with reduced ejection fraction.[59,73] This discrepancy may have been attributed to the difference in the assessment of inflammation, with clinical studies reporting at the blood level and preclinical studies measuring inflammatory markers at the tissue level.

ANTIOXIDANT EFFECTS OF SGLT2 INHIBITORS. Strong evidence demonstrates that chemotherapy- and radiotherapy-induced cardiotoxicity involved the generation of reactive oxygen species and increased cellular oxidative stress.[74,75] Particularly, DOX cardiotoxicity was associated with oxidative stress arising from an imbalance between reactive oxygen species and antioxidants.[67]

SGLT2 inhibitors have been shown to attenuate the generation of reactive oxygen species and enhance antioxidant mechanisms in various experimental models, including diabetic mice hearts,[76] cardiomyocytes isolated from mice exposed to a high-fat diet,[77] isolated murine cardiomyocytes undergoing hypoxia and reoxygenation,[78] a nondiabetic mouse model of pressure overload-induced HF,[79] and LV myocardial biopsies from patients with HF with preserved ejection fraction.[80]

In alignment with these findings, empagliflozin inhibited DOX-induced oxidative stress in a cardiorenal syndrome model by inhibiting NADPH oxidase 1, NADPH oxidase 2, and oxidized protein.[40] It also enhanced the activity of antioxidant enzymes in DOX-treated rats.[49] Furthermore, empagliflozin decreased malondialdehyde content in the heart, especially in the cardiac mitochondria, and reduced cardiac xanthine oxidase,[43] which is deeply involved in DOX-induced oxidative stress and cardiotoxicity.[81] Moreover, empagliflozin effectively mitigated DOX-induced mitochondrial reactive oxygen species production in isolated cardiomyocytes.[82]

Similarly, dapagliflozin has demonstrated similar effects on DOX-induced oxidative stress in H9c2 cardiomyoblasts.[44,47] Dapagliflozin rescued DOX-inhibited antioxidant (heme oxygenase 1, NAD[P]H

TABLE 4 In Vitro Studies Demonstrating the Anticancer Effects of SGLT2 Inhibitors

First Author (Year)	Cancer Type	Cell Type	SGLT2i Treatment	Key Finding	Results and Proposed Mechanism
Villani et al (2016)[24]	Prostate, lung, liver, breast cancer	Prostate (PC3, 22RV-1), lung (A549, H1299), liver (HepG2), and breast (MCF7) cancer cells	CANA DAPA (0-100 μM)	Only CANA at clinically relevant concentrations ↓ proliferation and clonogenic survival of cancer cells alone and in combination with cytotoxic therapies	CANA: ↓ Glucose uptake, mitochondrial complex I–supported respiration ↓ ATP and lipogenesis ↑ Phosphorylation of AMPK
Li et al (2017)[136]	Resistant NSCLC	HCC827, H1975 carrying specific EGFR mutations	CANA (0-100 μM)	↓ Growth of NSCLC cell lines	↑ Apoptosis ↓ EGFR phosphorylation ↓ Phosphorylation of Akt and ERK
Kuang et al (2017)[141]	RCC	ACHN, A498, and CaKi-1	DAPA (0-4 μM)	↓ Cell growth in a dose- and time-dependent manner	↑ G1 phase arrest ↑ Apoptosis ↓ SGLT2 expression and glucose uptake
Kaji et al (2018)[129]	HCC	Huh7 and HepG2 cells	CANA (10 μM)	↓ Liver cancer cell growth and angiogenic activity	↓ Glycolytic metabolism ↑ G2/M arrest and apoptosis ↓ Phosphorylation of ERK, p38, and AKT
Hung et al (2019)[130]	HCC	Huh-7 and Hep3B	CANA (0-50 μM)	↓ Growth of HCC cells	↓ Expression of β-catenin ↑ Proteasomal degradation of β-catenin protein by ↑ phosphorylation of β-catenin Direct inhibition of PP2A activity
Nasiri et al (2019)[23]	Breast and colon cancer	E0771 breast tumors and MC38 colon tumors	CANA DAPA (5 μM and 5 mM)	↓ Cancer cell growth rate	CANA ↓ both glucose uptake and oxidation at clinically relevant concentrations (5 μM) DAPA did not alter glucose uptake or tumor cell division at clinically relevant concentrations (0.5 μM) but did at a supraphysiologic concentration (5 mM)
Nakano et al (2020)[25]	HCC	Huh7 and HepG2	CANA (3 μM, 10 μM)	↓ Proliferation of HCC cells	Regulating metabolic reprogramming (alterations in metabolism of mitochondrial oxidative phosphorylation, fatty acid, and purine and pyrimidine) ↓ ATP synthase F1 subunit α Altered phosphorylation of AMPK
Zhou et al (2020)[143]	Breast cancer	MCF-7, ZR-75-1	CANA DAPA (0, 3.3, 11, 33, 100, 300 μM)	Both ↓ human breast cancer cells proliferation and growth	↑ Phosphorylation of AMPK ↓ Phosphorylation of p70S6K Cell cycle arrest in G1/GO phase ↑ Cell apoptosis (AMPK-mediated cell cycle arrest and apoptosis)
Xu et al (2020)[133]	Pancreatic cancer	Capan-1 and PANC-1	CANA (20, 40, 60 and 80 μM)	↓ Pancreatic cancer cell proliferation and colony formation	↑ Apoptosis ↓ Glycolysis via the PI3K/AKT/mTOR pathway
Xie et al (2020)[140]	Cervical cancer	HeLa and C33A	EMPA (50 μM)	↓ Migration of cervical cancer cells and ↑ apoptosis	↑ AMPK/FOXA1 pathway and ↓ expression of Shh
Komatsu et al (2020)[144]	Breast cancer	MCF-7 cells	IPRA (1–50 μM)	↓ Breast cancer cell proliferation	SGLT2 inhibition-dependent hyperpolarization of MCF-7 cell membrane Mitochondrial membrane instability ↓ DNA synthesis at high dose
Papadopoli et al (2021)[145]	Breast cancer	MCF7, SKBR3 and BT-474, NT2197	CANA DAPA (25, 50 μM)	CANA ↓ proliferation of breast cancer cell lines DAPA showed modest effect	Antiproliferative effects were not affected by glucose availability or the level of expression of SGLT2 ↓ Mitochondrial respiration and total ATP production ↓ Glutamine metabolism
Ren et al (2021)[134]	Pancreatic cancer	PANC-1 and BxPC-3	CANA (1 μM) SOTA (3 nM)	↓ Proliferation and invasion of pancreatic cancer cells	↓ Hippo pathway ↓ YAP1 expression
Yamamoto et al (2021)[137]	Lung cancer	A549, H1975, and H520	CANA (1-50 μM)	↓ Growth of cells in a dose-dependent manner	↓ DNA synthesis ↓ S phase entry (induced G1 arrest) ↓ ERK and MAPK phosphorylation Did not induce apoptosis Tumor weight was not decreased by CANA in vivo

Continued on the next page

TABLE 4 Continued

First Author (Year)	Cancer Type	Cell Type	SGLT2i Treatment	Key Finding	Results and Proposed Mechanism
Wu et al (2022)[22]	Osteosarcoma	MNNG/HOS and MG-63	CANA (0.5, 1, or 2 μM)	↓ Osteosarcoma progression	Inducing immune cell infiltration ↑ STING/IRF3/IFN-β pathway ↓ AKT pathway
Wang et al (2022)[142]	Papillary thyroid cancer	TPC-1 and BCPAP	CANA (10 μM) DAPA (0, 20, 40, 80 μM)	↓ Thyroid cancer cells growth in a dose- and time-dependent manner DAPA ↓ proliferation of the same cells	(Mechanisms only done with CANA) Dependent on SGLT2 expression ↓ Invasion of thyroid cancer cell ↓ Glucose uptake ↓ glycolysis ↑ AMPK pathway ↓ AKT/mTOR pathway ↑ Cell cycle arrest at G1/S checkpoint ↑ DNA damage and ATM/CHK2 pathway activation ↑ Apoptosis
Shoda et al (2023)[132]	Glioblastoma	U251MG (human), U87MG (human), and GL261 (murine)	CANA (40 μM)	↓ Glioblastoma cell proliferation	Dependent on SGLT2 expression ↓ Glucose uptake ↑ AMPK phosphorylation ↓ p70S6K phosphorylation
Ding et al (2023)[139]	NSCLC, ovarian, pancreatic cancers	H292, SKOV3, MIA PaCa-2, primary NSCLC, ovarian and pancreatic cancer patient-derived cancer cells	CANA (20 μM)	SGLT2 is a positive regulator of PD-L1 (the interaction between SGLT2 and PD-L1 on the cell membrane is required for maintaining PD-L1 protein)	↓ PD-L1 protein expression ↑ Proteasomal degradation of PD-L1
Biziotis et al (2023)[148]	Human adenocarcinoma, squamous cell, NSCLC	Human adenocarcinoma (A549, H1299 and H1975), squamous cell (SK-MES-1), and large cell (H460) NSCLC cells	CANA (5-30 μM)	↓ Proliferation of all cell lines ↓ Clonogenic potential of A549, H1299, and H1975 cells	↓ Oxygen consumption rate ↑ Extracellular acidification rate ↑ AMPK activity ↓ mTOR activity ↓ (MAPK) ERK1/2 ↓ HIF-1α ↓ HDAC2

ATP = adenosine triphosphate; EGFR = epidermal growth factor receptor; FOXA1 = forkhead box A1; HCC = hepatocellular carcinoma; HDAC2 = histone deacetylase 2; HIF-1α = hypoxia-inducible factor-1α; IFN = interferon; IPRA = ipragliflozin; IRF3 = interferon regulatory factor 3; MAPK = mitogen-activated protein kinase; NSCLC = non-small-cell lung cancer; PD-L1 = programmed cell death-ligand 1; PP2A = protein phosphatase 2A; Shh = sonic hedgehog signaling molecule; SOTA = sotagliflozin; STING = stimulator of interferon genes; YAP1 = YES-associated protein 1; other abbreviations as in Tables 1 and 2.

quinone dehydrogenase 1, and superoxide dismutase) activity and improved mitochondrial function via nuclear factor erythroid 2-related factor 2.[47] Dapagliflozin prevented DOX-inhibited nuclear factor erythroid 2-related factor 2 nuclear translocation, and hence the expression of the nuclear factor erythroid 2-related factor 2-dependent antioxidant enzymes, including heme oxygenase 1 and NAD(P)H quinone dehydrogenase 1.[47]

Empagliflozin additionally counteracted oxidative stress induced by trastuzumab in vivo and, in isolated neonatal mouse cardiomyocytes, ameliorated DNA damage.[21] In AC16 human cardiomyocytes, empagliflozin reduced the cardiotoxicity of ipilimumab by reducing reactive oxygen species production and lipid peroxidation.[55] Furthermore, dapagliflozin protected human cardiomyocytes from ipilimumab cytotoxicity by reducing lipid peroxidation and intracellular calcium overload.[54] Canagliflozin exhibited a cardioprotective effect against cisplatin-induced acute cardiotoxicity through the regulation of nuclear factor erythroid 2-related factor 2 expression.[19]

MITIGATING ER STRESS. Mitochondrial and ER stresses both played critical roles in DOX cardiotoxicity through a mutual interaction.[83] SGLT2 inhibitors have shown their potential to mitigate ER stress, which is particularly relevant in the treatment of cardiovascular events. Chang et al[44] reported that dapagliflozin protected against DOX cardiotoxicity in diabetic rats and H9c2 cardiomyoblasts by reducing ER stress, as evidenced by the decreased expression of the ER-related proteins, including glucose-regulated protein 78, protein kinase R-like endoplasmic reticulum kinase, eukaryotic initiation factor 2α, activating transcription factor 4, and C/EBP homologous protein.[44] SGLT2 inhibitors have shown similar findings in other cardiovascular disease models. In cardiomyocytes treated with angiotensin II, dapagliflozin has shown the ability to inhibit the protein kinase R-like endoplasmic reticulum kinase-eukaryotic initiation factor 2α-C/EBP homologous protein axis of the ER stress response via the activation of sirtuin 1.[84] Additionally, empagliflozin attenuated myocardial ischemia-reperfusion injury and cardiomyocyte apoptosis by inhibiting ER stress.[85]

INCREASED KETONE BODIES (KETOGENESIS). SGLT2 inhibitors, by promoting glycosuria, triggered a state resembling starvation marked by the hepatic production of ketone bodies, particularly β-hydroxy butyrate.[86] Furthermore, patients with HF exhibited elevated levels of ketone bodies, potentially serving as a fuel source for the failing heart.[87] Empagliflozin was shown to protect against acute and chronic DOX cardiomyopathy, presumably by increasing β-hydroxy butyrate levels.[39] To validate this, Oh et al[39] conducted experiments by incubating cardiac myocytes with β-hydroxy butyrate, resulting in reduced DOX cardiotoxicity.[39] Similarly, the combination of dapagliflozin with a low dose of angiotensin receptor neprilysin inhibitor modulated metabolic pathways and increased β-hydroxy butyrate levels, contributing to their protective mechanisms against DOX-induced acute and chronic HF.[48] Additionally, dapagliflozin modulated metabolic pathways, including glucose, ketone bodies, and fatty acids, by enhancing genes related to fatty acid transport, fatty acid oxidation, ketogenesis, and gluconeogenesis.[48]

Although dapagliflozin effectively modulated metabolic pathways, the role of ketone bodies in mediating the cardioprotective effects of SGLT2 inhibitors has been the subject of debate. First, empagliflozin increased cardiac adenosine triphosphate production without relying on the use of ketone bodies.[88] Second, in diabetic, obese, hypertensive rats with mild HF, empagliflozin reduced myocardial ketone body use despite elevated blood β-hydroxy butyrate levels.[88] Furthermore, β-hydroxy butyrate ameliorated mitochondrial dysfunction and inflammation in an HF with preserved ejection fraction mouse model independently of ketone oxidation.[89] Additionally, the EMPA-VISION (Assessment of Cardiac Energy Metabolism, Function and Physiology in Patients With Heart Failure Taking Empagliflozin) trial showed that empagliflozin did not enhance cardiac energetics or alter the levels of circulating ketone bodies in patients with HF with reduced ejection fraction or HF with preserved ejection fraction.[90] Despite the absence of conclusive evidence on whether the action of SGLT2 inhibitors in HF involves ketone metabolism, this does not preclude the potential therapeutic advantages from ketones. The available findings imply that the presence of ketones following SGLT2 inhibition might induce beneficial effects for cardiovascular protection. This could be attributed to their direct activation of nutrient deprivation signals rather than their function as a proficient source for adenosine triphosphate synthesis.[91]

ENHANCED ENERGY METABOLISM. Cells adjust their metabolic processes and functions in response to signals from their surroundings through the interplay of various regulatory proteins, including mammalian target of rapamycin (mTOR), sirtuins (sirtuin 1, sirtuin 3, sirtuin 6), and adenosine monophosphate-activated protein kinase (AMPK).[91,92] The dysregulation of these proteins has been associated with cardiovascular disease.[93] DOX-induced down-regulation of sirtuin 1 and AMPK activity was one of the key mechanisms of DOX cardiotoxicity, and AMPK activation by different approaches has demonstrated cardioprotective effects against DOX.[93,94] AMPK down-regulation was implicated in various molecular pathways associated with DOX cardiotoxicity, including mitochondrial dysfunction, enhanced apoptosis, disrupted autophagy, and increased fibrosis. AMPK regulated mitochondrial biogenesis through peroxisome proliferator-activated receptor-γ coactivator-1α signaling, promoted oxidative mitochondrial metabolism, suppressed apoptosis via mTOR signaling inhibition, enhanced autophagy via Unc-51 like autophagy activating kinase 1 activation, and inhibited fibrosis by targeting transforming growth factor-β signaling.[94]

SGLT2 inhibitors enhance energy metabolism by up-regulating the expression or activity of nutrient deprivation signaling, such as AMPK, sirtuins, and peroxisome proliferator-activated receptor-γ coactivator-1α. Simultaneously, they down-regulate nutrient surplus signaling, such as mTOR activation, in various stressed tissues.[91] SGLT2 inhibitors have been shown to activate AMPK via the inhibition of complex I of the mitochondrial respiratory chain.[95,96] Although SGLT2 inhibitors demonstrated cardioprotection by activating AMPK in cardiac fibroblasts, cardiomyocytes,[97,98] and murine hearts,[96,99] only canagliflozin activated AMPK in endothelial cells.[100,101] Empagliflozin and dapagliflozin have been shown to mitigate DOX cardiotoxicity through AMPK activation.[49,52] Empagliflozin activated the AMPK/sirtuin 1/peroxisome proliferator-activated receptor-γ coactivator-1α–mediated mitochondrial biogenesis,[49] and dapagliflozin attenuated short-term DOX cardiotoxicity by activating AMPK.[52] In addition, the administration of empagliflozin in DOX-treated mice activated mitochondrial biogenesis, likely through the up-regulation of peroxisome proliferator-activated receptor-γ coactivator-1α, thereby preventing DOX-induced acute cardiotoxicity.[42] Furthermore, empagliflozin mitigated cardiac dysfunction induced by sunitinib, both in vivo and in vitro, by activating AMPK, resulting in regulated cardiomyocyte

TABLE 5 In Vivo Studies Demonstrating the Anticancer Effects of SGLT2 Inhibitors

First Author (Year)	Cancer Type	Cancer Model	SGLT2 Inhibitor Treatment	Key Finding	Results and Proposed Mechanism
Scafoglio et al (2015)[135]	Pancreatic cancer	NSG mice with ASPC-1 cells	CANA DAPA (30 mg/kg/d for 4 wk, oral gavage)	CANA ↓ tumor growth rate equally with gemcitabine (positive control) DAPA caused modest insignificant ↓ in tumor growth, but a significant ↑ in tumor necrosis	↓ Tumor growth ↑ Necrosis in the tumor center dependent on SGLT2 inhibition
Villani et al (2016)[24]	Prostate cancer	BALB/c-Nude mice with PC3 cells	CANA (100 mg/kg, single dose, oral gavage)	↓ Tumor growth rate (in vitro)	Activates AMPK in cancer cells
Kuang et al (2017)[141]	RCC	CaKi-1 bearing athymic nude mice	DAPA (1.3 mg/kg, for 21 d, i.v.)	↓ Tumor growth	↑ Tumor necrosis ↓ SGLT2 expression
Kaji et al (2018)[129]	HCC	Huh7- and HepG2-derived xenograft tumors in BALB/c nude mice	CANA (100 mg/kg/d for 4 wk, oral)	↓ Human HCC xenograft tumor burden independently of glycemic status	↓ Glycolytic metabolism and intratumor vascularization Inhibition of in vivo tumor growth is strongly associated with SGLT2 expression No effect on tumor growth, tumor weight in SGLT2-null HLE-derived xenograft models
Shiba et al (2018)[131]	HCC in a mouse model of human NASH	MC4R-KO mice on high-fat diet for 1 y to develop HCC	CANA (30 mg/kg/d in diet for 8, 20, or 52 wk)	↓ Number of tumors in the liver ↓ Maximum tumor size	Antiproliferative in premalignant lesions ↓ Liver fibrosis ↓ Serum ALT ↓ Expression of Myc and Afp
Scafoglio et al (2018)[142]	NSCLC	KPluc GEMMs (tumor induced by intranasal Adeno-Cre) and patient-derived xenografts	CANA (30 mg/kg/d, for 6 wk or 3 mo, oral gavage)	↓ Tumor growth Delay onset of tumors ↑ Survival	↓ Glucose uptake
Wu et al (2019)[158]	HCC	Huh7 xenografted tumor model	CANA (100 mg/kg/d for 10 d then ↑ to 300 mg/d until day 30)	↓ Tumor growth ↑ Survival	↓ PP2A activity ↓ Glucose-influx-induced β-catenin up-regulation ↓ β-catenin expression
Nasiri et al (2019)[23]	Breast cancer Colon cancer	C57BL/6J mice with E0771 or MC38 cells with high-fat diet	DAPA (2.5 mg/kg/d, in drinking water)	↓ Tumor growth	↓ Tumor glucose uptake in an insulin-dependent manner Restoring hyperinsulinemia abrogated the effects of DAPA
Zhou et al (2020)[143]	Breast cancer	BALB/C-nu/nu mice with MCF-7 cells	DAPA (100 mg/kg/d for 4 wk, oral)	↓ Tumor growth	AMPK-mediated cell cycle arrest and apoptosis (mentioned only in vitro)
Xu et al (2020)[133]	Pancreatic cancer	PANC-1-bearing nude mice	CANA (25, 50, and 100 mg/kg/d for 5 wk, oral)	↓ Tumor growth	↓ Glycolysis via ↓ protein levels of PI3K/AKT/mTOR pathway (↓GLUT-1 and LDHA expression)
Xie et al (2020)[140]	Cervical cancer	HeLa cells treated with EMPA (50 μmol/L) transplanted into nude mice	EMPA	↓ Growth of tumors in nude mice ↓ Proliferation of cervical cancer cells and ↑ their apoptosis	↑ AMPK/FOXA1 pathway and ↓ the expression of Shh (dependent on SGLT2)
Ren et al (2021)[134]	Pancreatic cancer	PANC-1 tumor-bearing athymic nude (nu/nu) mice	CANA (not mentioned) SOTA (30 mg/kg)	↓ Growth of pancreatic tumor	
Wu et al (2022)[22]	Osteosarcoma	K7M2 tumor-bearing C57BL/6 mice	CANA (30 mg/kg/d, oral)	↓ Tumor growth	↑ Immune cell infiltration by ↑ STING expression and activating the IRF3/IFN-β pathway
Wang et al (2022)[142]	Papillary thyroid cancer	TPC-1 tumor in Balb/c nude mice	CANA (100 mg/kg/d for 28 d, oral)	↓ Tumor growth	All mechanisms are in vitro only
Shoda et al (2023)[132]	Glioblastoma	GL261-transplanted mice	CANA (100 mg/kg/d for 10 d, oral)	↓ Glioblastoma tumor growth	Activation of AMPK (mentioned only in vitro)
Ding et al (2023)[139]	NSCLC	CT26 mouse cancer model and NOD-*Prkdc*^{scid}*Il2rg*^{em1}/Smoc (NSG) mice humanized with PBMCs and Hu-SRC-SCID model	CANA (50 mg/kg/d for 1 wk, intragastric)	↓ Tumor growth equivalent to anti-PD-1 antibody	↓ PD-L1^{+} cells ↑ Infiltrating CD3^{+} T cells, activated CD8^{+} T cells, and IFN-γ production
Biziotis et al (2023)[148]	NSCLC	Male athymic BALB/c nude mice with A549 and H1299	CANA (60 mg/kg/d for 60 d for A549 and 36 d for H1299 tumors in the diet)	↓ Tumor growth ↑ Survival	↑ AMPK activity ↓ mTOR activity ↓ (MAPK) ERK1/2 ↓ HIF-1α ↓ HDAC2

Afp = alpha-fetoprotein; ALT = alanine transaminase; CD3 = cluster of differentiation 3; CD8 = cluster of differentiation 8; GEMM = genetically engineered murine model; IFN = interferon; Myc = myelocytomatosis oncogene; NASH = nonalcoholic steatohepatitis; NSG = NOD/SCID-ILR2-γ; RCC = renal cell carcinoma; other abbreviations as in Tables 1, 2, and 4.

autophagy.[20] Recent findings have shown that canagliflozin, unlike empagliflozin or dapagliflozin, mitigated carfilzomib-induced endothelial apoptosis by restoring AMPK expression.[57]

ENHANCED AUTOPHAGY. Autophagic clearance of damaged cellular constituents reduced cellular stress, mitigated proinflammatory and profibrotic responses, preserved cellular integrity, and prevented apoptosis, thereby maintaining and restoring organ structure and function.[91] As autophagy represents the primary cellular recycling mechanism, the dysregulation of autophagy became a critical mechanism of cancer therapy-related cardiotoxicity.[102] Previous studies have noted that DOX blocked the autophagic flux in cardiomyocytes.[103] Empagliflozin abrogated DOX cardiotoxicity by enhancing the autophagic flux in murine hearts and cardiomyocytes.[41] In their study, Wang et al[41] proposed that empagliflozin directly acts on sirtuin 3, facilitating the formation of a complex involving sirtuin 3, beclin 1, and Toll-like receptor 9, thereby enhancing autophagic flux. Likewise, empagliflozin ameliorated sunitinib-induced cardiac dysfunction by regulating cardiomyocyte autophagy, which was mediated by the AMPK/mTOR signaling pathway.[20] Similarly, empagliflozin enhanced the autophagic flux in human aortic endothelial cells treated with ponatinib, resulting in reduced cellular senescence.[56]

These findings align with the role of SGLT2 inhibitors in enhancing autophagy in HF. There is extensive evidence linking autophagy to the pathogenesis of HF, as dysfunctional basic autophagy may lead to its onset, and excessive or maladaptive autophagy may aggravate the condition.[104,105] Proteomic analyses of samples from the EMPEROR-Reduced and EMPEROR-Preserved clinical trials provide additional support for the notion that the effects of SGLT2 inhibitors are likely related to actions on the heart and kidney, promoting autophagic flux and nutrient deprivation signaling.[106] A recent review examining the influence of SGLT2 inhibitors on the autophagic flux concluded that enhanced AMPK activity and autophagic flux contributed to the elevated adenosine triphosphate production in the heart following SGLT2 inhibition. This further supports the notion that the cardioprotective effects of SGLT2 inhibitors can be attributed to their modulation of nutrient and energy sensors, leading to the promotion of autophagy.[91]

INHIBITING FERROPTOSIS. Ferroptosis, an iron-dependent and nonapoptotic type of cell death driven by excessive lipid reactive oxygen species and disrupted redox balance, has been linked to abnormal iron accumulation.[107] Accumulating evidence suggests the crucial role of maintaining iron homeostasis for normal heart function, with ferroptosis playing a significant role in cardiovascular disease.[108] Several anticancer medications, including DOX, etoposide, tyrosine kinase inhibitors, trastuzumab, and 5-fluorouracil, induce ferroptosis.[108] Notably, SGLT2 inhibitors have shown their ability to mitigate cardiotoxicity secondary to DOX and trastuzumab by inhibiting ferroptosis.[21,43] In a mouse model of DOX-induced acute cardiotoxicity, empagliflozin mitigated the deleterious cardiac effects of DOX by reducing iron overload and ferroptosis.[43] Similarly, dapagliflozin protected against trastuzumab-induced cardiotoxicity by ameliorating ferroptosis.[21]

These effects were consistent in other models of HF, in which canagliflozin suppressed ferroptosis in mice with diabetic cardiomyopathy[109] and in rats with HF with preserved ejection fraction.[110] Canagliflozin reduced ferroptosis by regulating AMPK in cardiomyocytes,[111] and dapagliflozin alleviated oxidative stress, lipid peroxidation, and ferrous iron overload. These effects were observed in a rat model of myocardial ischemia-reperfusion injury and in H9c2 cardiomyoblasts subjected to hypoxia and reoxygenation, achieved via mitogen-activated protein kinase signaling inhibition.[112] Additionally, large-scale proteomics analyses from clinical trials involving SGLT2 inhibitors revealed differential expression of proteins associated with improved iron homeostasis.[106,113]

INHIBITION OF ET-1. ET-1, a potent vasoconstrictor, has been implicated in breast cancer-induced cardiac remodeling and cancer treatment-related cardiotoxicity.[114,115] High-dose DOX significantly elevated serum and cardiac ET-1 in rats.[116,117] Similarly, ET-1 mediated sunitinib-induced hypertension and cardiac fibrosis in tumor-bearing mice[118] and induced systemic vasoconstriction in a swine model.[119] Furthermore, the up-regulation of ET-1 may have served as a predictor for chemotherapy-related cardiotoxicity in women undergoing anthracycline-based chemotherapy followed by trastuzumab.[114]

Interestingly, there is strong preclinical and clinical evidence suggesting that SGLT2 inhibitors can reduce ET-1 concentration. In the DAPA-HF trial, after a 12-month treatment period, dapagliflozin caused a small decrease in serum ET-1 levels in patients with HF.[120] In preclinical studies, empagliflozin inhibited ET-1 in human proximal tubular cells.[121] Therefore, it is plausible that the inhibition of ET-1 mediated the protective effects of SGLT2 inhibitors in cardio-

TABLE 6 Preclinical Studies Demonstrating the Effect of Combining SGLT2 Inhibitors With Cancer Treatments

First Author (Year)	Cell/Model Type	Anticancer Treatment	SGLT2 Inhibitor Treatment	Key Finding	Results and Proposed Mechanism
Villani et al (2016)[24]	Human prostate cancer PC3 cells	Radiation or docetaxel	CANA (0-100 μM)	CANA ↑ the efficacy of both therapies in prostate cancer cells	↓ Mitochondrial complex I
Quagliariello et al (2020)[55]	Breast cancer MCF-7 and MDA-MB-231 cells	Ipilimumab (100-500 nM)	EMPA (500 nM) under hyperglycemic conditions	EMPA ↑ responsiveness to ipilimumab	↑ ROS production ↑ MDA
Eliaa et al (2020)[162]	Triple-negative breast cancers MDA-MB-231	DOX (1.3 μM)	EMPA (50 μM)	DOX+EMPA showed a slightly ↓ cytotoxic activity against the MDA-MB-231 cell line compared with DOX alone, but more characteristic arrest in the growth of cells	↑ Cell sensitivity to the DOX and ↑ antitumor effects: dose dependent ↓ Cancer growth, ↓ cell cycle proliferation, ↑ apoptosis ↓ Expression of MDR1 ↓ Bcl-2, JNK gene expression ↑ p21 gene expression
Zhong et al (2020)[163]	Hepatocellular carcinoma HepG2, HepG2-ADR, breast cancer MCF7 cells	DOX (0-2.8 or 4.2 μM)	CANA (40 μM)	CANA ↑ the cytotoxic effect of DOX CANA ↑ intracellular accumulation of DOX in HepG2 cells	↓ p-gp protein in HepG2 cells without affecting its gene expression ↓ Glucose uptake and ATP levels ↓ Autophagy at the early stage by ↑ ULK1 phosphorylation
	HepG2-xenograft BALB/c nude mice			Stronger inhibition of DOX activity against tumor growth than DOX alone	↑ Tumor necrosis
Quagliariello et al (2021)[43]	Estrogen-responsive and triple-negative breast cancer cells (MCF-7 and MDA-MB-231 cell lines)	DOX (0.1-50 μM)	EMPA (10, 50, 500)	EMPA did not affect anticancer effects of DOX in breast cancer cells	
Biziotis et al (2023)[148]	Human adenocarcinoma (A549, H1299, and H1975), squamous cell (SK-MES-1), and large cell (H460) NSCLC cells and male athymic BALB/c nude mice	Radiation	CANA (5-30 μM)	Additive antiproliferative effects in A549, H1299, and H1975 cells and synergistic effects in SK-MES-1 and H460 cells ↓ Clonogenic survival (additive in A549 and H1299 cells and synergistic in H1975 cells) ↓ Tumor growth in vivo	↑ Anaerobic metabolism ↑ AMPK activity ↓ mTOR activity ↓ (MAPK) ERK1/2 ↓ HIF-1α ↓ HDAC2

JNK = c-Jun N-terminal kinase; MDR1 = multidrug resistance 1; p-gp = phosphorylated glycoprotein; ULK1 = Unc-51 like autophagy activating kinase 1; other abbreviations as in Tables 1, 2, and 4.

oncology. Nevertheless, as of now, there are no published studies reporting this mechanism.

HIGHLIGHTS

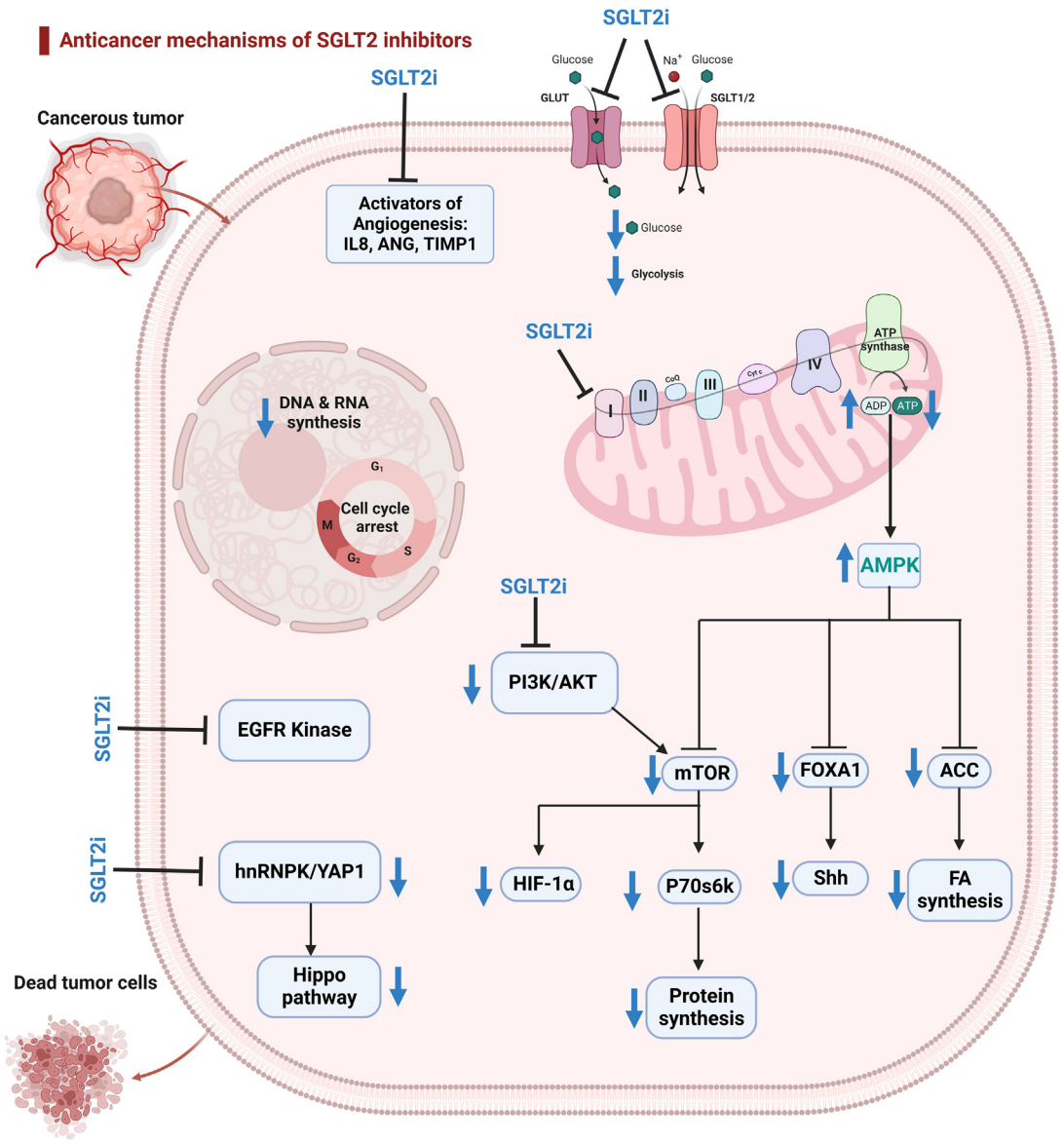
- SGLT2 inhibitors offer multifactorial cardioprotective effects in cancer treatment-related cardiotoxicity.
- Mechanisms include anti-inflammatory, antioxidant, ER stress mitigation, ketogenesis, enhanced energy metabolism, autophagy, inhibition of ferroptosis, and inhibition of ET-1.

ANTICANCER EFFECTS OF SGLT2 INHIBITORS

Following the demonstration of the cardioprotective effects of SGLT2 inhibitors against cancer therapy-related cardiovascular toxicity, it is crucial to investigate their impact on the anticancer effects of cancer treatments. This investigation is essential to confirm that combining SGLT2 inhibitors with cancer treatments would not compromise their chemotherapeutic benefits.

Initially, concerns were raised regarding the risk for cancer with SGLT2 inhibitors, especially bladder cancer with dapagliflozin.[122,123] However, subsequent studies and meta-analyses have examined these concerns, ultimately concluding that there was no overall risk for malignancy with SGLT2 inhibitors.[124-126] Furthermore, recent epidemiologic studies have revealed a positive association between the use of SGLT2 inhibitors and improved overall survival among patients with non-small-cell lung cancer (NSCLC)[127] and hepatocellular carcinoma[128] with pre-existing diabetes, irrespective of patients' demographics, tumor characteristics, and cancer treatments. Notably, a longer duration of SGLT2 inhibitor use, especially with canagliflozin, was associated with better survival. However, it is important to note that no randomized clinical trials have investigated the

FIGURE 2 Mechanisms of the Anticancer Effects of SGLT2i



SGLT2 inhibitors (SGLT2i) inhibit glucose uptake by inhibiting SGLTs (SGLT-1 and SGLT-2) and glucose transporters (GLUTs). SGLT2 inhibitors, especially canagliflozin, inhibit mitochondrial complex I–supported cellular respiration, reducing adenosine triphosphate production and activating AMPK. Activated AMPK inhibits acetyl-coenzyme A carboxylase (ACC), suppressing fatty acid synthesis. It also down-regulates forkhead box A1 (FOXA1) and sonic hedgehog signaling molecule (Shh) and inhibits mTOR and p70S6K, thereby suppressing protein synthesis. Inhibited mTOR results in the down-regulation of hypoxia-inducible factor-1α (HIF-1α). SGLT2 inhibitors inhibit the phosphoinositide 3-kinase (PI3K)/AKT pathway. SGLT2 inhibitors inhibit the Hippo signaling pathway by down-regulating the heterogeneous nuclear ribonucleoprotein K (hnRNPK)/YES-associated protein 1 (YAP1) axis. Additionally, SGLT2 inhibitors inhibit epidermal growth factor receptor (EGFR) kinase and angiogenesis activators. Created using BioRender.com. ANG = angiogenin; FA = fatty acid; IL8 = interleukin 8; TIMP1 = tissue inhibitor of metalloproteinase 1; other abbreviations as in Figure 1.

anticancer effects of SGLT2 inhibitors. To confirm these observations, several preclinical studies have provided evidence for potential anticancer effects of SGLT2 inhibitors on their own, particularly canagliflozin and dapagliflozin, in both experimental cell lines (Table 4) and animal models (Table 5).

These studies have consistently demonstrated the ability of SGLT2 inhibitors to impede the growth of

tumors across the following cancer models: hepatocellular carcinoma,[24,25,129-131] glioblastoma,[132] osteosarcoma,[22] pancreatic cancer,[133-135] prostate cancer,[24] lung cancer,[24,136-139] cervical cancer,[140] renal cancer,[141] papillary thyroid cancer,[142] colon cancer,[23] and breast cancer.[23,24,143-145] Importantly, in preclinical studies, the combination of SGLT2 inhibitors with other chemotherapies and ionizing radiation enhanced their efficacy and increased cancer cell responsiveness to treatments (**Table 6**). This combination strategy carries the potential to lower the therapeutic doses of cancer treatments, thereby ameliorating their adverse effects, particularly cardiotoxicity. Furthermore, this combined approach holds promise in attenuating cancer cell resistance to treatment.

MECHANISMS OF THE ANTICANCER EFFECTS OF SGLT2 INHIBITORS. Several comprehensive review articles have discussed the potential anticancer mechanisms of SGLT2 inhibitors.[146,147] Importantly, the presence of SGLTs (SGLT1 and/or SGLT2) has been confirmed in various types of cancer cells, including hepatocellular carcinoma; pancreatic, prostate, lung, and breast cancers; and brain, head, and neck tumors.[22,129,132,135,138,140-143] Consequently, some mechanisms underlying the anticancer effects of SGLT2 inhibitors are dependent upon the inhibition of SGLT2, whereas others are independent of SGLT2 inhibition. These mechanisms include the inhibition of complex I and the α subunit of adenosine triphosphate synthase F1 in the mitochondrial electron transport chain, cell cycle arrest, reduction in the adhesion of cancer cells, disruption of glutamine metabolism, and inhibition of several other pathways, including β-catenin action, mTOR, DNA and RNA synthesis, proangiogenic factors, cellular sodium influx, and L858R/T790M epidermal growth factor receptor kinase.[146,147]

Inhibition of mitochondrial complex I and AMPK activation. The mechanisms involved with the anticancer effects of SGLT2 inhibitors are depicted in **Figure 2**. The activation of AMPK was the most frequently reported mechanism underlying the anticancer properties of SGLT2 inhibitors,[24,25,129,132,140,142,143,145,148] particularly with canagliflozin. Mechanistically, canagliflozin inhibited mitochondrial complex I-supported cellular respiration and oxidative phosphorylation, leading to reduced adenosine triphosphate production and an elevated adenosine monophosphate/adenosine triphosphate ratio, which in turn induced AMPK phosphorylation and activation. Activated AMPK resulted in the inhibition of the mTOR, inhibition of p70S6K, cell cycle arrest, and induction of apoptosis.[129,133,142,143]

Notably, canagliflozin emerged as the most potent SGLT2 inhibitor in inhibiting mitochondrial complex I in vitro compared with other SGLT2 inhibitors.[95] This may explain why, at clinically relevant concentrations, only canagliflozin exhibited antiproliferative properties,[24,135,145] whereas dapagliflozin required suprapharmacologic concentrations to show the same effects.[23] Further supporting this, maintaining cellular respiration in the presence of canagliflozin through the overexpression of the yeast mitochondrial NADH dehydrogenase (complex I) negated its antiproliferative effects.[24] This underscores the critical role of inhibiting mitochondrial complex I-supported respiration in the antiproliferative effects of canagliflozin in cancer cells.

Activated AMPK also down-regulated forkhead box A1 and the sonic hedgehog signaling molecule.[149] The sonic hedgehog signaling molecule pathway was highly expressed in several malignant tumors, facilitating tumor cell proliferation, resistance to chemotherapy, and tumor metastasis.[150] Forkhead box A1 activated the sonic hedgehog signaling molecule pathway, inhibiting apoptosis and promoting abnormal cell proliferation.[151] In cervical carcinoma cells and tumor-bearing mice, empagliflozin has been demonstrated to activate AMPK, and down-regulate the expression of forkhead box A1, thereby inhibiting the expression of sonic hedgehog signaling molecule, further inhibiting the malignant proliferation of cervical cancer cells, and inducing apoptosis.[140] It is noteworthy that, to our knowledge, this study stands as the only report on the anticancer properties of empagliflozin.

Hypoxia-inducible factor-1α, a pivotal regulator of the hypoxic transcriptional response in cancer biology, plays a crucial role in various aspects, including glucose metabolism, initiation of the Warburg effect, angiogenesis, cell proliferation and survival, and invasion and metastasis, ultimately contributing to tumor resistance against cytotoxic agents.[152] In a recent study, canagliflozin not only inhibited the proliferation and clonogenic survival of NSCLC in vitro and in vivo but also enhanced the effectiveness of radiotherapy to mediate these effects.[148] Canagliflozin down-regulated hypoxia-inducible factor-1α protein levels and genes regulating its stability. Down-regulated hypoxia-inducible factor-1α has been attributed to the activation of AMPK and inhibition of mTOR, which serve as critical activators of hypoxia-inducible factor-1α signaling.[153]

Inhibition of glucose uptake. Inhibiting glucose uptake through SGLT2 inhibitors enhanced their

anticancer effects.[23,24,129,132,138,141,142] Notably, canagliflozin, in addition to inhibiting SGLT2, exhibited a higher affinity for inhibiting SGLT1 compared with other SGLT2 inhibitors[154] and may also have inhibited the glucose transporter glucose transporter 1.[133] Tumor cells of various types tended to overexpress both SGLTs (SGLT1 and SGLT2) and glucose transporters,[155] relying heavily on aerobic glycolysis and accelerated glucose uptake, which is known as the Warburg effect.[156] Inhibiting glucose uptake in cancer cells led to an energetic crisis and apoptosis, thereby decreasing cancer cell proliferation.[156] However, inhibiting glucose uptake was unlikely to be the primary mechanism behind the antiproliferative effects of SGLT2 inhibitors. This is supported by findings showing that canagliflozin demonstrated similar antiproliferative effects under both low- and high-glucose conditions, as well as under pyruvate- or acetate-supplemented conditions.[24] Furthermore, canagliflozin, and to a lesser extent dapagliflozin, inhibited the proliferation of breast cancer lines characterized by high rates of aerobic glycolysis, and glucose uptake remained consistent regardless of the presence or absence of glucose.[145]

Enhancing anticancer immune response. Intriguingly, 2 recent studies have demonstrated that SGLT2 inhibitors boosted tumor-immune response and increased infiltrating immune cells through 2 distinct mechanisms.[22,139] In the first study, SGLT2 was identified as a positive regulator of programmed cell death-ligand 1 (PD-L1) in SGLT2-expressing cancer cells,[139] with their interaction on the cell membrane proving essential for maintaining the PD-L1 protein level. Importantly, PD-L1, expressed on tumor cells, bound to programmed cell death 1 on active T cells, facilitating tumor immune escape by preventing the T lymphocyte from targeting and destroying the cancer cells.[157] Canagliflozin disturbed the physical interaction between SGLT2 and PD-L1, triggering the ubiquitination and proteasome-mediated degradation of PD-L1. This led to the down-regulation of PD-L1 expression on the cell membrane by preventing the recycling of internalized PD-L1 in NSCLC, ovarian cancer, and pancreatic cancer cell lines.[139] When tested in vivo, both canagliflozin and silencing SGLT2 reduced PD-L1 expression, resulting in a restriction of tumor progression equivalent to the effect of anti-programmed cell death 1 antibody.[139] This effect correlated with increased activity of antitumor cytotoxic T cells.[139]

In the second in vivo study,[22] canagliflozin inhibited osteosarcoma tumor growth and increased infiltration of immune cells. This effect was achieved by up-regulating the expression of stimulator of interferon genes and activating the interferon regulatory factor 3/interferon beta pathway, known for its ability to induce immune cells.[158] In this study, the expression level of SGLT2 was negatively correlated with the infiltration level of immune cells in sarcoma, including $CD8^+$ T cells, $CD4^+$ T cells, and $CD4^+$ T helper type 2 cells.[22] As a result, inhibiting SGLT2 using canagliflozin or silencing increased the number of infiltrated immune cells, thereby inhibiting tumor growth.[22] The investigators attributed the activation of the stimulator of interferon genes/interferon regulatory factor 3/interferon beta pathway via protein kinase B (AKT) inhibition by canagliflozin. This association is based on previous reports indicating a negative correlation between the stimulator of interferon genes pathway and the level of AKT phosphorylation.[158]

Inhibition of phosphoinositide 3-kinase/AKT pathway. SGLT2 inhibitors have been shown to inhibit the phosphoinositide 3-kinase/AKT pathway in cancer cells,[22,129,133,136,142] which is the most commonly activated pathway in human cancers.[159] The oncogenic activation of the phosphoinositide 3-kinase/AKT pathway in cancer cells induced metabolic reprogramming, promoting abnormal cell growth, whereas the inhibition of this pathway resulted in reduced cellular proliferation and enhanced cellular death.[159]

INHIBITION OF THE HIPPO PATHWAY. The Hippo pathway is a highly conserved signaling pathway that controls organ size, tissue homeostasis, and cancer development.[160] Recent studies have revealed that the Hippo signaling pathway might have contributed to tumorigenesis and cancer development.[161] SGLT2, in particular, has been shown to interact with heterogeneous nuclear ribonucleoprotein K, promoting its nuclear translocation, which in turn promoted the expression of YES-associated protein 1, the downstream regulator of the Hippo pathway.[134] SGLT2 inhibition by canagliflozin has been shown to inhibit the Hippo signaling pathway by down-regulating YES-associated protein 1 expression in pancreatic cancer.[134]

HIGHLIGHTS

- Epidemiologic studies associate SGLT2 inhibitors with improved overall survival in specific cancers.
- Preclinical studies demonstrate potential anticancer effects of SGLT2 inhibitors, whether used alone or in combination with standard cancer treatments.

- Potential mechanisms underlying the anticancer effects of SGLT2 inhibitors include AMPK activation, inhibition of mitochondrial complex I, inhibition of glucose uptake, and enhancement of immune response.

CONCLUSIONS AND FUTURE DIRECTIONS

In conclusion, considering the favorable tolerability profile and widespread use of SGLT2 inhibitors in the management of T2DM, HF, and chronic kidney disease, these agents hold promise as potential candidates for drug repurposing in cardio-oncology and cancer treatment. This review sheds light on abundant preclinical evidence supporting the use of SGLT2 inhibitors in cardio-oncology. Despite this progress, a multitude of unanswered questions persists, prompting the need for further in-depth exploration.

First, it is imperative to conduct further head-to-head comparisons among different SGLT2 inhibitors, examining both cardioprotective and anticancer effects. Most studies demonstrating cardioprotective effects have used empagliflozin and dapagliflozin, whereas those investigating anticancer effects have used canagliflozin. Furthermore, although the reviewed studies have consistently shown the cardioprotective effects of SGLT2 inhibitors against cancer treatment-related cardiotoxicity in tumor-free models, none has yet concurrently demonstrated the cardioprotective and the anticancer effects of SGLT2 inhibitors in tumor-bearing models. There is a pressing need to investigate these effects in tumor-bearing models to assess their efficacy and safety in a more clinically relevant context, aiming to safeguard the heart in the presence of cancer and its treatments. However, from a clinical prospective, the support for the use of SGLT2 inhibitors in cardio-oncology is grounded predominantly in anecdotal evidence derived from observational and epidemiologic studies. Given the inherent nature of these studies, which included primarily patients with both diabetes and cancer, there arises a critical need for randomized clinical trials. These trials should specifically investigate the safety and efficacy of SGLT2 inhibitors in patients undergoing potentially cardiotoxic cancer treatments, encompassing both those with and without diabetes.

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