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Review

Double Duty: SGLT2 Inhibitors as Cardioprotective and Anticancer Allies

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Abstract: Sodium glucose cotransporter-2 inhibitors (SGLT2i), originally developed for type II diabetes mellitus, have recently been approved for the treatment of heart failure in both diabetic and non-diabetic patients due to their significant cardiovascular benefits. Beyond their established role in diabetes and heart failure management, current research is exploring the potential applications of SGLT2 inhibitors in the field of cardio-oncology. This interest is driven by dual possible benefits: cardioprotection against the adverse effects of antitumor therapies and inherent antitumor properties. Patients affected by cancer often face the challenge of managing cardiovascular toxicity induced by antineoplastic treatments. SGLT2 inhibitors have shown promise in mitigating toxicities, thereby enhancing the cardiovascular health of these patients. Additionally, emerging evidence suggests that SGLT2 inhibitors may possess direct antitumor effects, further contributing to their therapeutic potential in oncology. This review aims to provide a comprehensive overview of the molecular mechanisms through which SGLT2 inhibitors exert their cardioprotective and antitumor effects. Furthermore, we will examine the current body of evidence supporting the use of these inhibitors in a cardio-oncology setting.

Keywords: SGLT2 inhibitors; cardio-oncology; cardiotoxicity; heart failure; cardiovascular pharmacology

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1. Introduction

Sodium glucose cotransporter-2 inhibitors (SGLT2i) were initially developed for the treatment of type II diabetes mellitus (T2DM) because of their ability to enhance renal glucose excretion [1]. However, in recent years, extensive evidence has shown that SGLT2i can provide cardiovascular benefits independently of their glucose-lowering effects [2–6]. As a result, two SGLT2i, dapagliflozin and empagliflozin, have now been approved for the treatment of heart failure (HF), irrespective of ejection fraction [7,8]. The mechanisms by which SGLT2i confer cardiovascular benefits are not yet fully understood, but they are believed to exert pleiotropic effects. These effects include improving hemodynamics and cardiomyocyte energy metabolism, reducing myocardial inflammation, modulating sympathetic and parasympathetic activity, and protecting endothelial function [9–11]. Moreover, recent, large real-world studies have confirmed the nephroprotective efficacy of SGLT2i from randomized trials. Furthermore, the beneficial effects of these agents may extend to the nondiabetic population according to the positive results of current studies [12]. Therefore, SGLT2i might be used for the prevention and treatment of numerous pathological conditions. In this regard, recent research has been focusing on the potential role of SGLT2i as a cardioprotective strategy to counteract the cardiotoxic effects of cancer therapies [2]. To date, the introduction of new cancer therapies has significantly improved overall survival (OS) and progression-free survival (PFS) in patients with malignancies. However, this

positive outcome is counterbalanced by the increase of numerous cardiovascular adverse effects. Therefore, it is essential to develop pharmacological strategies that can prevent and treat cardiotoxic damage without compromising antitumor efficacy of therapies. In this context, both preclinical and clinical evidence to date suggest that SGLT2i not only mitigate the cardiotoxic effects of cancer therapies, but also exert direct anticancer activity in several types of cancer, enhancing the efficacy of antiproliferative treatments [13,14]. Based on these premises, SGLT2i represent a highly promising strategy in the field of cardio-oncology. Their ability to mitigate cardiotoxic effects associated with cancer therapies, coupled with their potential direct anticancer effects across various malignancies, positions them as pivotal agents in improving therapeutic outcomes while safeguarding cardiovascular health in oncology patients. In this review we aim to offer a thorough examination of the molecular mechanisms underlying the cardioprotective and anticancer effects of SGLT2i. Furthermore, the existing body of evidence supporting their application in cardio-oncology will be critically summarized.

2. Materials and Methods

This review follows guidelines for systematic reviews, ensuring transparency in reporting. PubMed was the primary database used, employing Medical Subject Headings (MeSH) terms and keywords such as "SGLT2 inhibitors", "cardioprotection", "cardiovascular risk", "cardio-oncology", and related synonyms. Boolean operators (AND, OR) were used to refine search queries and enhance relevance. Articles were limited to English-language publications, without date restrictions, to capture a broad range of findings. Qualitative analysis identified common themes and trends, addressing discrepancies in study outcomes. Factors such as study design, sample size, and methodological differences were considered in interpreting reported associations.

3. Cardiovascular Benefits of SGLT2i

SGLT2i act through various cellular and molecular mechanisms at vascular, renal, cardiac, and systemic levels, with their cardiorenal effects being particularly significant for their cardiovascular benefits [10]. Although many of these effects are related to the primary action of SGLT2 on renal tubules, SGLT2i also have impacts that occur independently of this pathway. Supporting this idea, empagliflozin has been shown to provide cardioprotective effects in mice lacking renal SGLT2 expression [15,16]. Discussing in detail the molecular mechanisms underlying the cardiovascular and renal benefits is beyond the scope of this review. Therefore, Figure 1 summarizes the main molecular mechanisms underlying the cardiovascular and renal benefits of SGLT2i.

The EM-PA-REG OUTCOME trial highlighted the cardioprotective benefits of SGLT2 inhibitors (SGLT2i), which found empagliflozin reduced hospitalizations for heart failure (HF) by 35% in patients with T2DM and cardiovascular disease [17]. Subsequent trials like CANVAS [6] and DECLARE-TIMI 58 [4] confirmed that SGLT2i decrease HF hospitalizations and cardiovascular death while improving renal outcomes. Investigations expanded to heart failure with reduced ejection fraction (HFrEF) in studies such as EMPEROR-Reduced [3] and DAPA-HF [5], which demonstrated significant reductions in HF hospitalizations and cardiovascular death. For heart failure with preserved ejection fraction (HFpEF), EMPEROR-Preserved [18] and DELIVER [19] showed promising results. Additionally, the EMPULSE TRIAL [20] advocates for early SGLT2i initiation during acute HF hospitalization, with benefits similar to those in chronic HF patients and no significant safety differences when started before or after discharge. SGLT2i also slow kidney function decline and improve HF outcomes in chronic kidney disease, highlighting their dual benefits [21,22].

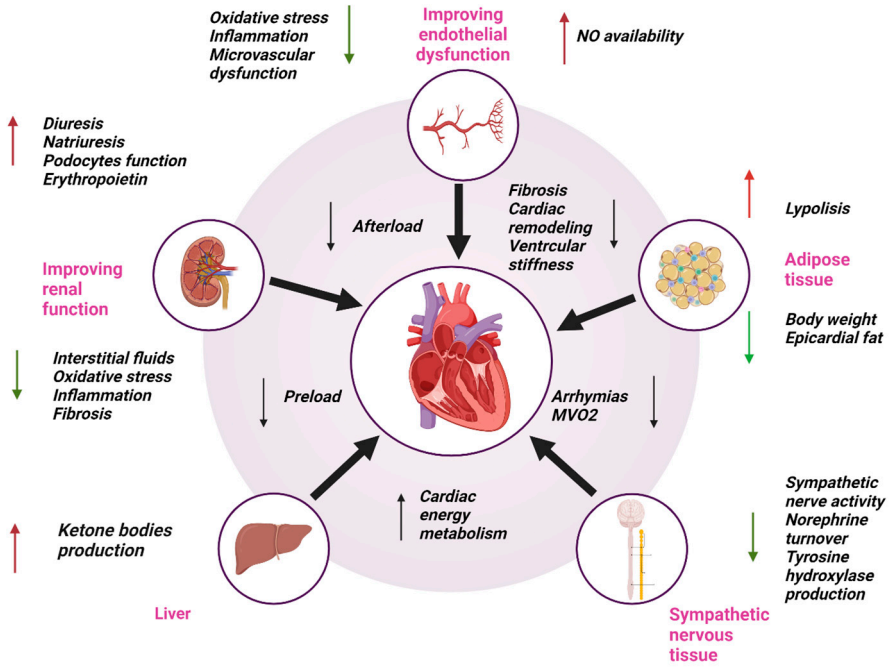

Figure 1. Overview of SGLT2i beneficial effects. MVO2, myocardial oxygen consumption. **The figure was created using BioRender** (www.biorender.com).

4. Molecular Mechanisms of SGLT2i in Cardioprotection Against Cardiotoxic Drugs

The mechanisms through which SGLT2i may mitigate cardiotoxicity are multifactorial and not yet fully understood. Scientific evidence supports several mechanisms, including their effects on inflammation, oxidative stress, endoplasmic reticulum stress, cellular metabolism improvement, vasoconstriction, and autophagy. To date, the majority of evidence pertains to the SGLT2 effect on anthracyclines cardiotoxicity. Nevertheless, we also discuss evidence related to other cardiotoxic drugs.

4.1. Anthracyclines

The mechanisms behind anthracycline-induced cardiotoxicity are complex and involve various pathways, including DNA damage, mitochondrial impairment, oxidative stress, inflammation, and the promotion of apoptosis [17]. Anthracyclines disrupt mitochondrial respiratory chain complexes, causing oxidative stress and reactive ROS formation, exacerbated by iron. This ROS production leads to mitochondrial and DNA damage, promoting cardiomyocyte apoptosis and necrosis [17]. SGLT2i reduce oxidative stress through various mechanisms and as evidence of this, several studies on animal models and human hearts have demonstrated a reduction in oxidative stress following the administration of anthracyclines. Empagliflozin was found to reduce oxidative stress caused by doxorubicin (DOX) in a cardiorenal syndrome model by inhibiting NADPH oxidase 1 and 2, as well as lowering levels of oxidized proteins [18]. It also boosted the activity of antioxidant enzymes in rats treated with DOX [19]. Additionally, empagliflozin decreased malondialdehyde levels in the heart, particularly within cardiac mitochondria, and lowered the activity of cardiac xanthine oxidase, which plays a significant role in DOX-related oxidative stress and cardiotoxicity [20]. Moreover, empagliflozin effectively reduced mitochondrial ROS production in isolated cardiomyocytes [21]. Dapagliflozin, on the other hand, blocked the DOX-induced suppression of nuclear factor erythroid 2–related factor 2 (Nrf2) nuclear translocation, thereby promoting the expression of Nrf2-dependent antioxidant enzymes, including heme oxygenase 1 and NAD(P)H quinone dehydrogenase 1 [22]. Moreover, Dapagliflozin also directly increased the levels of antioxidant enzymes such as catalase and superoxide dismutase, as demonstrated by the study conducted by Hazem [23]. In a recent study conducted by Quagliarello et al., human cardiomyocytes exposed to DOX ± dapagliflozin

were examined. The group treated with dapagliflozin exhibited a significant reduction in intracellular calcium levels, which correlated with improved mitochondrial function. Furthermore, dapagliflozin attenuated lipid peroxidation and reduced levels of ROS [24].

Anthracyclines trigger pro-inflammatory pathways that involve nuclear factor-kB (NF-kB) and tumor necrosis factor-alpha (TNF-α), resulting in the increased transcription of NLRP3, interleukin (IL)-1β, and IL-6, ultimately leading to apoptosis. The death of cardiomyocytes further activates inflammatory processes and promotes ROS production, causing functional and structural alterations in the myocardium, which are characterized by fibrosis and electrical disturbances

SGLT2i possess anti-inflammatory properties due to their direct effects on inflammatory pathways and improvements in cellular metabolism. Numerous preclinical studies have shown that empagliflozin and dapagliflozin may reduce the inflammation induced by DOX administration. In these studies, SGLT2i significantly mitigate the expression of NLRP3 and thus the levels of inflammatory cytokines such as IL-1β, IL-6, TNF-α, and NF-kB [20,22,25–28]. For example, in a recent study conducted by Quagliarello et al., the authors found that cardiomyocytes exposed to dapagliflozin and DOX exhibited significantly lower intracellular levels of cytokines and NLRP3-Myd88 compared to cardiomyocytes exposed to DOX alone. Notably, the levels in cardiomyocytes treated with dapagliflozin were comparable to those in cardiomyocytes not exposed to the chemotherapeutic agent. Additionally, the authors performed histological analysis to further evaluate the anti-inflammatory properties of dapagliflozin and they found that DOX induces tissue overexpression of p65/NF-κB. Notably, dapagliflozin significantly altered the renal and cardiac inflammatory profile by markedly reducing the expression of p65/NF-κB and preserving the tissue microstructure of cardiomyocytes and kidneys [24]. Moreover, it is known that anthracyclines cause systemic inflammation [29] and in the same study the authors found that dapagliflozin is able to reduce hs-CRP, IL-1, and Galectin-3 significantly, indicating systemic anti-inflammatory effects [24]. Interestingly, recent findings suggest that SGLT2i, and especially canagliflozin, may possess immune-regulating properties [30,31]. Consistent with these studies, Quagliarello et al. found a significant reduction in IL-2 secretion in activated human peripheral blood mononuclear cells (hPBMCs) exposed to dapagliflozin, indicating potential immune effects of SGLT2i [24].

Autophagy is an essential and conserved process in eukaryotic cells that plays a crucial role in maintaining cellular balance and ensuring cell survival in both normal and stressful situations. However, stress can disrupt autophagy regulation in the heart, potentially leading to cardiac dysfunction and HF. DOX can induce both excessive and insufficient expression of genes related to autophagy, which contributes to its cardiotoxic effects [32]. On one hand, anthracyclines cause excessive activation of autophagy, leading to the degradation of organelles and cellular components, thereby promoting cell death. On the other hand, anthracyclines inhibit autophagic flux, thereby favoring apoptosis [17]. Empagliflozin reduced doxorubicin (DOX)-induced cardiotoxicity by enhancing autophagic flux in murine hearts and cardiomyocytes. Wang et al. found that it directly interacts with sirtuin 3, forming a complex with beclin 1 and Toll-like receptor 9 to boost autophagy [33]. Meanwhile, Chang et al. reported that dapagliflozin protects diabetic rats and H9c2 cardiomyoblasts from DOX-induced cardiotoxicity by lowering endoplasmic reticulum (ER) stress, as shown by decreased ER-related proteins [34]. Additionally, Malik et al. recently published a study assessing the potential role of empagliflozin in mitigating ER stress in cardiomyocytes of rats treated with DOX. They found that cardiomyocytes pretreated with empagliflozin exhibited a significant reduction in mortality, primarily due to decreased ER stress. This was demonstrated by the reduced expression of ER stress-related apoptotic proteins. Moreover, mice pretreated with empagliflozin showed increased levels of IRE1, a key factor for effective protein folding and the degradation of misfolded proteins [35].

Ferroptosis is a form of regulated cell death. It is characterized by iron overload and ROS accumulation, resulting in lipid peroxidation of cell membranes. An increasing

number of studies have found that ferroptosis plays a vital role in the development of anthracycline-induced cardiotoxicity (AIC) [36]. Various preclinical studies show that SGLT2i may mitigate the cardiotoxicity induced by DOX by reducing the levels of ROS and lipid peroxidation, thus preventing ferroptosis [20,24,37]. Although, to our current knowledge, no specific studies have investigated the combination of canagliflozin and anthracyclines, preclinical studies on animal models of diabetic cardiomyopathy and HFpEF have demonstrated that canagliflozin can inhibit ferroptosis [38,39].

Cells adapt their metabolic processes and functions in response to environmental cues through the regulation of proteins such as mTOR, sirtuins (sirtuin 1, sirtuin 3, sirtuin 6), and AMPK. Dysregulation of these proteins is linked to cardiovascular disease. One key mechanism of DOX-induced cardiotoxicity is the down-regulation of sirtuin 1 and AMPK activity, leading to mitochondrial dysfunction, increased apoptosis, impaired autophagy, and heightened fibrosis [2]. SGLT2i improve cellular energy metabolism by boosting the expression or activity of signals associated with nutrient deprivation, including AMPK, sirtuins, and peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α) [40], while simultaneously reducing nutrient surplus signals such as mTOR activation in stressed tissues.

These inhibitors activate AMPK by inhibiting complex I of the mitochondrial respiratory chain [41–43]. Empagliflozin and dapagliflozin have been found to reduce DOX cardiotoxicity by activating AMPK. Empagliflozin triggers AMPK, sirtuin 1, and peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α)-mediated mitochondrial biogenesis. Dapagliflozin, on the other hand, mitigates short-term DOX cardiotoxicity through AMPK activation [28,44]. Moreover, empagliflozin administration in mice treated with DOX promotes mitochondrial biogenesis, likely by increasing PGC-1α expression, thereby preventing acute DOX-induced cardiotoxicity [37].

As previously discussed, SGLT2i increase circulating ketone levels, which serve as an energy source for the heart during "starving" conditions in heart failure. It has been hypothesized that SGLT2i may mitigate anthracycline-induced cardiotoxicity by increasing levels of beta-hydroxybutyrate (BHB). In a study conducted by Oh et al., cardiomyocytes incubated with BHB showed reduced AIC [45]. Furthermore, administration of dapagliflozin was associated with increased levels of BHB and reduced cardiotoxicity [46].

4.2. Trastuzumab

Human epidermal growth factor receptor-2 (HER-2) is overexpressed in various types of cancers, such as breast cancer, ovarian cancer, gastrointestinal cancer and bladder cancer. Trastuzumab is the main humanized monoclonal antibody against HER-2. Besides its presence in tumor tissue, HER2 has also been found in adult cardiomyocytes, along with other family members [40]. His ligand NRG1, released by cardiac microvascular endothelial cells during hemodynamic stress, binds to HER4, triggering HER4/HER2 dimerization and activating pathways like MAPK and PI3K-Akt. These pathways enhance cardiomyocyte survival, metabolism, and protection from oxidative stress. Trastuzumab blocking the HER2/NRG1 signaling, inhibits these pathways, leading to increased ROS and cardiomyocyte apoptosis and thus contributing to trastuzumab-induced cardiotoxicity (TIC) [47,48]. The NRG1/HER signaling pathway in the heart serves as a compensatory mechanism that is activated in response to stress, such as cardiotoxic drug exposure or ischemia. This may help explain why trastuzumab can heighten cardiotoxicity when used in conjunction with anthracyclines [49]. In this regard, in a recent preclinical study, empagliflozin effectively counteracted trastuzumab-induced oxidative stress in vivo and, in isolated mouse cardiomyocytes, mitigated DNA damage [21]. Moreover, recent studies have also demonstrated that one underlying mechanism of TIC is ferroptosis [50,51]. In line with these results, in a study conducted by Min et al., trastuzumab (TZM) significantly elevated serum lactate dehydrogenase (LDH) and troponin I levels, induced adverse myocardial remodeling (increased heart weight, chamber size, cardiomyocyte area, and interstitial fibrosis), and resulted in contractile dysfunction, improper handling of intra-

cellular calcium, oxidative stress, lipid peroxidation, mitochondrial injury, DNA damage, apoptosis, and ferroptosis [52]. Empagliflozin effectively attenuated these effects, showing robust cardioprotective benefits. In vitro studies showed that TZM-induced DNA damage correlated with lipid peroxidation and cardiomyocyte dysfunction. Additionally, the ferroptosis inducer erastin diminished empagliflozin's protection against lipid peroxidation and cardiomyocyte dysfunction (excluding DNA damage). Furthermore, inhibiting ferroptosis both in vivo and in vitro replicated empagliflozin's cardioprotective effects against TZM. Overall, these results suggest that empagliflozin may mitigate TZM-induced cardiotoxicity, possibly through mechanisms involving DNA damage and ferroptosis.

Recent evidence confirms that trastuzumab induces cardiotoxicity through the stimulation of the inflammatory response, as demonstrated by increased expression of NLRP3 and elevated levels of interleukins and ROS. Notably, trastuzumab-induced activation of NLRP3 enhances anthracycline-induced cardiotoxicity [53]. Supporting this, in an in vitro model, dapagliflozin demonstrated the ability to reduce trastuzumab-induced activation of NLRP3 and pro-inflammatory cytokines, thereby mitigating its cardiotoxic effects [54].

Another mechanism of TIC involves the inhibition of autophagy. Research indicates that trastuzumab lowers the expression of key autophagy-related proteins, including ATG5-12, ATG7, ATG14, and Beclin 1, leading to elevated ROS production in cardiomyocytes [48]. As discussed earlier, SGLT2i are capable of reactivating autophagy pathways, which could potentially serve as an additional mechanism of cardioprotection against TIC. However, to our current knowledge, there are no direct studies addressing this aspect.

Recent studies have shown that clinically relevant doses of trastuzumab negatively affect contractile and calcium regulation functions in cardiomyocytes, but do not cause cell death. Further RNA sequencing and functional analysis indicated that mitochondrial dysfunction and disrupted cardiac energy metabolism are the primary contributors to trastuzumab-induced cardiac dysfunction. This suggests that metabolic modulators may be crucial in the treatment of TIC [55]. Recently, two studies in human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) have shown trastuzumab to dysregulate metabolism likely at the level of AMPK [55,56]. Despite the plausible and appealing pathophysiological hypothesis, to date, no study has demonstrated that SGLT2i, through their previously discussed ability to enhance energy metabolism, can mitigate TIC.

4.3. Other Anticancer Therapies

Immune check-point inhibitors (ICIs) have recently revolutionized the prognosis of various types of cancer. The development of immune checkpoint inhibitors (ICIs) as a cancer treatment is based on their ability to activate immune checkpoint pathways, such as Programmed Cell Death Protein 1 (PD-1) and its ligand (PD-L1), as well as Cytotoxic T-lymphocyte Associated Protein 4 (CTLA-4). This activation enables the immune system to effectively engage T-cells against tumor cells [57]. However, given that immune checkpoints play a crucial role in maintaining immunological tolerance and preventing self-reactivity, it is not unexpected that the use of ICIs can lead to increased T-cell activity against healthy tissues. This hyperactivity can result in immune-related adverse events (IRAEs), including those affecting the heart. ICIs-induced cardiotoxicity is thought to stem from a pro-inflammatory cytokine storm within myocardial tissues. In this context, the anti-inflammatory and antioxidant properties of SGLT2 inhibitors may be significant in mitigating cardiotoxic effects associated with ICIs [58]. In line with this theory, recent findings indicate that dapagliflozin and empagliflozin may reduce the activation of the NLRP3 inflammasome and lower levels of pro-inflammatory cytokines in reaction to cardiotoxic effects caused by ipilimumab in AC16 human cardiomyocytes [20,54]. The authors also found that empagliflozin and dapagliflozin reduced ipilimumab-induced cytotoxicity by reducing lipid peroxidation, circulating levels of ROS and intracellular calcium overload in human cardiomyocytes. Moreover, in an experimental model of autoimmune myocarditis, canagliflozin markedly alleviated cardiac inflammation and improved cardiac function,

by reducing NLRP3 expression and circulating levels of pro-inflammatory cytokines and Th-17 cells infiltration in myocardial tissue [20].

Cyclophosphamide (CP) is a widely used anticancer alkylating agent. Unfortunately, it has well-known serious cardiotoxic effects that restrict its dosing regimen, lowering its effectiveness or even leading to cessation of the treatment [59]. A recent study by Mahmoud Refaie et al. found that CP can cause cardiac injury, indicated by increased levels of cardiac enzymes, blood pressure, MDA, TNFα, HIF1α, SGLT2, and cleaved caspase-3, along with toxic histopathological changes. In contrast, reduced glutathione (GSH), total antioxidant capacity (TAC), VEGF, and eNOS levels were significantly lower. Co-administration of dapagliflozin significantly alleviated CP-induced cardiac damage, likely due to its SGLT2 inhibition and antioxidant, anti-inflammatory, and anti-apoptotic effects [59].

Tyrosine kinase inhibitors (TKIs) are anticancer therapeutics often prescribed for long-term treatment [60]. However, TKI-induced cardiotoxicity poses a significant risk, potentially leading to death or a decreased quality of life. Effective treatments to mitigate cardiac damage caused by TKIs are limited, primarily due to an incomplete understanding of the underlying molecular pathology. Recently Wang et al. demonstrated that the main mechanisms of TKIs cardiotoxicity include ER-stress, pro-inflammatory properties and oxidative stress [60]. Empagliflozin has been demonstrated to reduce cardiac dysfunction caused by sunitinib in both in vivo and in vitro studies by activating AMPK, which plays a role in regulating cardiomyocyte autophagy through the AMPK/mTOR signaling pathway. Furthermore, recent research shows that canagliflozin, in contrast to empagliflozin or dapagliflozin, alleviates carfilzomib-induced endothelial apoptosis by restoring AMPK levels. Additionally, empagliflozin promotes autophagic flux in human aortic endothelial cells exposed to ponatinib, resulting in decreased cellular senescence. These results collectively highlight the protective effects of SGLT2i against various TKI-induced cardiotoxicities through mechanisms involving AMPK activation and autophagy regulation [61–63].

5. The Potential Role of SGLT2i in Cardioncology: From Bench to Bedside

A growing body of preclinical and clinical evidence highlights the promising role of SGLT2i as a cardioprotective strategy for cancer patients receiving cardiotoxic therapy. Most of the available data pertains to anthracyclines, owing to their widespread use and the well-documented and thoroughly understood cardiotoxic effects.

5.1. Preclinical Studies

Table 1 summarizes in vivo and in vitro studies conducted to date on the potential role of SGLT2i in mitigating the cardiotoxic effects of various cancer therapies. The majority of these studies have focused on empagliflozin and dapagliflozin, while a smaller number have explored the role of canagliflozin in cancer patients.

Empagliflozin has exhibited extensive cardioprotective properties against DOX-induced cardiotoxicity, including the preservation of cardiac functionality and prevention of left ventricular (LV) remodeling. This is shown by improved LV ejection fraction and fractional shortening, alongside preserved LV dimensions and preventing hypertrophic changes and fibrosis [18–20,27,33,45]. Additionally, empagliflozin has been shown to improve myocardial strain and decrease cardiac fibrosis in DOX-treated murine models [64]. Additionally, empagliflozin prevented the prolongation of QT and corrected QT intervals induced by DOX [37]. In related studies, it alleviated hypertension and cardiac dysfunction caused by sunitinib, effectively reversing impairments in left ventricular LV systolic and diastolic function while also restoring coronary flow reserve [61]. Dapagliflozin also demonstrated considerable cardioprotective effects against DOX-induced cardiotoxicity. It increased ejection fraction and fractional shortening, mitigated hemodynamic declines, and reduced LV dimensions [22,27,28,34,46,65]. Dapagliflozin also corrected electrocardiographic abnormalities caused by DOX [66]. Moreover, both empagliflozin and dapagliflozin have been found to decrease the senescence of human aortic endothelial cells treated with ponatinib [62].

To date, there is no evidence from in vivo or in vitro studies supporting the cardioprotective effects of canagliflozin against anthracycline-induced cardiotoxicity. However, a single study has shown its efficacy against carfilzomib-induced cardiotoxicity [63]. Similarly, empagliflozin has demonstrated efficacy in mitigating these effects, albeit in single study [67].

Table 1. Preclinical studies.

Author	SGLT2i	Chemoterapy	Major Findings
Oh et al. (2019) [45]	EMPA	DOX	↑ FS and contractility. ↓ TnI, BNP and cardiac fibrosis
Yang et al. (2019) [18]	EMPA	DOX	↑ FE ↓ BNP and LV remodelling
Wang et al. (2020) [68]	EMPA	DOX	↑ FS and contractility. ↓ TnI, BNP and cardiac fibrosis
Sabatino et al. (2020) [64]	EMPA	DOX	↑ FE and FS ↓ BNP and LV remodelling
Baris et al. (2021) [37]	EMPA	DOX	↑ FE and FS ↓ QTc interval and myofibrill loss
Chang et al. (2021) [34]	DAPA	DOX	↑ FE and FS
Hsieh et al. (2022) [22]	DAPA	DOX	↑ FE and FS
Belen et al. (2022) [26]	DAPA	DOX	↓ TnI, BNP and TNF
Hu et al. (2023) [27]	DAPA	DOX	↑ FS and contractility. ↓ LVIDd and LVIDs and LV remodelling
Quagliarello et al. (2023) [28]	DAPA	DOX	↑ FE
Ali et al. (2023) [69]	CANA	Cisplatin	↓ AST, ALT, CK-MB, LDH

5.2. Clinical Studies

Table 2 summarizes the results of key clinical studies conducted so far, which have evaluated the effectiveness of SGLT2i in mitigating cardiotoxic damage caused by various cancer therapies.

Gongora et al. [70] conducted a retrospective observational study including 96 cancer patients treated with anthracyclines and 32 cancer patients treated with anthracyclines and SGLT2i. Primary cardiac outcome was a composite of cardiac events (HF incidence, HF admissions, new cardiomyopathy [>10% decline in ejection fraction to <53%], and clinically significant arrhythmias). The primary safety outcome was overall mortality. The incidence of cardiac events was significantly lower in case patients compared to control participants (3% versus 20%; $p = 0.025$). Additionally, case patients showed reduced overall mortality in comparison to control participants (9% versus 43%; $p < 0.001$), as well as a lower incidence of the combined outcomes of sepsis and neutropenic fever (16% versus 40%; $p = 0.013$). In the same year, Hendryx et al. [71] published the results of their study, which tracked 3185 newly diagnosed HCC patients aged 66 years or older with pre-existing T2DM from 2014 to 2019. The initiation of SGLT2i was linked to a significantly lower mortality risk after adjusting for potential confounders (HR = 0.68, 95% CI = 0.54–0.86). This association was even more pronounced with prolonged use (HR = 0.60, 95% CI = 0.41–0.88). Furthermore, the reduction in mortality risk, ranging from 14% to 60%, was consistent regardless of patient demographics, tumor characteristics, and cancer treatments.

Similarly, Abdel Qadir et al. [72] conducted a population-based cohort study involving individuals over 65 years of age with treated diabetes and no prior HF who received anthracyclines between 1 January 2016 and 31 December 2019. The study outcomes included hospitalization for HF, new HF diagnoses (both in-hospital and out-of-hospital), and documentation of any cardiovascular disease in future hospitalizations. The study included 933 patients, 99 of whom were treated with SGLT2i. SGLT2i exposure was associated with an HR of 0 for HF hospitalization ($p < 0.001$), indicating no HF hospitalizations in the SGLT2i group. However, there was no significant difference in the incidence of new HF diagnoses (HR: 0.55; 95% CI: 0.23–1.31; $p = 0.18$) or CVD diagnoses (HR: 0.39; 95%

CI: 0.12–1.28; $p = 0.12$). There was also no significant difference in mortality (HR: 0.63; 95% CI: 0.36–1.11; $p = 0.11$).

In another retrospective study [73] involving 8640 cancer patients with diabetes receiving various anticancer treatments, those on SGLT2i had a hospitalization rate for new HF that was three times lower than those not receiving SGLT2i (2.92 vs. 8.95 per 1000 patient-years, $p = 0.018$). Cox regression and competing risks models indicated that SGLT2i were linked to a 72% decrease in the risk of hospitalization for HF ($p = 0.013$). Furthermore, SGLT2i usage was associated with improved overall survival rates (85.3% vs. 63.0% at 2 years, $p < 0.001$). The safety profile of SGLT2i was also favorable, with similar risks of serious adverse events such as hypoglycemia and sepsis in both groups. Recently, a nationwide Korean cohort of 81,572 patients treated with AC chemotherapy between 2014 and 2021 was analyzed. Patients were grouped into those with T2DM taking SGLT2i (n = 780), those with T2DM taking other hypoglycemic agents (non-SGLT2i; n = 3455), and non-diabetic patients (non-DM; n = 77,337). The primary outcome was a composite of HF, hospitalization, acute myocardial infarction, ischemic stroke, and death. After propensity score matching, 779 SGLT2i users were compared with 7800 non-DM patients and 2337 non-SGLT2i users. The SGLT2i group had significantly better outcomes than the non-DM group (adjusted hazard ratio [HR] = 0.35, 95% confidence interval [CI] = 0.25–0.51) and the non-SGLT2i group (adjusted HR = 0.47, 95% CI = 0.32–0.69), indicating fewer cardiovascular events and deaths among SGLT2i users [74].

Luo et al. [75] conducted a retrospective cohort study including 24,915 patients with non-small-cell lung cancer (NSCLC) and pre-existing T2DM, 531 of whom receiving SGT2i. They found that the use of SGLT2i was associated with a significantly reduced mortality risk after adjusting for potential confounders (HR = 0.68, 95% CI = 0.60–0.77), with an even stronger association observed for longer durations of use (HR = 0.54, 95% CI = 0.44–0.68). Additionally, SGLT2i use significantly reduced mortality risk across different patient demographics, tumor characteristics, and cancer treatments.

Interestingly, in a recent retrospective study, Avula et al. [76] evaluated the effectiveness of SGLT2i in patients who developed cardiac dysfunction due to various cancer therapies. The study included 1280 patients aged 18 years and older with histories of T2DM, cancer, and exposure to various potentially cardiotoxic cancer treatments, who were diagnosed with cardiomyopathy or HF. Patients were split between those using SGLT2i and those who did not. During a follow-up period of two years, the ones on SGLT2i had a lower risk of acute HF exacerbation (OR: 0.483 [95% CI: 0.36–0.65]; $p < 0.001$) and all-cause mortality (OR: 0.296 [95% CI: 0.22–0.40]; $p = 0.001$). Patients receiving SGLT2i had a lower incidence of all-cause hospitalizations or emergency department visits (OR: 0.479; 95% CI: 0.383–0.599; $p < 0.001$), atrial fibrillation/flutter (OR: 0.397 [95% CI: 0.213–0.737]; $p = 0.003$), acute kidney injury (OR: 0.486 [95% CI: 0.382–0.619]; $p < 0.001$), and the need for renal replacement therapy (OR: 0.398 [95% CI: 0.189–0.839]; $p = 0.012$). Finally, in a recent retrospective analysis, Perelman studied patients diagnosed with cancer and T2DM who were treated with ICIs at their medical center. Patients were categorized into two groups based on whether they received SGLT2i as part of their baseline treatment or not. The study comprised 119 patients, among whom 24 (20%) were in the SGLT2i group. Over a median follow-up period of 28 months, 61 (51%) patients died. Importantly, the SGLT2i group exhibited a significantly lower all-cause mortality rate compared to the non-SGLT2i group (21% vs. 59%, $p = 0.002$). While there were no statistically significant differences in the occurrence of major adverse cardiac events (MACE) between the groups, it is noteworthy that no cases of myocarditis or atrial fibrillation were observed in the SGLT2i group, whereas the non-SGLT2i group experienced 2 cases of myocarditis and 6 cases of atrial fibrillation [58].

Table 2. Clinical studies.

Author	Cancer Type	SGLT2i	Major Findings
Gongora et al. (2022) [70]	Various	CANA (34% [n ¼ 11]), DAPA (16% [n ¼ 5]), EMPA (50% [n ¼ 16]	↓ HF admissions, CV events and rate of cardiac dysfunction in patients receiving SGLT2i
Abdel qadir et al. (2023) [72]	Various	CANA, DAPA, EMPA	↓ HF admissions, no differences in HF incidence in patients receiving SGLT2i
Chiang et al. (2022) [73]	Various; mostly GI and GU cancer	CANA, DAPA, EMPA	↓ HF admissions. ↑OS in patients receiving SGLT2i
Hwang et al. (2023) [77]	Various	CANA, DAPA, EMPA	↓ CV composite outcome (HF admissions, stroke, MI, death) in SGLT2i group
Luo et al. (2023) [75]	NSCLC	CANA mostly	↓ mortality risk with stronger association wih longer duration use in SGLT2i group
Avula et al. (2024) [76]	Various	CANA, DAPA, EMPA	↓ HF exacerbations, AF, kidney injury, CRRT and all-cause mortality in SGLT2i patients
Perelman et al. (2024) [58]	NSCLC, RCC and HCC	DAPA, EMPA	↓ All-cause mortality in SGLT2i group. ↓ MACE, including myocarditis, acute coronary syndrome, heart failure, and arrhythmia

6. Anticancer Properties of SGLT2i

An effective cardioprotective strategy in cardio-oncology should achieve a reduction in the potential cardiotoxic effects of cancer therapies without compromising their antitumor efficacy, thus enhancing PFS and OS in cancer patients. Therefore, given the positive effects of SGLT2i in reducing cardiotoxicity associated with cancer therapies, it is crucial to explore their influence on the antitumor effectiveness of these treatments

In the past, there were concerns about the potential carcinogenic risk associated with SGLT2i. Specifically, empagliflozin was suspected to be linked to an increased risk of bladder cancer [78,79]. However, subsequent evidence has dispelled these concerns, showing that SGLT2i do not increase the risk of developing malignant tumors [80,81]. Instead, they are associated with improved survival rates in cancer patients, as previously reported. Building on this evidence, several preclinical studies consistently show that SGLT2i effectively inhibit tumor growth in a range of cancer types, such as hepatocellular carcinoma [14,82–84], glioblastoma [85], osteosarcoma [13], pancreatic cancer [86], prostate cancer [82], lung cancer [38,82,87–89], cervical cancer [68], renal cancer [90], papillary thyroid cancer [91], colon cancer [92], and breast cancer [82,93–95]. Moreover, combining SGLT2i with other chemotherapy agents and ionizing radiation in these preclinical studies enhances treatment efficacy and improves cancer cell responsiveness to therapy.

Several mechanisms have been proposed to explain the antitumor properties of SGLT2i, as detailed in the literature [96–98]. Notably, recent investigations have revealed significant upregulation of SGLT2 in numerous tumors and that it plays a pivotal role in promoting cancer cell survival [98].

Here we report the key mechanisms underlying antitumor effects of SGLT2i (Figure 2).

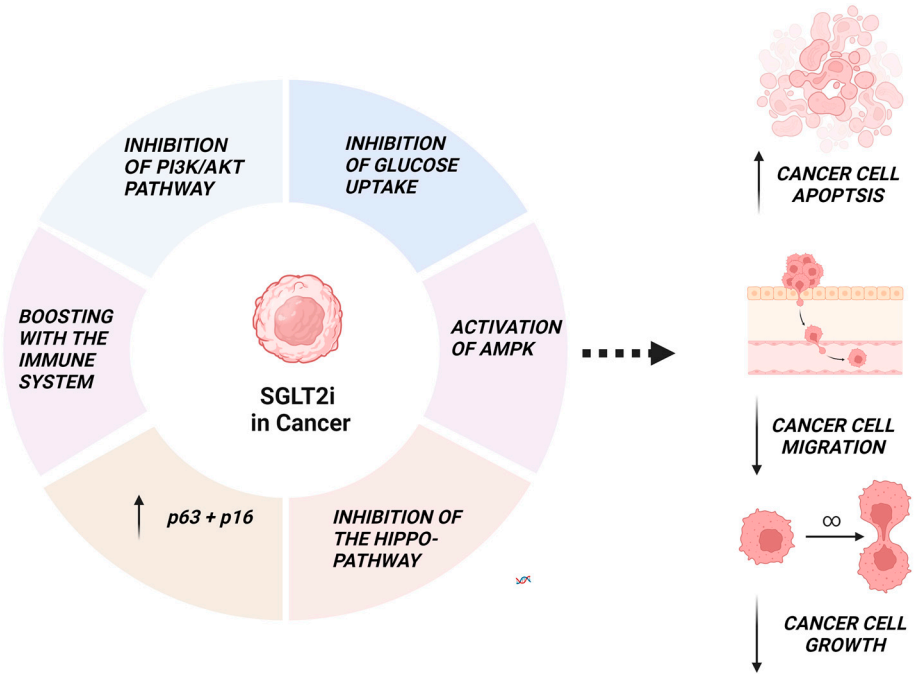

Figure 2. Anticancer properties of SGLT2i. SGLT2i exert direct antitumor effects through various molecular pathways. They reduce the activation of the PI3K/AKT pathway, leading to decreased metabolic activity, growth, and survival of tumor cells. Additionally, SGLT2i diminish glucose uptake, thereby inhibiting the growth and metabolism of tumor cells that predominantly rely on glucose. They activate AMPK, resulting in the inhibition of cell growth, metastasis, and chemoresistance. SGLT2i also enhance the host immune response against tumor cells. Furthermore, they increase the expression of proteins p16 and p64, which are essential for halting tumor cell growth. Canagliflozin additionally reduces the Hippo pathway, a critical regulator of tumor cell growth and proliferation. ↑, promotes; ↓, inhibites. **The figure was created using BioRender** (www.biorender.com).

6.1. Inhibition of Phosphoinositide 3-Kinas (PI3K)/AKT Pathway

The phosphoinositide 3-kinase (PI3K)-AKT signaling pathway is the most frequently activated pathway in human cancers. Normally, this pathway is triggered by insulin, growth factors, and cytokines, regulating essential metabolic functions such as glucose metabolism, macromolecule biosynthesis, and redox balance. These processes are crucial for maintaining systemic metabolic stability as well as supporting the growth and metabolism of individual cells [99]. Abnormal activation of this signaling network is among the most common occurrences in human cancer, leading to a loss of regulation over cell growth, survival, and metabolism from exogenous growth stimuli. In this regard, preclinical studies show that SGLT2i inhibit this key pathway in cancer cells, resulting in reduced cellular proliferation [13,83,86,89].

6.2. Inhibition of Glucose Uptake

Cancer cells consume elevated amounts of glucose even in the presence of oxygen, leading to increased lactate production. This process, known as aerobic glycolysis or the Warburg effect, has been observed in various tumor types [100]. As previously noted, many cancer cells overexpress both SGLT2 and SGLT1 receptors. Consequently, SGLT2i interfere with glucose uptake and aerobic glycolysis, inducing an energy crisis that ultimately triggers apoptosis [52,82,83,85,89,91,101,102]. Interestingly, canagliflozin may also inhibits glucose transporters and it exhibited an higher affinity for SGLT1 and SGLT2 [103].

6.3. Activation of AMPK Pathway

One of the primary mechanisms underlying the antitumor properties of SGLT2i, as reported in the literature, is the activation of AMPK [14,68,82,83,85,91,95,104]. SGLT2i

inhibit the mitochondrial complex I, resulting in phosphorylation and activation of AMPK. Activated AMPK inhibits the mTOR/p70S6K pathway, resulting in cell cycle arrest and apoptosis [83,85]. Importantly, canagliflozin has been identified as the most effective SGLT2 inhibitor in vitro, demonstrating a greater ability to inhibit mitochondrial complex I compared to other SGLT2 inhibitors [105]. This may explain why canagliflozin exhibits antiproliferative properties at clinically relevant concentrations, whereas dapagliflozin requires suprapharmacologic levels to achieve similar effects [92]. However, in a recent study, empagliflozin also showed similar properties, enhancing the activation of AMPK and inhibiting the expression of mTOR, leading to NF-κB inactivation and inhibition of hepatocellular and breast cancer growth [106,107]. Activated AMPK also reduces the expression of forkhead box A1 (FOXA1) and the sonic hedgehog (SHH) signaling molecule, which is prominently expressed in numerous tumor types and contributes to tumor cell proliferation, resistance to chemotherapy, and metastasis [108]. In a recent in vitro study, empagliflozin activated the AMPK signaling pathway, inhibited the expression of FOXA1 and SHH to inhibit the proliferation, migration and induction of apoptosis in cervical cancer cells [68].

Moreover, the AMPK-mTOR pathway is a key activator of hypoxia-inducible factor 1-α (HIF-1-α), which is pivotal in numerous processes, including glucose metabolism, the onset of the Warburg effect, angiogenesis, cell growth and survival, and invasion and metastasis. These functions collectively contribute to the tumor's resistance to cytotoxic agents [109,110]. Recently, Biziotis et al. showed that canagliflozin may inhibit the proliferation and survival of NSCLC cells by down-regulating HIF-1-α protein levels [104].

6.4. Boosting with the Immune System

Recent findings have demonstrated that SGLT2i exhibit antitumor properties by enhancing the host immune response against cancer cells through at least two distinct mechanisms. A key mechanism involves the expression of the immune checkpoint PD-L1 by cancer cells [111]. PD-L1, by binding to PD-1 on T cells, enables cancer cells to evade the immune response [112]. In cancer cells expressing SGLT2, the interaction between SGLT2 and PD-L1 is crucial for maintaining high levels of PD-L1 expression. Canagliflozin, by disrupting this interaction, leads to the downregulation of PD-L1 levels, thereby facilitating the immune response against NSCLC, pancreatic and ovarian cancer cells [111].

Additionally, another study found that canagliflozin suppressed osteosarcoma tumor growth and enhanced immune cell infiltration [13]. This effect was mediated by the upregulation of stimulator of interferon genes (STING) and the activation of the interferon regulatory factor 3 (IRF3)/interferon-beta (IFN-β) pathway, which is known to promote immune cell activation. The research indicated a negative correlation between SGLT2 expression levels and immune cell infiltration in sarcoma, including CD8+ T cells, CD4+ T cells, and CD4+ T helper type 2 cells. As a result, inhibiting SGLT2 with canagliflozin or silencing SGLT2 led to an increase in the number of infiltrating immune cells, thereby reducing tumor growth.

6.5. Other Potential Mechanisms

The Hippo pathway is the major regulator of organ growth and proliferation and recent studies have demonstrated that it might contribute to cancer development [113]. SGLT2 promotes the expression of the YES-associated protein 1, which is a positive key regulator of the Hippo pathway [101]. Canagliflozin has been shown to inhibit the expression of the YES-associated protein 1, thus down-regulating the activation of the hippo pathway [113]. One of the fundamental mechanisms underlying carcinogenesis is the abnormal progression of the cell cycle, which makes cell cycle regulators promising targets for anticancer therapies. In a recent study [102], the simultaneous administration of canagliflozin combined with doxorubicin (DOX) and empagliflozin with DOX effectively disrupted cell cycle progression during the S phase. Notably, only the canagliflozin and DOX combination (CAN + DOX) resulted in a significant increase in the expression of the p16 gene, recognized as a critical

tumor suppressor. The activation of p16 inhibits the cyclin-dependent kinases CDK4/6 and CDK2, which are essential for proper cell cycle regulation and are often aberrantly activated in nearly all cancer cells [114]. Additionally, all treatments were associated with a marked increase in the expression of the p63 gene, which is widely regarded as a tumor suppressor protein [102].

7. Conclusions, Limitations and Future Perspectives

Given the numerous cardiovascular and renal benefits of SGLT2i observed in recent years, these medications could represent a promising strategy for cardioprotection in cancer patients undergoing potentially cardiotoxic therapies. The evidence gathered in our review indicates that SGLT2i not only mitigate the cardiotoxic effects of various anticancer treatments but may also enhance the antitumor efficacy of chemotherapy. This dual benefit could potentially lead to reduced dosages of chemotherapeutic agents, decreased cardiotoxicity, and improved OS and PFS for these patients.

However, several limitations must be acknowledged. Most of the studies included in this review are preclinical, with the majority focusing on SGLT2i in non-cancerous mice treated with chemotherapy, rather than in mice with cancer undergoing chemotherapy. Additionally, with the exception of a single study, there is a lack of direct comparative studies between different SGLT2i.

Clinical data available are primarily derived from retrospective studies, which limits the robustness of the evidence. Furthermore, clinical studies have predominantly involved samples composed mostly of patients with DM.

To address these limitations, future research should prioritize conducting studies on animal models with established cancers to better understand the effects of SGLT2i in the context of malignancy and chemotherapy. Moreover, direct comparative studies between various SGLT2i could provide valuable insights into their relative efficacy and safety profiles. Expanding clinical trials to include a more diverse patient population, including those without DM, will also be crucial for generalizing findings and assessing the broader applicability of SGLT2i in cancer therapy.

Finally, moving beyond retrospective analyses to prospective, randomized controlled trials will be essential for generating more robust clinical evidence. In this regard, the EMPACT (EMPAgliflozin in Prevention of Chemotherapy-related CardioToxicity) (NCT05271162) trial is currently underway. It is a randomized, multi-center, double-blind trial assessing the efficacy of empagliflozin in preventing LV dysfunction in cancer patients receiving high doses of anthracyclines. It will include 220 patients with cancer, no prior heart failure, and LV ejection fraction (EF) $\geq$ 50%, randomized to receive either 10 mg of empagliflozin daily or a placebo. The primary objective is to evaluate whether empagliflozin can prevent a reduction in LVEF, monitored by echocardiography and cardiovascular magnetic resonance (CMR). Secondary endpoints include all-cause and cardiovascular deaths, myocardial infarction, ischemic stroke, as well as structural myocardial changes, global longitudinal strain (GLS), and cardiac biomarkers.

In conclusion, SGLT2i represent a highly promising strategy in the field of cardio-oncology. Their ability to mitigate cardiotoxic effects associated with cancer therapies, coupled with their potential direct anticancer effects across various malignancies, positions them as pivotal agents in improving therapeutic outcomes while safeguarding cardiovascular health in oncology patients.

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