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REVIEW

SGLT2 Inhibitors in Combination Therapies for Tumors: A Novel Approach to Synergistic Treatment Strategies

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Abstract: Sodium-glucose cotransporter 2 (SGLT2) inhibitors, originally developed for glycemic control in type 2 diabetes, have shown potential therapeutic effects in cancer treatment. Studies suggest that SGLT2 inhibitors can suppress tumor growth and proliferation through the modulation of metabolic reprogramming in tumor cells, inhibition of tumor glucose uptake, and regulation of the tumor microenvironment. Recent studies have emphasized the potential benefits of combining SGLT2 inhibitors with conventional anticancer therapies, including chemotherapy (CT), immunotherapy, and targeted therapies. Several clinical trials are currently evaluating the safety and efficacy of these combinations. Both preclinical and clinical studies primarily explore the effectiveness of SGLT2 inhibitors in inhibiting tumor growth, reducing metastasis, and enhancing treatment outcomes. Identifying combination therapies with SGLT2 inhibitors could enable more personalized treatment selection and optimization. This review provides a comprehensive summary of the antitumor effects and underlying mechanisms of SGLT2 inhibitors when combined with conventional anticancer therapies, aiming to elucidate their emerging role in cancer treatment. Combination regimens involving SGLT2 inhibitors have the prospect to overcome certain limitations of monotherapy, offering promising clinical benefits and improving patient outcomes.

Keywords: SGLT2 inhibitors, tumor metabolism, antineoplastic agents, anticancer therapy, combination therapy

Introduction

Sodium-glucose cotransporter 2 (SGLT2) is a membrane protein located in the brush border of the proximal tubule and plays a crucial role in reabsorbing filtered glucose into the bloodstream. Approximately 90% of filtered glucose is reabsorbed by SGLT2, while the remaining 10% is reabsorbed by SGLT1.[1] SGLT2 inhibitors are antihyperglycemic drugs that target the glucose transporter. The transporter is predominantly expressed in the proximal renal tubules and is responsible for the majority of glucose reabsorption in the kidneys.[2] By inhibiting renal glucose reabsorption, SGLT2 inhibitors selectively enhance urinary glucose excretion and lower blood glucose levels. The mechanism is through an insulin-independent pathway, and mainly contributing to improved metabolic profiles.[3,4] SGLT2 inhibitors are currently approved for the treatment of Type 2 diabetes[5] (Figure 1). The glucose-lowering effects of SGLT2 inhibitors are accompanied by several additional benefits. In addition to reducing blood glucose levels, these inhibitors promote weight loss, lower blood pressure, reduce the risk of cardiovascular diseases, and exhibit renoprotective activity.[6,7]

Notably, the anticancer effects of SGLT2 inhibitors have emerged as a growing area of research, with an increasing study focusing on their anticancer properties, which has gradually developed into a field alongside diabetology, cardiology, and nephrology. Accumulating studies have indicated the potential clinical benefits of these agents in cancer

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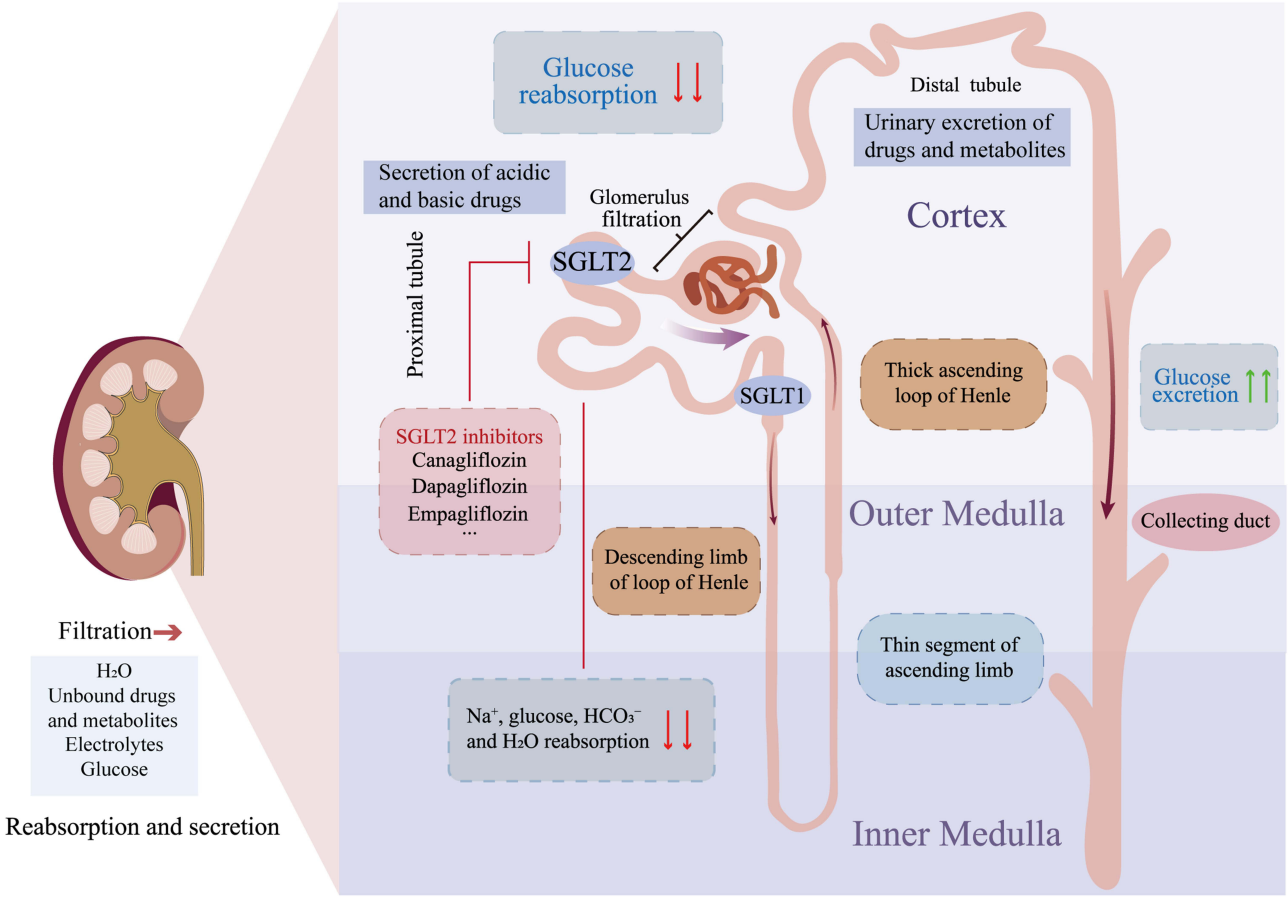

Figure 1 Role of SGLT2 inhibitors in renal glucose handling. SGLT2 inhibitors act on the proximal tubule to block SGLT2-mediated glucose reabsorption, leading to decreased glucose uptake from the filtrate. The inhibition reduces glucose uptake from the filtrate and increases urinary glucose excretion. The schematic representation delineates key nephron structures, including the glomerulus, proximal tubule, loop of Henle, distal tubule, and collecting duct. Red arrows indicate the attenuation of glucose reabsorption in the proximal tubule, while green arrows represent the consequent augmentation of glucose excretion in the urine.

therapy.[3,8,9] Tumor cells primarily depend on glycolysis for energy production, whereas normal cells rely on mitochondrial oxidative phosphorylation. Hyperglycemia creates a favorable environment for cancer cell growth and proliferation.[10,11] Studies have shown that SGLT2 is overexpressed in tumor cells, leading to increased glucose uptake. Inhibiting SGLT2 expression has been demonstrated to effectively suppress tumor growth and metastasis in various cancers, including breast cancer, lung cancer, liver cancer, prostate cancer, and glioma.[12–15] In addition to reducing glucose uptake, SGLT2 inhibitors enhance anticancer activity by lowering inflammation, modulating metabolic reprogramming, and decreasing oxidative stress.[16–18] For instance, SGLT2 inhibitors have been shown to upregulate *SIRT3 (sirtuin 3)* expression, leading to increased oxidative stress, autophagy, and apoptosis in CRC (colorectal cancer).[19]

Cancer, characterized by high adaptability and heterogeneity, remains challenging to treat with monotherapy, particularly within the complex tumor microenvironment (TME). Such monotherapies often lead to limited clinical efficacy, notable adverse effects, inadequate tumor coverage, and high risk of drug resistance. Thus, current research in oncology has increasingly focused on combination therapies. For instance, combining chemotherapy with immune checkpoint inhibitors not only directly eliminates tumor cells but also enhances the immune response against residual cancer cells. Similarly, integrating radiotherapy with targeted therapies can improve local tumor control and help overcome resistance mechanisms. The combining with chemotherapy, radiotherapy, or immune checkpoint inhibitors has shown promise in enhancing antitumor efficacy through synergistic mechanisms—such as amplifying metabolic stress, improving immune responsiveness, or sensitizing tumor cells to cytotoxic agents. By employing complementary mechanisms, combination therapies can more effectively inhibit tumor progression, reduce adverse effects, increase drug

sensitivity, lower relapse rates, and suppress metastasis. Similarly, the use of SGLT2 inhibitors as monotherapy for cancer presents notable limitations. A major challenge is that the therapeutic concentrations required for efficacy may exceed clinically achievable or safe levels.[20] This could lead to undesirable side effects or toxicity, particularly in patients with preexisting conditions, such as kidney disease, or in elderly individuals, where renal excretion pathways may be compromised.[21] In addition, the ability of SGLT2 inhibitors to inhibit tumor growth mainly attribute to the mechanisms such as the reduction of oxidative damage and regulation of glucose metabolism. However, not all tumors exhibit the same degree of metabolic reliance on glucose or on other pathways targeted by SGLT2 inhibitors, which may limit their potential clinical applications.

Given these limitations, a growing interest in exploring combination therapy approaches has been exhibited, with the aim of enhancing the efficacy of SGLT2 inhibitors and expanding their therapeutic applications. When used in combination with cancer therapies, SGLT2 inhibitors exert multiple mechanisms of action that effectively enhance the efficacy of traditional anticancer agents. For example, in combination with radiotherapy (RT), radiosensitivity is significantly enhanced by SGLT2 inhibitors through the disruption of metabolic pathways and the elevation of oxidative stress.[22,23] When combined with chemotherapeutic agents such as paclitaxel and cisplatin (CPT), SGLT2 inhibitors reduce glucose uptake in cancer cells, activate the AMPK pathway, and inhibit key signaling pathways like PI3K/AKT, promoting apoptosis and enhancing immune cell infiltration.[24–26] Furthermore, SGLT2 inhibitors mitigate the cardiotoxicity associated with anthracycline drugs and antibody therapies. The effects of the antidiabetic SGLT2 inhibitors in improving tumor growth and metastasis have been explored in both in vitro and in vivo tumor models[27,28] (Tables 1 and 2). Despite recent advances in research on SGLT2 inhibitors in combination cancer therapies, several challenges and research gaps remain.[29,30] A primary limitation is the lack of a systematic understanding of the synergistic antitumor mechanisms between SGLT2 inhibitors and other therapeutic modalities.[12] Current studies are mostly confined to specific tumor types or experimental models, lacking comprehensive, cross-cancer comparisons and integrative analyses. Furthermore, optimal dosing regimens, treatment sequencing, and clinical efficacy remain insufficiently defined, while clinical validation data are still limited.[29] Future studies should focus on delineating the molecular basis of the synergistic effects of SGLT2 inhibitors in multimodal regimens, optimizing their integration with existing anticancer therapies, and systematically evaluating their safety, pharmacodynamic characteristics, and translational potential to advance their clinical application in oncology.[31,32]

This review provides a comprehensive overview of the emerging role of SGLT2 inhibitors in cancer therapy. It summarizes current understanding of their biological mechanisms, metabolic regulatory functions, and therapeutic effects across diverse cancer types. Particular emphasis is placed on their capacity to modulate tumor metabolism, oxidative stress, and immune responses, as well as on their synergistic interactions with chemotherapy, radiotherapy, and immunotherapy. By integrating mechanistic insights with translational perspectives, this review establishes a conceptual framework for the rational application of SGLT2 inhibitors in precision oncology, offering new avenues to overcome therapeutic limitations and improve clinical outcomes for cancer patients.

The Anti-Tumor Mechanism of SGLT2 Inhibitors

SGLT2 Inhibitors and Tumor Inflammation

Inflammation plays a critical role in tumor initiation and progression and is closely associated with the onset and malignant progression of various cancer types. Inflammatory mediators produced during the inflammatory response, including cytokines, chemokines, substance P, proteolytic enzymes, and lipid mediators, contribute to aberrant inflammatory signaling pathways by altering the expression of tumor-associated genes, which promote angiogenesis and inhibit apoptosis, ultimately influencing tumor progression.[54] SGLT2 inhibitors exhibit anti-inflammatory properties, primarily through the modulation of the AMPK pathway, various cytokines, and the NLRP3 inflammasome. Numerous preclinical studies have evaluated the role of SGLT2 inhibitors, including empagliflozin, dapagliflozin, canagliflozin, and tofogliflozin, in mitigating tumor-associated inflammation.

Tofogliflozin has been reported to downregulate cytokines such as TNF-α and IL-6, consequently mitigating the inflammatory cascade associated with liver fibrosis and tumorigenesis. Additionally, it has been shown to reduce macrophage infiltration in non-alcoholic steatohepatitis (NASH).[38] In WD-fed MC4R-KO mice, canagliflozin treatment

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Table 1 Anti-Cancer Potential Effects of SGLT2i in vivo

First Author (Year)	Cancer Type	Cancer Model	SGLT2i Treatment	Key Findings	Results and Proposed Mechanism
Akingbesote et al (2022)[24]	Breast cancer	MMTV-PyMT and 4T1 mouse	Dapagliflozin (2.5 mg/kg)	↓ Fasting and postprandial insulin levels ↓ Tumor glucose uptake ↓ Tumor growth	↑ Sensitivity to Dapagliflozin treatment. (Tumors with mutations upstream of the PI3K/Akt insulin signaling pathway)
Sabaa et al (2022)[33]	Breast cancer	FemaleWistar rats	Canagliflozin (10 mg/kg)	↓ Tumor weight and volume ↓ MDA ↑ TAC ↓ Tumor inflammatory mediators (NLRP3, GSDMD, NF-κB, IL-1β)	↑ BRCA-1 expression ↓ mTOR inflammatory pathway ↓ Oxidative stress ↓ Tumor proliferation biomarker (Ki67)
Bora et al (2021)[34]	Metastatic cancer	BALB/c mouse with metastatic B16-F1 cell	Empagliflozin (1.3 mg/kg) Dapagliflozin (0.65 mg/kg)	↓ Tumor proliferation rate ↑ Body mass markers ↓ Skeletal muscle atrophy	↓ Inflammation (TNF-α, Il-6 and CRP) Improved glucose metabolism: ↓ Serum glucose levels, ↓ Serum insulin levels, ↑ Serum GLP-1 levels ↑ Glycogen storage
Rogava et al (2024)[35]	Melanoma	C57BL/6 J female mouse	Canagliflozin (6 mg/kg)	↓ Liver metastasis	↓ Hepatic insulin levels
Xie et al (2020)[36]	Cervical carcinoma	Nude mouse with HeLa cell	Empagliflozin in solution (50 μmol/L)	↓ Tumor tissue proliferation ↑ Apoptosis ↑ FOXA1 ↓ The migration of HeLa cells	↑ AMPK activation ↑ FOXA1 nuclear translocation ↑ AMPK/FOXA1 pathway activation ↓ SHH expression ↓ Malignancy
Jojima et al (2019)[37]	Hepatocellular carcinoma	The mouse model of NASH	Canagliflozin (30 mg/kg)	↓ NAS score ↓ Hepatic tumors ↓ GS-positive nodules ↓ α-Fetoprotein mRNA ↑ Cell cycle arrest / apoptosis	↓ Steatosis ↓ Inflammation ↓ Tumor growth via direct SGLT2 inhibition in tumor cells ↑ Caspase 3 activation
Shiba et al (2018)[38]	Hepatocellular carcinoma	Mouse model of human NASH	Canagliflozin (20–30 mg/kg)	↓ NAS score ↓ Hepatic steatosis ↓ Inflammatory changes, ↓ Hepatic tumors ↓ Liver fibrosis	↓ Steatosis ↓ Inflammation ↓ Oxidative stress in adipose tissue ↓ Ectopic fat accumulation in the liver
Nasiri et al (2019)[39]	Breast cancer, Colon cancer	C57bl/6J mouse with MC38 cell or E0771 cell	Dapagliflozin (2.5 mg/kg)	↓ Plasma glucose and insulin concentrations ↓ Tumor growth rate	↓ Glucose uptake ↓ Oxidation

Kaji et al (2018)[40]	Hepatocellular carcinoma	Athymic nude mouse (BALB/cSlc1nu/nu)	Canagliflozin (100 mg/kg)	↓ Proliferation ↑ G2/M arrest ↑ Apoptosis	↓ The phosphorylation of p38, ERK1/2, and AKT ↑ Caspase 3 ↓ Glucose uptake ↓ Glycolysis
Yoshioka et al (2021)[41]	Hepatocellular carcinoma	Mc4r KO mouse	Tofogliflozin (5 mg/kg)	↓ NASH-related liver tumor number and size ↓ Hepatic lipid accumulation ↓ Tissue inflammation and fibrosis ↓ Expression of senescence-associated genes	↓ Insulin/glucagon ratio ↓ Bax ↓ F4/80 ↓ p21 and other SASP factors
Hsieh et al (2019)[42]	Squamous cell carcinomas	LSL-Kras^{G12D} mouse, Lkb1$^{flox/flox}$ mouse and LSL-Luciferase mouse	Canagliflozin (20 mg/kg)	↓ Proliferation ↑ Oxidative stress ↓ Tumor growth	↓ Glucose Metabolism ↑ Antioxidant Production ↓ Insulin/AKT Pathway
De Jonghe et al (2017)[43]	Kidney tumors	Male Sprague-Dawley rats	Canagliflozin (65 or 100 mg/kg)	↓ Presence of renal tubular tumors ↓ Adrenal medullary hyperplasia	↓ Glucose uptake

Notes: ↑ indicates an increase or enhancement; ↓indicates a decrease or suppression of the measured parameter compared with baseline or control.

Abbreviations: AMPK, AMP-activated protein kinase; AKT, protein kinase B; α-Fetoprotein (AFP), alpha-fetoprotein; BRCA1, breast cancer 1; C57BL/6J, inbred strain of laboratory mouse; CRP, C-reactive protein; ERK1/2, extracellular signal-regulated kinase 1/2; FOXA1, forkhead box protein A1; F4/80, EGF-like module-containing mucin-like hormone receptor-like 1 (macrophage marker); GLP-1, glucagon-like peptide-1; GSDMD, gasdermin D; GS, glutamine synthetase; Lkb1, liver kinase B1; MDA, malondialdehyde; MC38, murine colon adenocarcinoma cell line; mTOR, mechanistic target of rapamycin; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; p21, cyclin-dependent kinase inhibitor 1A; PI3K, phosphoinositide 3-kinase; p38, p38 mitogen-activated protein kinase; SASP, senescence-associated secretory phenotype; SHH, sonic hedgehog; TAC, total antioxidant capacity; TNF-α, tumor necrosis factor alpha.

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Table 2 Anti-Cancer Potential Effects of SGLT2i in vitro

First Author (Year)	Cancer Type	Cell Type	SGLT2i Treatment	Key Finding	Results and Proposed Mechanism
Anastasio et al (2024)[19]	Colorectal cancer	HCT 116, HT-29, SW480 and LoVo	Canagliflozin (50 μM)	↑ Autophagy ↑ ER stress ↑ Cell cycle arrest, apoptosis, autophagy ↓ Glucose metabolism	↑ SIRT3 upregulation ↑ AMPK activation ↓ DPP4 protein levels ↑ Mitochondrial dysfunction
Wu et al (2022)[44]	Osteosarcoma	MNNG/HOS, MG-63, 143B, and U2OS	Canagliflozin (1 μM)	↑ Immune cell infiltration	↑ STING/IRF3/IFN-β pathway ↓ AKT phosphorylation
Nakano et al (2022)[45]	Hepatocellular Carcinoma	Hep3B and Huh7	Canagliflozin (10 μM)	↓ Proliferation, ↓ Invasion,	↓ CXCL1, CXCL8, CXCL10, M-CSF
Nalla et al (2024)[46]	Breast cancer	MCF-7, MDA-MB-231	Empagliflozin (80 μM/160 μM)	↑ Ferroptosis sensitivity in anoikis-resistant cells.	↑ miR-128-3p ↓ CD98hc and SP1 levels ↑ ROS and lipid peroxidation
Wang et al (2019)[47]	Hepatocellular carcinoma	Human HepG2	Trilobatin (50, 100 μM)	↓ Cell proliferation ↑ The ratio of G0/G1 phase	↓ Glucose uptake ↓ Cell cycle arrest at S phase
Papadopoli et al (2021)[48]	Breast cancer	SKBR3, BT-474, MCF7, NT2196, NT2197	Canagliflozin (50 μM) Dapagliflozin (50 μM)	↓ Proliferation ↓ Mitochondrial respiration.	↓ Oxygen consumption ↓ Glutamine metabolism
Shoda et al (2022)[49]	Glioblastoma	U251MG, U87MG, GL261	Canagliflozin (5, 10, 20, 40 μM)	↑ Expression of SGLT2 in the U251MG and U87MG cell line ↓ Cell proliferation ↓ Glucose uptake	↑ Phosphorylated AMPK ↓ Phosphorylated p70S6K
Yamamoto et al (2021)[50]	Lung cancer	A549, H1975, H520	Canagliflozin (1–50 μM)	↓ Lung cancer cell proliferation ↓ Cell cycle progression	↓ Proliferation via G1 to S phase inhibition
Wang et al (2022)[51]	Thyroid cancer	TPC-1 and BCPAP	Canagliflozin (10 μM)	↓ Glucose uptake and glycolysis ↓ Proliferation ↑ Apoptosis	↓ AKT/mTOR ↑ AMPK ↑ ROS-mediated DNA damage ↑ ATM/CHK2 activation ↑ G1/S arrest and apoptosis
Ren, Kaijie et al (2024)[52]	Gastric cancer	AGS/MKN-1	Dapagliflozin (0, 25, 50, 100 μM)	↓ Proliferation ↓ Migration	↓ OTUD5 ↑ YAP1 ubiquitination,
Okada et al (2020)[53]	Colon cancer	HCT116, HepG2, PANC-1, H1792	Dapagliflozin (0.125, 0.25, 0.5,1.0, or 2.0 mM)	↓ Cell adhesion to Collagen I and IV ↑ Cancer cell detachment	↑ Ectodomain shedding of DDR1 ↑ ADAM10 activity ↓ Y792 Tyrosine Phosphorylation of DDR1

Notes: ↑ indicates an increase or enhancement; ↓indicates a decrease or suppression of the measured parameter compared with baseline or control.

Abbreviations: AMPK, AMP-activated protein kinase; ADAM10, a disintegrin and metalloproteinase 10; AKT, protein kinase B; ATM, ataxia telangiectasia mutated; CD98hc, CD98 heavy chain; CHK2, checkpoint kinase 2; CXCL1, C-X-C motif chemokine ligand 1; CXCL8, C-X-C motif chemokine ligand 8; CXCL10, C-X-C motif chemokine ligand 10; DDR1, discoidin domain receptor 1; DPP4, dipeptidyl peptidase-4; ER, endoplasmic reticulum; IFN-β, interferon beta; IRF3, interferon regulatory factor 3; miR-128-3p, microRNA-128-3p; M-CSF, macrophage colony-stimulating factor; mTOR, mechanistic target of rapamycin; OTUD5, OTU domain-containing deubiquitinase 5; p70S6K, 70 kDa ribosomal protein S6 kinase; ROS, reactive oxygen species; SGLT2, sodium-glucose cotransporter 2; SIRT3, sirtuin 3; SP1, specificity protein 1; STING, stimulator of interferon genes; YAP1, yes-associated protein 1.

reduced the number of crown-like structures (CLS) in obese tissues, which are associated with inflammation and fibrosis. The reduction in CLS may be associated with improved insulin sensitivity and the suppression of fibrotic pathways,[33] ultimately reducing tissue damage and suppressing tumor-associated inflammation. Canagliflozin has been shown to inhibit the progression of 7, 12 di-methyl-benzaanthrathene (DMBA)-induced breast cancer, not only inhibiting *Breast Cancer Gene 1 (BRCA1)* expression but also suppressing mechanistic target of rapamycin (mTOR)-mediated inflammatory signaling pathways through the downregulation of caspase-1, IL-1β, and NF-κB.[33] Additionally, empagliflozin treatment attenuates cardiac fibrosis and inflammation induced by doxorubicin, accompanied by a marked reduction in fibrosis-related markers, including pro-collagen type I α1 (COL1A1) and matrix metalloproteinase-9 (MMP-9), and downregulates NLRP3 and MyD88 signaling pathways, which are implicated in oxidative stress and cytokine activation. These effects collectively contribute to decreased extracellular matrix deposition and myocardial stiffness, thereby improving myocardial strain and preserving cardiac function.[34] In cancer cachexia empagliflozin and dapagliflozin treatment led to an increased collagen content in heart tissue. The reduction in serum creatine kinase levels suggests a decrease in myocardial fibrosis, indicating a potential alleviation of cardiac atrophy associated with cancer cachexia.[55] Simultaneously, empagliflozin alleviates DOX-induced cardiotoxicity by suppressing NLRP3 inflammasome activation, leading to a reduction in IL-1β, IL-6, and IL-8 levels as well as myocardial fibrosis biomarkers such as MMP-9. It also decreases apoptotic cell numbers in cardiac tissue, suggesting a potential role in mitigating cardiac fibrosis and myocardial apoptosis.

Recent studies suggest that SGLT2 inhibitors can modulate the tumor microenvironment (TME) through immunoregulatory pathways. Immunity and inflammation are intricately linked with various inflammatory factors being produced by specialized immune cells, including macrophages, mast cells, monocytes, and T cells. In an osteosarcoma model, canagliflozin significantly increased tumor-infiltrating lymphocytes (TILs), particularly the $CD4^+$ and $CD8^+$ T cell subsets. Mechanistic studies revealed that this effect was mediated through the activation of the *STING-TBK1-IRF3* signaling axis, which promoted type I interferon secretion and remodeled the immunosuppressive TME. Canagliflozin treatment induced immune cell infiltration, particularly $CD4^+$ and $CD8^+$ T cells, by upregulating *STING* expression and activating immune response pathways. This activation led to the phosphorylation of STING, interferon regulatory factor 3 (IRF3), and TBK1, resulting in increased interferon-β (IFN-β) production and the initiation of immune activation within the TME.[44] Additionally, canagliflozin modulates the chemokine and cytokine profile in hepatocellular carcinoma (HCC) cells by downregulating pro-inflammatory chemokines, including CXCL1, CXCL8, CXCL10, and M-CSF, which in turn reduces tumor invasiveness. Simultaneously, it upregulates anti-inflammatory cytokines such as IL-12 and TNF-α in Hep3B and Huh7 cells, leading to enhanced immune responses.[45] The downregulation of CXCL1, CXCL8, and CXCL10 is a critical mechanism driving tumor growth, immune evasion, and metastasis, as observed in Hepa1-6 HCC cells in mice,[56] hepatic cancer stem cells,[57] and rat HCC cells.[58] Through this mechanism, dapagliflozin has been shown to reduce tumor invasiveness, highlighting the role of SGLT2 inhibitors in tumor immunity and inflammation.

SGLT2 Inhibitors and Tumor Oxidation

Reactive oxygen species (ROS) are byproducts of cellular respiration and function as crucial redox mediators. In cancer, ROS exert a dose-dependent dual regulatory effect: at low concentrations, tumor cells promote carcinogenesis by inducing DNA damage, whereas excessive accumulation triggers programmed cell death. ROS-induced genomic instability contributes to malignant transformation, facilitating tumor progression. Conversely, excessive ROS accumulation within tumor cells can induce apoptosis, pyroptosis, and ferroptosis, resulting in selective cancer cell elimination.[59,60] Typically, ROS in tumor cells generate oxidative stress, characterized by an imbalance between oxidative and antioxidative processes. This imbalance leads to the oxidation of cellular components, including proteins, lipids, and DNA, contributing to cellular dysfunction and tumor progression.[61] SGLT2 inhibitors have been shown to exert antioxidative effects by attenuating free radical production and enhancing antioxidant defense mechanisms, such as upregulating superoxide dismutase (SOD) and glutathione (GSH). These effects protect against oxidative stress-induced tissue damage and have been shown to reduce oxidative stress across various cancer types, ultimately inhibiting tumor cell proliferation. Notably, empagliflozin activates the AMPK pathway, which enhances the sensitivity of MCF-7 breast cancer cells to tamoxifen and helps overcome resistance to endocrine therapy. Mechanistically, dapagliflozin attenuates

doxorubicin (DOX)-induced oxidative stress and mitochondrial dysfunction by modulating the PI3K/AKT/Nrf2 signaling axis. This regulation restores antioxidant capacity and suppresses the overproduction of reactive oxygen species (ROS), thereby improving cardiac function.[62] In H9c2 cardiomyocytes, doxorubicin (DOX) treatment reduces cell viability, downregulates the expression of key antioxidant enzymes such as heme oxygenase 1 (HO-1), NADPH quinone dehydrogenase 1 (NQO1), and superoxide dismutase (SOD), increases ROS levels, and induces mitochondrial dysfunction. Co-treatment with dapagliflozin restores AKT phosphorylation, promotes nuclear translocation of Nrf2, upregulates antioxidant enzyme expression, reduces ROS accumulation, and improves mitochondrial membrane potential. These findings indicate that dapagliflozin mitigates DOX-induced oxidative stress and mitochondrial injury through activation of the PI3K/AKT/Nrf2 signaling pathway.

Additionally, Tamoxifen upregulates FOXO3a, a key transcription factor that enhances the expression of antioxidant genes. FOXO3a regulates multiple cellular processes, including metabolism, autophagy, and stress responses. Its activation induces autophagy, which can lead to cell death.[63] The antioxidative capacity of empagliflozin extends beyond cancer cells. In a DOX-induced rat model, empagliflozin mitigated DOX-induced oxidative stress by reducing malondialdehyde (MDA) levels and increasing nuclear factor erythroid 2-related factor 2 (Nrf2), heme oxygenase-1, and GSH levels, which helped to prevent myocardial fibrosis.[64] In TZM-treated cardiomyocytes, empagliflozin reduced oxidative stress markers, including serum lactate dehydrogenase (LDH) and troponin I, indicating its ability to alleviate TZM-induced cardiotoxicity and oxidative damage. Furthermore, empagliflozin decreased lipid peroxidation, a key indicator of oxidative stress, by lowering MDA levels and protecting cardiomyocytes from oxidative injury. Beyond their antioxidative effects, SGLT2 inhibitors also exhibit anticancer activity by modulating ferroptosis pathways, a form of regulated cell death driven by iron-dependent lipid peroxidation.[65,66] Empagliflozin has been shown to mimic the function of miR-128-3p, a microRNA involved in ferroptosis and suppressing critical cancer progression processes.[67] The study conducted by Nalla et al demonstrated that empagliflozin increases the sensitivity of apoptosis-resistant cancer cells to ferroptosis by activating miR-128-3p while downregulating the expression of SP1 and CD98hc.[46] This cascade leads to a reduction in metastatic tumor burden, highlighting the potential of empagliflozin as an adjunct to CT.

In cancer treatment, most chemotherapeutic agents directly or indirectly induce the accumulation of ROS to promote tumor cell death. Widely used anticancer agents, including DOX, cisplatin, 5-fluorouracil, paclitaxel, and cyclophosphamide, exert their cytotoxic effects primarily through ROS-mediated mechanisms. However, excessive ROS accumulation induced by these agents can also inflict significant damage on normal tissues and organs, contributing to DNA mutations and mitochondrial dysfunction. In models of DOX-induced vascular endothelial injury using mice and human umbilical vein endothelial cells (HUVECs), DOX treatment has been shown to elevate both intracellular and mitochondrial ROS levels, leading to a loss of mitochondrial membrane potential (MMP), the opening of mitochondrial permeability transition pores (mPTP), and the activation of ROS-induced ROS release (RIRR) mechanisms. This ROS-driven positive feedback loop exacerbates mitochondrial dysfunction and ultimately results in endothelial damage.[68] Similarly, in cisplatin-treated ovarian cancer cells, the downregulation of Nrf2 and upregulation of transferrin receptor (TFR) suggest that cisplatin-induced ovarian dysfunction may be associated with dysregulated iron metabolism. Elevated mitochondrial ROS levels, MMP depolarization, and mitochondrial hyperpolarization contribute to excessive mitochondrial ROS production, leading to ferritin accumulation and mitochondrial disintegration.[69] Preclinical studies have demonstrated that empagliflozin mitigates DOX-induced oxidative stress. DOX administration significantly increases MDA levels while reducing the activity of key antioxidant enzymes, including SOD and catalase (CAT).[70,71] Empagliflozin treatment counteracts these effects by lowering MDA levels and enhancing SOD and CAT activity,[64] suggesting that its antioxidative properties are mediated via the AMPK/SIRT-1/PGC-1α signaling pathway, which in turn offers cardioprotective benefits during CT.

SGLT2 Inhibitors and Tumor Metabolic Reprogramming

Metabolic reprogramming in tumors refers to alterations and regulation of metabolic pathways during tumor progression. While normal cells primarily generate ATP through oxidative phosphorylation, tumor cells predominantly rely on glycolysis for ATP production. In addition, metabolic reprogramming involves dysregulated lipid and amino acid metabolism, enhanced lactate production, mitochondrial biogenesis, and activation of the pentose phosphate pathway.[72,73] These metabolic adaptations enable tumor cells to meet the increased energy and biosynthetic demands required for growth and survival, ultimately

driving tumor progression.[74–76] In breast and colon cancer models, the reduction in insulin levels mediated by dapagliflozin has been associated with a decrease in tumor growth. This effect is reversed following exogenous insulin infusion, indicating an insulin-dependent mechanism that enhances the efficacy of chemotherapeutic agents, such as paclitaxel.[24] These findings highlight the potential of dapagliflozin as an adjunct therapy in cancer treatment. Wang et al reported that trilobatin inhibits tumor cell proliferation by reducing glucose and energy supply, leading to slower tumor growth.[47] Interestingly, Papadopoli et al demonstrated that canagliflozin suppresses breast cancer cell proliferation independently of glucose levels and SGLT2 expression. This antiproliferative effect has been primarily attributed to a reduction in oxygen consumption and glutamine metabolism, leading to alterations in the tricarboxylic acid (TCA) cycle, depletion of key intermediates, and an increase in glutamine accumulation. Consequently, cancer cell proliferation is impaired through the disruption of glutamine metabolism.[48] In glioblastoma (GBM), canagliflozin suppresses tumor growth through metabolic reprogramming.[49]

In a mouse GBM model, canagliflozin has been shown to reduce glucose uptake in GBM cells, activate the AMPK pathway, and decrease cellular respiration, ultimately leading to tumor growth inhibition. These findings suggest a potential therapeutic approach for GBM patients with hyperglycemia or diabetes. In breast cancer, dapagliflozin has been found to significantly inhibit tumor growth in obese mice, likely by reversing fasting hyperinsulinemia. By reducing insulin-driven glucose uptake, dapagliflozin slows tumor progression, indicating a metabolism-dependent mechanism.[24] The metabolic effects of SGLT2 inhibitors on tumor cells are multifaceted. By reducing glucose uptake, these agents induce an energy crisis, disrupting the Warburg effect, which is the metabolic shift from oxidative phosphorylation to glycolysis.[77] This disruption is further exacerbated by the inhibition of mitochondrial complex I, which impairs ATP production and subsequent activation of AMPK. AMPK activation, in turn, induces downstream effects, including mTOR inhibition, cell cycle arrest, and apoptosis.[35]

In this context, empagliflozin has been shown to suppress tumor growth and induce apoptosis in HeLa cells via AMPK activation, leading to *forkhead box A1 (FOXA1)* suppression. This inhibition disrupts the *Sonic Hedgehog (SHH)* signaling axis, resulting in decreased SHH expression, reduced tumor cell proliferation, and enhanced apoptosis. The ability of empagliflozin to target the AMPK/FOXA1/SHH pathway suggests its potential as an effective therapy for cervical cancer.[36] Similarly, Nakachi et al demonstrated that in acute-type adult T-cell leukemia (ATL) cells, tofogliflozin disrupts glucose metabolism through SGLT2 inhibition, resulting in decreased ATP and NADPH levels.[78] This energy shift induces G0/G1 cell cycle arrest, which suppresses ATL cell growth through metabolic reprogramming. Abdel-Rafei et al investigated the effects of the canagliflozin combined with gamma irradiation (g-IR) on HepG2 HCC cell proliferation.[22] The results demonstrated that canagliflozin enhances the antitumor effects of g-IR by inhibiting glucose uptake and lactate production while simultaneously promoting the shift from autophagy to apoptosis through activation of the endoplasmic reticulum (ER) stress pathway. These findings suggest that SGLT2 inhibitors, such as canagliflozin, may provide dual benefits by targeting metabolic reprogramming and enhancing cancer cell death. Similarly, canagliflozin has been shown to inhibit aerobic glycolysis in HCC by targeting pyruvate kinase M2 (PKM2), a key enzyme in the glycolytic pathway. This inhibition disrupts glutamine metabolism, induces ferroptosis, and sensitizes HCC cells to cisplatin (CPT).

Other Effects

Recent studies have highlighted the potential antitumor effects of SGLT2 inhibitors in suppressing the proliferation of various tumor types, with SGLT2 expression detected in non-diabetic tumor tissues and cancer cell lines.[35,50] Canagliflozin has been shown to significantly inhibit the proliferation of A549 lung cancer cells in vitro, partially through the suppression of HIF-1α. This mechanism involves the downregulation of histone deacetylase 2, a key regulator of transcriptional reprogramming, and it's silencing further enhances the antiproliferative effects of canagliflozin.[79,80] In HCC, canagliflozin exhibits significant antitumor activity by inducing G2/M phase cell cycle arrest and promoting apoptosis.[37,40] This effect is mediated by the downregulation of key cell cycle regulators, including *CDK1, CDK2*, and *Cyclin B1 (CCNB1)*, along with the upregulation of checkpoint proteins such as checkpoint kinase 1 (CHK1) and p21. Additionally, canagliflozin induces cleavage of caspase-3, leading to apoptotic pathway activation and a reduction in tumor cell viability.

Notably, canagliflozin also inhibits mitochondrial oxidative phosphorylation, activates AMPK, and suppresses mTOR signaling, collectively contributing to the reduction of tumor cell proliferation and colony formation.[79] The antiproliferative effects of canagliflozin have been associated with its ability to inhibit DNA synthesis, as tumor cells treated with canagliflozin undergo cell cycle arrest at the G1/S transition.[23,81] Wang et al further investigated the impact of canagliflozin on cell cycle progression, demonstrating that the drug induces G1/S checkpoint arrest by downregulating key regulators, including cyclin D1 and cyclin E1. Inhibiting cell cycle progression concurrently enhances DNA damage, leading to the accumulation of double-strand breaks.[51] Furthermore, canagliflozin suppresses GBM growth and proliferation by enhancing AMPK phosphorylation and inhibiting the phosphorylation of p70S6 kinase and S6 ribosomal protein.[49] Similarly, in breast cancer, canagliflozin induces tumor growth arrest, reduces glucose uptake, activates AMPK signaling, and inhibits the mTOR pathway.[82] Xie et al discovered that empagliflozin inhibits HeLa cell migration and induces apoptosis in vitro by activating the AMPK/FOXA1 pathway and downregulating *SHH* expression. Consistent with these findings, in vivo studies demonstrated that empagliflozin treatment suppressed tumor growth in a nude mouse model.[36]

Additionally, SGLT2 inhibition activates miR128-3p, a tumor suppressor, in breast cancer, leading to reduced expression of the CD98hc (CD98 heavy chain), a type II transmembrane glycoprotein, along with decreased ROS levels and lipid peroxidation. This metabolic shift subsequently induces ferroptosis in anoikis-resistant cells, ultimately reducing the metastatic burden of breast cancer.[46] Dapagliflozin inhibits gastric cancer cell migration by downregulating epithelial-mesenchymal transition (EMT) markers, including N-cadherin and Snai1. In vivo, dapagliflozin treatment suppresses xenograft gastric tumor growth and prolongs overall survival in severe combined immunodeficiency mouse models. Furthermore, dapagliflozin impedes gastric cancer progression by reducing the protein levels of yes1-associated transcriptional regulator (YAP1), a key effector of the Hippo signaling pathway. This effect is mediated through the downregulation of OTUD5, a deubiquitinase that stabilizes YAP1, promoting its degradation and suppressing tumor growth.[52]

Recent studies have demonstrated that dapagliflozin induces detachment of HCT116 cells from the extracellular matrix. This loss of adhesion, characterized by disrupted adhesion to the extracellular matrix or neighboring cells, was particularly evident in HCT116 cells but absent in other cancer cell lines, including HepG2, PANC-1, and H1792. These findings suggest that dapagliflozin selectively influences cell adhesion properties across different cancer cell lines.[53] The observed effect is associated with SGLT2 and UGT1A9 expression, where higher SGLT2 levels and lower UGT1A9 expression correlate with increased sensitivity to dapagliflozin.[83] Mechanistically, the underlying mechanism involves the activation of a disintegrin and metalloproteinase domain 10 (ADAM10) and the extracellular shedding of discoidin domain receptor 1 (DDR1), resulting in impaired adhesion to extracellular matrix proteins, particularly collagen I and IV. This disruption in cell adhesion further enhances the antitumor efficacy of dapagliflozin by modulating the TME.[53] Clinical case reports have also demonstrated that dapagliflozin improves tumor marker levels in patients with colorectal, pancreatic, and liver cancers, further supporting the therapeutic potential of SGLT2 inhibitors in cancer treatment[84] (Figure 2).

SGLT2 Inhibitors Combination Therapy

The Combination of SGLT2 Inhibitors and Radiotherapy

In cancer treatment, radiotherapy serves as a critical local therapeutic modality, primarily exerting its effects through ionizing radiation-induced DNA damage, inhibiting or eliminating tumor cells (Table 3). However, its clinical efficacy is often limited by tumor radioresistance and the potential for damage to normal tissues.[85] This resistance is primarily associated with the metabolic reprogramming of tumor cells, enhanced DNA damage repair mechanisms, and the immunosuppressive characteristics of the TME.[86] Consequently, strategies designed to enhance radiosensitivity and overcome radioresistance are essential for improving the efficacy of radiotherapy.[87] Studies have demonstrated that SGLT2 inhibitors exhibit adjuvant effects in enhancing radiosensitivity and mitigating radioresistance. Canagliflozin improves radiotherapy efficacy by inhibiting glucose uptake in tumor cells and attenuating metabolic reprogramming.[84,88] Specifically, canagliflozin suppresses mitochondrial respiration, activates the AMPK signaling pathway, and downregulates the mTOR-p70S6k/4EBP1 and MAPK pathways, ultimately reducing cancer cell proliferation and survival following radiation exposure.[23] In prostate cancer, canagliflozin further inhibits tumor cell proliferation and enhances radiosensitivity in both androgen-sensitive and androgen-resistant prostate cancer models by blocking

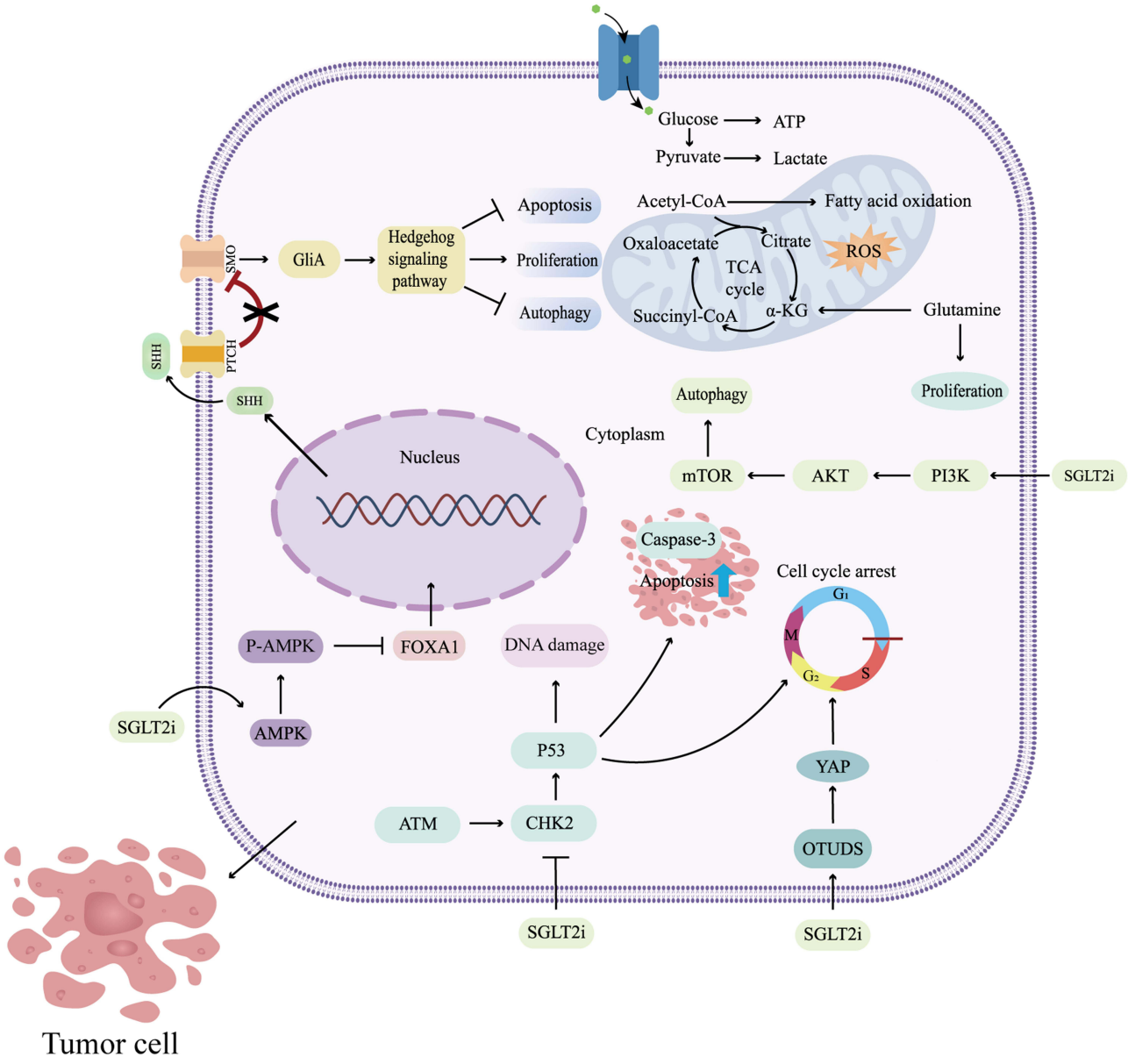

Figure 2 Mechanisms of SGLT2 inhibitors-mediated anti-cancer effects. SGLT2 inhibitors modulate multiple signaling pathways to suppress tumor progression. SGLT2 inhibitors activate AMP-activated protein kinase (AMPK), leading to phosphorylation of AMPK (p-AMPK) and downregulation of forkhead box A1 (FOXA1). This cascade induces DNA damage, activating the ATM/CHK2/P53 pathway. Cell cycle arrest and apoptosis occur via caspase-3 activation. SGLT2 inhibitors suppress the phosphoinositide 3-kinase (PI3K)/AKT/mTOR pathway, reducing cellular proliferation and enhancing autophagy. Hedgehog signaling is attenuated by blocking sonic hedgehog (SHH)-mediated activation of GliA, increasing apoptosis and decreasing proliferation and autophagy. YAP1/OTUD5 signaling is disrupted, contributing to cell cycle arrest. Metabolic alterations include reduced ATP production and lactate formation. The tricarboxylic acid (TCA) cycle, fatty acid oxidation, and reactive oxygen species (ROS) generation are modulated. The figure illustrates these interconnected signaling pathways and metabolic effects, highlighting the antitumor mechanisms of SGLT2 inhibitors.

mitochondrial respiration, activating AMPK signaling, and suppressing the MAPK and mTOR-p70S6k/4EBP1 pathways. Additionally, the DNA damage response in G2-phase cells is closely linked to the early G2/M checkpoint. Modulating the transition of irradiated G2-phase cells into mitosis has been shown to enhance sensitivity to low-dose radiation, particularly through mechanisms involving G2-phase enrichment and checkpoint abrogation, which contribute to low-dose hyper-radiosensitivity. Notably, canagliflozin induces G2/M-phase cell cycle arrest and promotes apoptosis, increasing cellular susceptibility to radiation-induced damage.[23,84]

Furthermore, canagliflozin modulates the PI3K/AKT/GSK-3β/mTOR and Wnt/β-catenin signaling pathways, which play crucial roles in cell proliferation and survival. In HepG2 cells treated with canagliflozin, phosphorylation levels of

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Table 3 Anti-Cancer Potential Effects of SGLT2i in Combination with Conventional Therapies

First Author (Year)	Species/Strain	Anticancer Treatment	SGLT2i Treatment	Key Findings	Proposed Mechanisms
Abdel-Rafei et al (2021)[22]	HepG2	Radiotherapy	Canagliflozin (10–60 μM)	↓ Proliferation and clonogenic survival. ↓ Glucose uptake ↓ Glycolytic metabolism ↓ Cytoprotective autophagy	↓ ATP ↑ H_2O_2 levels ↓ ATF-6, IRE-1α, XBP-1u, XBP-1s, and CHOP ↓ p-PI3KTyr508, p-Akt, Thr308, p-mTORC1ser2481, p-GSK-3-βser9 ↑ Caspase-12 and caspase-3
Ali et al (2023)[23]	LNCap, 22RV1, PC3, DU145	Radiotherapy	Canagliflozin (5–30 μM)	↓ Proliferation and survival, ↑ Radiotherapy response, ↓ Mitochondrial respiration, ↑ Cell cycle checkpoints,	↑ AMPK activity, ↓ MAPK and mTOR-p70S6k/4EBP1 pathways
Longaray et al (2024)[26]	MCF-7, MDA-MB-231	Paclitaxel	Dapagliflozin (10–200 μM)	↑ PTX cytotoxicity ↑ Apoptosis	↑ Arrested cells at G2/M ↓ CD73-mediated immune evasion
Bardaweel et al (2022)[27]	A-549, Caco-2, MCF-7, Du-145, Panc-1	Doxorubicin	Canagliflozin (1–500 μM) Ipragliflozin (1–500 μM)	↓ Cell proliferation ↑ Synergistic effect	↓ P-glycoprotein
Angelopoulou et al (2018)[88]	PDV C57 tumor model mouse, A549 and PDVC57	Radiotherapy	Canagliflozin (5, 15, 20, 50 μg/mL), CANA-loaded IO/PMAA-g-PEGMA nanoparticles (19, 56, 75, 185 μg/mL)	↓ Tumor growth ↑ Antitumor activity ↑ Sensitivity of radiotherapy	↓ Glucose uptake ↑ Magnetic targeting ↑ Drug release
Choi et al (2023)[89]	LN229, U118MG, LN18	Radiotherapy	Canagliflozin (50 μM Dapagliflozin (30μM) Empagliflozin (30μM)	↓ Proliferation ↓ Clonogenic survival	↑ DNA damage signaling ↑ Radiosensitizes GBM cells
Huang et al (2024)[90]	ES-2, SCC131, HepG2, SW480	Paclitaxel	Canagliflozin (10–50 μM)	↑ Paclitaxel growth inhibition ↑Apoptosis and DNA damage ↓ Mitotic progression ↓ Spindle assembly checkpoint ↑ Abnormal mitotic cells	↓ Glucose uptake ↑ PARP, caspase-7, and caspase-9 cleavage ↓ SAC ↑ γ-H2AX
Park et al (2022)[91]	HK-2	Cisplatin	Canagliflozin (1–25 μM)	↓ Apoptosis ↓ Cisplatin-induced AKI	↓ AMPK activation ↓ Caspase-3, cleaved PARP, and γ-H2AX
Fujiyoshi et al (2024)[92]	Male nude mouse (Balb/cSlc-nu/nu)	Cisplatin	Dapagliflozin (1 mg/kg)	↓ Cisplatin resistance	↓ Glucose uptake
Zeng et al (2023)[93]	LM3, Huh-7	Cisplatin	Canagliflozin (10 μM)	↓ Proliferation and migration ↑ The sensitivity of HCC to CPT ↑ Ferroptosis ↓ Cisplatin resistance	↓ Targeting aerobic glycolysis ↓ Glutamine utilization ↓ c-Myc ↓ PKM2

Quagliariello et al (2021)[94]	C57Bl/6 mouse	Doxorubicin	Empagliflozin (10 mg/kg)	↑ The viability of cardiomyocytes ↓ Myocardial strain ↓ Cardiac fibrosis and pro-inflammatory cytokines ↓ Ferroptosis and MDA content in heart ↓ Apoptosis	↓NLRP3 and MyD88-related pathways ↓ NF-κB activation ↓ Xanthine oxidase ↓ Pro-collagen 1α1
Karim et al (2024)[95]	MCF-7	Doxorubicin	Canagliflozin (10–40 μM)	↓ Intracellular ATP and lactate levels ↓ Cell cycle progression	↓ Glucose uptake ↓ CDK2 ↑ p16:
Chang et al (2024)[96]	Male rats	Doxorubicin	Empagliflozin (30 mg/kg)	↓ Dox-induced cardiotoxicity ↓ Cardiac energy metabolism impairment	↑AMPK/SIRT-1/PGC-1α signaling pathway
Luo et al (2024)[97]	Male C57BL/6 mouse	Doxorubicin	Canagliflozin (10 mg/kg)	↓ Myocardial fibrosis ↓ Apoptosis ↑ Nuclear translocation of LC3	↑ Autophagic flux ↑ SIRT1 ↓ PI3K/Akt/mTOR signaling pathway
Min et al (2023)[98]	C57BL/6 mouse	Trastuzumab	Empagliflozin (10 mg/kg)	↓ TZM-induced cardiotoxicity ↓ Interstitial fibrosis ↓ Lipid peroxidation	↓ TZM-induced rises in LDH and troponin I ↓ Superoxide anion (O_2^-) production ↓ Mitochondrial ultrastructural damage ↓ DNA damage
Ding et al (2023)[99]	BALB/c female mouse with CT26 cells NSG male mouse	Nivolumab	Canagliflozin (50 mg/kg)	↑ Immune system function ↓ Tumor growth	↑ IFN-γ production ↑ $CD3^+$ and $CD8^+$ T cells ↓ PD-L1

Notes: ↑ indicates an increase or enhancement; ↓indicates a decrease or suppression of the measured parameter compared with baseline or control.

Abbreviations: AMPK, AMP-activated protein kinase; ATF6, activating transcription factor 6; Akt, protein kinase B; ATP, adenosine triphosphate; CHOP, C/EBP homologous protein; CD3, cluster of differentiation 3; CD8, cluster of differentiation 8; CDK2, cyclin-dependent kinase 2; CD73, ecto-5'-nucleotidase; CPT, cisplatin; Caspase-3, cysteine-aspartic acid protease-3; Caspase-7, cysteine-aspartic acid protease-7; Caspase-9, cysteine-aspartic acid protease-9; Dox, doxorubicin; 4EBP1, eukaryotic translation initiation factor 4E-binding protein 1; GBM, glioblastoma multiforme; GSK-3β, glycogen synthase kinase 3 beta; HCC, hepatocellular carcinoma; IFN-γ, interferon gamma; IRE-1α, inositol-requiring enzyme 1 alpha; LDH, lactate dehydrogenase; LC3, microtubule-associated protein 1A/1B-light chain 3; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; mTOR, mechanistic target of rapamycin; mTORC1, mTOR complex 1; MyD88, myeloid differentiation primary response 88; NLRP3, NOD-like receptor family pyrin domain containing 3; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PARP, poly(ADP-ribose) polymerase; PD-L1, programmed death-ligand 1; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3K, phosphoinositide 3-kinase; PKM2, pyruvate kinase isozyme M2; PTX, paclitaxel; SAC, spindle assembly checkpoint; SIRT1, sirtuin 1; SIRT-1, sirtuin 1; Sp1, specificity protein 1; TZM, trastuzumab; XBP1u, unspliced X-box binding protein 1; XBP1s, spliced X-box binding protein 1.

PI3K, AKT, mTORC1, and GSK-3β were significantly reduced, while phosphatase and tensin homolog expression was restored.[100] These findings indicate that canagliflozin effectively blocks γ-irradiation-induced signaling activation, inhibiting tumor cell metabolic reprogramming and therapy resistance. Notably, the combination of canagliflozin and γ-irradiation markedly increased intracellular ROS levels, leading to ATP depletion and activation of caspase-12 and caspase-3. These findings suggest that this combination therapy effectively induces apoptosis.[22] Moreover, downregulation of p53 and BCL-2 expression in canagliflozin-treated cells further promotes apoptosis. The combination of SGLT2 inhibitors and radiotherapy not only enhances radiosensitivity but may also overcome radioresistance by modulating tumor cell metabolism and signaling pathways.[89] Additionally, the regulatory effects of SGLT2 inhibitors on the TME provide new avenues for combination therapy strategies. Thus, the integration of SGLT2 inhibitors with radiotherapy may represent a novel therapeutic approach in cancer treatment. Future clinical studies will further evaluate the safety and efficacy of this combination strategy, potentially offering more effective treatment options for patients.

Combination of SGLT2 Inhibitors and Chemotherapy Drugs

Paclitaxel

Paclitaxel is a widely utilized chemotherapeutic agent that exerts its anticancer effects by promoting microtubule assembly while inhibiting depolymerization. Through the stabilization and enhancement of tubulin polymerization, microtubule disassembly is prevented, leading to the disruption of tumor cell mitosis and the inhibition of cancer cell proliferation. Consequently, its antitumor effects are ultimately exerted.[101] Paclitaxel is broadly utilized in the treatment of various malignancies, including breast cancer, ovarian cancer, pancreatic cancer, non-small cell lung cancer, malignant gliomas, and GBM multiforme.[102–104] Despite its significant antitumor efficacy, the clinical application of paclitaxel is often limited by drug resistance, dose-limiting toxicity, and adverse effects on normal tissues. Resistance to paclitaxel can arise through multiple mechanisms, including increased drug efflux, dysregulation of cell cycle control, and alterations in the TME. Additionally, paclitaxel is associated with severe side effects, including neurotoxicity, immunosuppression, and cardiovascular complications,[102] which can negatively impact treatment tolerance and patient quality of life.

Given these limitations, the development of combination therapy strategies is essential for improving cancer treatment outcomes. A randomized, multicenter, placebo-controlled, double-blind clinical trial (NCT04542291) was conducted to evaluate the efficacy of dapagliflozin in combination with paclitaxel by assessing its impact on tumor biomarkers, lipid metabolism, and tumor response. The results, based on changes in tumor size and necrotic area following treatment ($P < 0.05$), demonstrated significant therapeutic effects. The objective response rate (ORR) and disease control rate (DCR) were 20% and 60%, respectively, suggesting that dapagliflozin may serve as a promising adjunct to paclitaxel therapy.[105] In both in vitro and in vivo studies, the combination of paclitaxel with SGLT2 inhibitors has demonstrated synergistic anticancer effects. Huang et al reported that the co-administration of canagliflozin and paclitaxel significantly inhibited the proliferation and clonogenic capacity of HepG2 hepatocellular carcinoma cells. This combination therapy led to an increase in intracellular ROS levels, inducing apoptosis.[90] Furthermore, SGLT2 inhibitors have been shown to modulate signaling pathways associated with tumor proliferation and drug resistance, including the PI3K/AKT and purinergic signaling pathways. Inhibition of these pathways has been found to enhance the antitumor efficacy of paclitaxel. Akingbesote et al investigated 4T1 murine tumors driven by upstream PI3K/AKT-related proteins and identified PI3K/AKT as a key mediator of insulin signaling.[24] Dapagliflozin was found to reduce circulating insulin levels, decreasing tumor glucose uptake and creating a more favorable metabolic environment for paclitaxel, which enhances its antitumor effects. Similarly, Longaray et al reported that dapagliflozin inhibits purinergic signaling by reducing adenosine production, which subsequently diminishes cell viability.[26] This mechanism was shown to potentiate the efficacy of chemotherapeutic agents, ultimately decreasing the survival rate of the MDA-MB-231 breast cancer cell line.

On the other hand, the combination therapy of SGLT2 inhibitors and paclitaxel primarily aims to enhance tumor cell sensitivity to paclitaxel. SGLT2 inhibitors reduce glucose uptake in tumor cells, leading to decreased ATP production and an increased AMP/ATP ratio. This metabolic shift activates AMPK, which inhibits the mTOR pathway and promotes apoptosis, enhancing the antitumor effects of paclitaxel.[25] Additionally, studies have demonstrated that SGLT2 inhibitors regulate tumor cell proliferation by modulating the expression of cell cycle-related proteins.[106] One of the key mechanisms of paclitaxel involves disrupting normal microtubule assembly and function, particularly affecting spindle

formation, which impairs proper mitotic progression. Notably, paclitaxel activates the spindle assembly checkpoint, leading to cell cycle arrest in the M phase.[107] This arrest prevents cells from progressing to the next division phase until all chromosomes are correctly attached to the spindle apparatus. Upon co-treatment with SGLT2 inhibitors, tumor cells exhibit G2/M phase arrest, accelerating apoptosis. This provides new insights into optimizing cell cycle regulation in cancer therapy. In the study by Huang et al, canagliflozin was further found to induce aberrant mitotic spindle formation. Immunofluorescence staining of microtubule structures in ES-2 cells treated with 10 nM paclitaxel and 30 μM canagliflozin for 24 hours revealed that canagliflozin exacerbated paclitaxel-induced multipolar spindle formation, potentially leading to increased mitotic abnormalities.[90] In conclusion, the combination of paclitaxel and SGLT2 inhibitors has demonstrated significant anticancer effects in both theoretical and experimental studies. This strategy not only mitigates paclitaxel-associated resistance and adverse effects but also enhances its anticancer efficacy by modulating tumor cell metabolism and key signaling pathways. Future research should further investigate the underlying mechanisms of this combination therapy and its potential clinical applications, with the goal of developing more effective treatment options for cancer patients.

Cisplatin

Cisplatin is a widely utilized chemotherapeutic agent with proven efficacy against various malignancies, including testicular, ovarian, bladder, and lung cancers.[108] Platinum-based compounds exert their cytotoxic effects primarily through the formation of DNA adducts, which subsequently induce cell cycle arrest and apoptosis.[109] The anticancer mechanisms of cisplatin involve deficiencies in DNA repair, increased oxidative stress, and modulation of the immune microenvironment.[110,111] However, cisplatin is a well-documented nephrotoxin, posing a significant risk of renal injury and necessitating close monitoring during treatment. Additionally, it induces neurotoxicity, which can result in hearing loss and peripheral neuropathy in some patients. Cisplatin therapy is also associated with gastrointestinal toxicity, including nausea and vomiting, while long-term use has been linked to an increased risk of secondary malignancies and other severe late-stage complications.[112]

Currently, SGLT2 inhibitors have been shown to exert renoprotective effects, making their combination with platinum-based CT a promising cancer treatment strategy. This combination enhances cisplatin efficacy while mitigating its associated toxicities. A study by Abd Elmaaboud et al demonstrated that empagliflozin pretreatment protects the kidney primarily by reducing apoptosis and increasing levels of reduced GSH.[113] Empagliflozin elevated GSH levels in renal tissues, where GSH, a key endogenous antioxidant, neutralizes free radicals and alleviates oxidative stress-induced cellular damage. Given that oxidative stress is a primary mechanism underlying cisplatin-induced nephrotoxicity, the elevation of GSH levels by empagliflozin contributes to the protection of renal cells from oxidative injury. Histological analysis further confirmed that empagliflozin pretreatment reduced inflammatory cell infiltration, hemorrhage, and tubular degeneration, consistent with its nephroprotective effects. Similarly, Park et al validated the renoprotective effects of canagliflozin in cisplatin-induced cytotoxicity of human renal proximal tubular cells (HK-2 cells) through the regulation of the AMPK-mTOR pathway.[91] Mechanistically, canagliflozin reduced the expression of apoptotic markers, including cleaved caspase-3, cleaved PARP, and γ-H2AX, in a dose-dependent manner. Furthermore, canagliflozin protected HK-2 cells by promoting AMPK phosphorylation and suppressing mTOR phosphorylation, in an AMPK activation-dependent manner.

Additionally, SGLT2 inhibitors exert their effects by inhibiting SGLT2 protein activity, which reduces renal glucose reabsorption and improves glycemic control in diabetic patients. This mechanism not only enhances blood glucose regulation but also induces metabolic alterations in tumor cells, potentially potentiating the efficacy of cisplatin.[92] For instance, Zeng et al demonstrated that canagliflozin enhances the sensitivity of HCC to cisplatin via the PKM2 pathway. Specifically, canagliflozin targets PKM2 to suppress aerobic glycolysis in HCC, facilitating ubiquitination-mediated c-Myc degradation and reducing glutamine levels. This ultimately induces ferroptosis and restores HCC sensitivity to cisplatin.[93] In conclusion, the combination of SGLT2 inhibitors and cisplatin shows significant potential in improving cancer treatment outcomes. This synergistic strategy not only mitigates the limitations of cisplatin, such as nephrotoxicity and drug resistance, but also harnesses the metabolic and immunomodulatory properties of SGLT2 inhibitors to enhance

therapeutic efficacy. Future studies should further investigate the mechanisms underlying this combination therapy and its clinical applications, with the goal of providing more effective treatment options for cancer patients.

Anthracycline Chemotherapy Drugs

Anthracyclines, including DOX, daunorubicin, and epirubicin, are widely used chemotherapeutic agents due to their multifaceted mechanisms of action. These include DNA intercalation, inhibition of topoisomerase II, free radical generation, cell cycle interference, immune activation, angiogenesis inhibition, and apoptosis induction.[114] Despite their well-documented efficacy, the clinical application of anthracyclines is often limited by adverse effects, particularly cardiotoxicity, myelosuppression, and the development of drug resistance. Anthracycline-induced cardiotoxicity is primarily attributed to oxidative stress and myocardial cell damage, which can result in long-term complications, including heart failure.[115]

Preclinical and clinical studies have investigated the combination therapy of SGLT2 inhibitors and anthracyclines. Given their cardioprotective properties, SGLT2 inhibitors have been explored as adjunctive therapy to mitigate anthracycline-induced cardiotoxicity. In a study by Quagliariello et al, empagliflozin alleviated DOX-induced cardiotoxicity in non-diabetic mice. The study demonstrated that empagliflozin reduced myocardial stress and cardiac fibrosis, while also lowering circulating levels of pro-inflammatory cytokines, including IL-1β, IL-6, and IL-8. These cytokines play a critical role in cardiac inflammatory responses, and their overexpression is associated with myocardial injury, fibrosis, and dysfunction.[94] In this study, empagliflozin treatment decreased these inflammatory markers, attenuating DOX-induced cardiotoxicity and improving cardiac function. Additionally, Bardaweel et al demonstrated that co-administration of canagliflozin with anthracyclines in MCF-7 and HepG2 cell lines reduced the half-maximal inhibitory concentration (IC50), enhancing their therapeutic effects. This combination therapy was associated with increased ROS levels, further promoting apoptosis.[27] Moreover, the co-administration of SGLT2 inhibitors and DOX significantly inhibited glucose consumption, leading to reduced intracellular ATP and lactate levels. These findings suggest that this combination may enhance therapeutic efficacy by disrupting cancer cell energy metabolism.[95]

Mechanistically, SGLT2 inhibitors mitigate the cytotoxicity of anthracyclines primarily by downregulating key signaling pathways associated with autophagy and apoptosis, such as the c-Jun N-terminal kinase (JNK) and PI3K/AKT pathways. For instance, Chang et al demonstrated that empagliflozin attenuates DOX-induced cardiomyocyte apoptosis by inhibiting the JNK signaling pathway and its downstream ROS and oxidized nicotinamide adenine dinucleotide (NAD+) pathways. In cardiomyocytes derived from pluripotent and embryonic stem cells, empagliflozin pretreatment reduced the expression of the apoptosis marker caspase-3 and suppressed the phosphorylation of JNK and p38. Additionally, empagliflozin effectively diminished DOX-induced increases in ROS levels and decreases in NAD+ levels.[96] Animal studies further confirmed that empagliflozin ameliorates DOX-induced cardiac dysfunction and fibrosis.

Similarly, Luo et al reported that, in cardiomyocyte models, canagliflozin upregulates SIRT1 expression, promoting the translocation of microtubule-associated protein 1 light chain 3 from the nucleus to the cytoplasm and activating autophagy. Concurrently, it inhibits the PI3K/Akt/mTOR signaling pathway, enhancing autophagic flux and ultimately protecting cardiomyocytes from DOX-induced damage.[97] Furthermore, SGLT2 inhibitors may enhance the efficacy of anthracyclines by modulating the TME. Karim et al demonstrated that the combination of SGLT2 inhibitors with DOX suppresses tumor cell growth and proliferation by reducing glucose uptake and ATP production, while further enhancing DOX's antitumor effects through alterations in cell cycle progression and apoptosis-related gene expression. Specifically, co-treatment with canagliflozin and DOX inhibited glucose uptake and ATP generation in MCF-7 cells, limiting intracellular energy supply and restraining tumor cell proliferation. Additionally, the canagliflozin + DOX combination induced S-phase cell cycle arrest and upregulated pro-apoptotic genes, including *BAK1 (BAK), BCL2L13 (BOK)*, and *BAX (Bcl-2-associated X protein)*, while downregulating CDK2 expression and upregulating p16[112]. These gene expression changes contribute to apoptosis induction, further potentiating the cytotoxic effects of DOX.[95] In summary, the combination of SGLT2 inhibitors and anthracyclines holds great promise for improving cancer treatment outcomes. This synergistic strategy not only addresses key limitations of anthracyclines, such as cardiotoxicity and resistance, but also leverages the metabolic and immunomodulatory properties of SGLT2 inhibitors to enhance overall therapeutic

efficacy. Future research should focus on elucidating the underlying mechanisms of this combination therapy and exploring its clinical applications to provide more effective treatment options for cancer patients.

SGLT2 Inhibitors and Targeted Therapy

Targeted therapy refers to the precise identification and selective elimination of tumor cells by targeting specific tumor-associated markers. While targeted therapies offer advantages such as precise drug delivery and high therapeutic efficacy, their clinical application is often limited by dose-dependent toxic side effects and the development of drug resistance. Consequently, the development of novel combination strategies has become a key focus of research. The targeted application of SGLT2 inhibitors primarily involves their co-encapsulation with nanomaterials to formulate SGLT2 inhibitors-loaded nanoparticles.[116] Nanoparticle-based drug delivery systems represent an advanced therapeutic approach, enabling controlled, targeted, and site-specific drug release.[117] By formulating SGLT2 inhibitors into nanoparticles, higher efficacy can be achieved even at lower doses, potentially reducing adverse effects and drug-related toxicity. Moreover, SGLT2 inhibitors can be combined with monoclonal antibodies and other targeted therapies to overcome resistance mechanisms, presenting a promising strategy for advancing cancer treatment. This combination approach may enhance the therapeutic potential of SGLT2 inhibitors while improving overall treatment efficacy and minimizing side effects.[118]

Angelopoulou successfully covalently conjugated canagliflozin with IO/PMAA-g-PEGMA magnetic nanoparticles, facilitating accelerated drug release through targeted delivery. In cell-based experiments, canagliflozin-loaded nanoparticles exhibited enhanced cytotoxicity against A549 and PDVC57 cancer cells compared to non-nanoparticle-conjugated canagliflozin, with apoptosis induction further amplified under a magnetic field. Additionally, in a murine PDVC57 tumor model, canagliflozin-loaded nanoparticles combined with RT demonstrated superior antitumor activity, significantly delaying tumor growth compared to RT with non-nanoparticle-conjugated canagliflozin, while maintaining favorable treatment tolerance.[88] Similarly, dapagliflozin has demonstrated promising efficacy in targeted therapy. Studies have shown that magnetic nanoparticles loaded with dapagliflozin facilitate targeted drug delivery to tumor sites, ensuring precise and controlled release. Compared to free dapagliflozin, nanoparticle-loaded dapagliflozin exhibited enhanced anticancer activity against A549 human lung cancer cells in vitro, with increased cytotoxicity observed following enhanced nanoparticle uptake under an external magnetic field gradient. This approach significantly improves the therapeutic efficacy of dapagliflozin while minimizing off-target effects.[119]

Another SGLT2 inhibitor, phloridzin, and its aglycone phloretin, have also demonstrated antitumor potential. However, due to the low oral bioavailability of phloretin, its clinical application remains limited. Payne et al reported that conjugating phloridzin and phloretin with gold nanoparticles (AuNPs) not only enabled nanoscale drug delivery but also enhanced their antitumor efficacy. Compared to the free drugs, AuNP-conjugated phloridzin and phloretin exhibited significantly increased cytotoxicity against HeLa cancer cells, which was attributed to a synergistic effect between the AuNPs and the drugs.[116] These findings suggest that selective nanoparticle-mediated delivery of SGLT2 inhibitors to tumor sites, when combined with RT or CT, represents a promising anticancer strategy. This approach may help overcome tumor hypoxia-induced drug resistance, enhance therapeutic efficacy, and reduce adverse effects on normal tissues.[116] On the other hand, the combination of SGLT2 inhibitors with monoclonal antibodies has garnered increasing attention. For instance, empagliflozin combined with TZM has demonstrated synergistic potential in the treatment of HER2 (human epidermal growth factor receptor 2)-positive breast cancer. TZM specifically binds to the extracellular domain of the HER2, blocking HER2-mediated signaling pathways and, consequently, inhibiting tumor cell proliferation.[120] However, targeted therapies such as TZM are often associated with cardiotoxicity, which limits their widespread clinical application. Therefore, combining TZM with SGLT2 inhibitors may help mitigate TZM-induced cardiotoxicity, broadening its therapeutic potential and improving its clinical applicability.

Recent studies suggest that empagliflozin, as a key SGLT2 inhibitors, can attenuate TZM-induced cardiotoxicity. In animal models, TZM-treated mice exhibited significant cardiac dysfunction and morphological alterations, including elevated serum LDH and troponin I levels, increased heart weight and ventricular size, enlarged cardiomyocyte area, and exacerbated interstitial fibrosis. However, co-administration of empagliflozin alleviated these adverse effects by reducing oxidative stress markers, such as superoxide (O_2^-) and MDA, as well as DNA damage indicators, including γ-H2AX and

8-hydroxy-2'-deoxyguanosine (8-OHd). Moreover, empagliflozin exerted cardioprotective effects by reversing mitochondrial dysfunction and improving cardiomyocyte contractility and calcium handling. These findings suggest that empagliflozin may mitigate TZM-induced cardiotoxicity by inhibiting DNA damage and ferroptosis pathways, offering a novel strategy for combination therapy in HER2-positive breast cancer.[98] Furthermore, clinical evidence indicates that dapagliflozin, when combined with cetuximab, exhibits antitumor potential in the treatment of CRC with liver metastases. A case report described a 69-year-old male patient whose carcinoembryonic antigen (CEA) levels drastically decreased from 1104 ng/mL to 112.4 ng/mL following dapagliflozin treatment, with CT imaging revealing a reduction in liver metastatic lesions. Molecular analysis revealed that the patient's CRC cells expressed SGLT2 but lacked UGT1A9, potentially allowing dapagliflozin to inhibit glucose uptake and exert direct cytotoxic effects as an unmetabolized drug, thus suppressing tumor growth. These findings highlight the potential of dapagliflozin in combination with cetuximab as an antitumor strategy in CRC with liver metastases, offering a novel therapeutic approach for patients with diabetes and concomitant CRC.[121]

Combination of SGLT2 Inhibitors and Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICIs) have led to significant advancements in cancer treatment by enhancing immune responses against various malignancies, including melanoma, non-small cell lung cancer, and renal cell carcinoma.[122] The antitumor immune response is augmented by ICIs through the blockade of inhibitory pathways, particularly via the suppression of the Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and PD-1 pathways, which are critical in regulating T cell activity and facilitating tumor immune evasion.[123] CTLA-4 inhibits early T cell activation by binding to B7 molecules, which suppresses T cell proliferation and cytokine secretion.[124] In contrast, PD-1 and its ligand PD-L1 exert potent immunosuppressive effects within the TME, leading to the inhibition of T cell activation and function and ultimately attenuating antitumor immunity.[125] Consequently, the inhibition of these immune checkpoints can restore T cell function and enhance the immune system's ability to recognize and eliminate tumor cells.

Although ICIs have demonstrated efficacy against various cancers, the therapeutic response remains limited in certain patients, and severe immune-related adverse events (irAEs), including myocarditis, colitis, and pneumonia, may occur.[126] The occurrence of irAEs and tumor resistance has prompted researchers to investigate combination therapies aimed at enhancing efficacy while mitigating toxicity.[127] SGLT2 inhibitors have demonstrated potential to enhance the efficacy of ICIs by modulating the TME and immune responses, particularly under hyperglycemic conditions.[99] Hyperglycemia has been shown to accelerate tumor progression by promoting tumor cell proliferation, migration, and invasion. In contrast, SGLT2 inhibitors have been associated with reduced all-cause mortality in cancer patients with type 2 diabetes mellitus (DM2) undergoing ICI therapy,[128] providing new insights into the therapeutic application of ICIs.

Furthermore, the rationale for combining ICIs with SGLT2 inhibitors lies in their complementary mechanisms of action. Hyperglycemia has been shown to activate the NLRP3 inflammasome, leading to the secretion of pro-inflammatory cytokines and the exacerbation of immune tolerance.[129] By lowering blood glucose levels, SGLT2 inhibitors can mitigate this inflammatory response, enhancing the overall antitumor efficacy of ICIs. A study by Quagliariello et al demonstrated that the combination of SGLT2 inhibitors with ICIs was more effective in inhibiting tumor growth compared to monotherapy.[130] In a breast cancer model, concurrent treatment with empagliflozin and ICIs significantly increased T cell infiltration within the TME, a critical factor for the success of immunotherapy. Additionally, this combination therapy reduced the expression of immunosuppressive markers, including PD-L1 and IL-6, suggesting a shift in the TME toward a more favorable immune landscape.[131] The mechanisms underlying the combined use of SGLT2 inhibitors and ICIs are multifaceted. SGLT2 inhibitors enhance immune responses by reducing pro-inflammatory cytokine and ROS levels while also modulating metabolic pathways essential for T cell activation and proliferation.[132] By improving the TME and enhancing T cell activity, SGLT2 inhibitors effectively amplify the therapeutic effects of ICIs. Recent studies by Ding et al further support this hypothesis, demonstrating that canagliflozin enhances immune responses by disrupting the interaction between SGLT2 and PD-L1, leading to reduced PD-L1 stability. This not only decreases PD-L1 expression on tumor cells but also increases the infiltration of $CD3^+$ and $CD8^+$ T cells, promoting antitumor immunity.[99] Furthermore, SGLT2 inhibitors induce metabolic stress by increasing oxygen demand and promoting ketone body production, which enhances the immunogenicity of tumor cells under nutrient-deprived

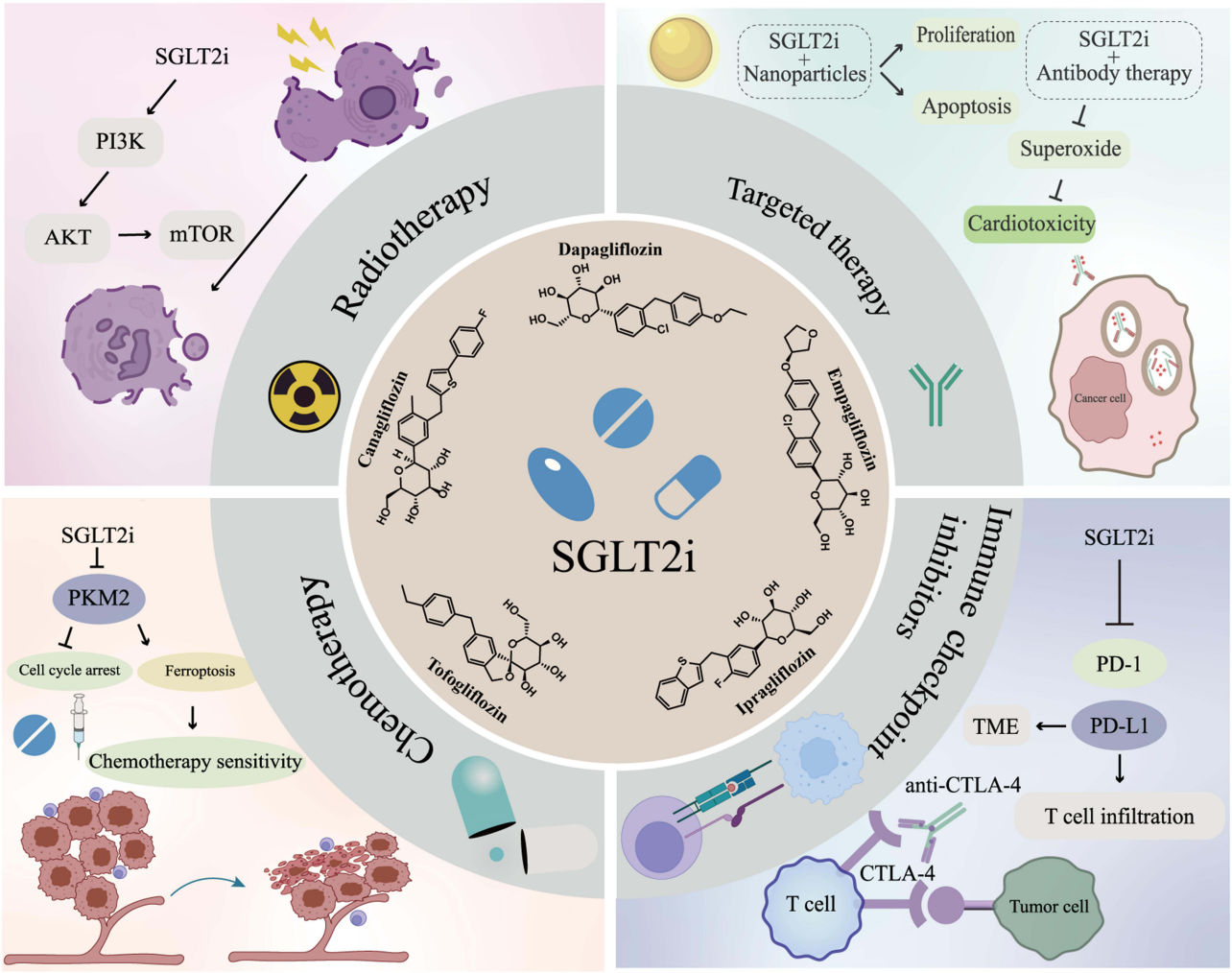

Figure 3 Synergistic anti-cancer effects of SGLT2 inhibitors in combination with various cancer therapies. SGLT2 inhibitors enhance cancer treatment efficacy by modulating key molecular pathways. Suppression of the PI3K/AKT/mTOR pathway increases radiosensitivity, while inhibition of PKM2 induces cell cycle arrest and ferroptosis, enhancing chemosensitivity. SGLT2 inhibitor-based nanoparticles regulate tumor proliferation and apoptosis, and antibody conjugation reduces superoxide-mediated cardiotoxicity. Downregulation of PD-L1 expression facilitates T cell infiltration and improves anti-CTLA-4 immunotherapy responses.
Abbreviations: PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin; PKM2, pyruvate kinase M2; PD-1, programmed death-1; PD-L1, programmed death ligand-1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4.

conditions. By targeting immune evasion mechanisms and optimizing the TME, the combination of SGLT2 inhibitors and ICIs holds the potential to address hyperglycemia-induced immune suppression while fostering beneficial immune characteristics, enhancing ICI efficacy, and reducing associated toxicity[128] (Figure 3).

Clinical Trials

Clinical trials have been conducted to evaluate the effects of SGLT2 inhibitors in anticancer combination therapy strategies. A prospective randomized controlled trial assessed the combination of dapagliflozin with standard gemcitabine and nab-paclitaxel (GnP) for the treatment of advanced pancreatic ductal adenocarcinoma. While gemcitabine and nab-paclitaxel are the standard CT regimen for pancreatic ductal adenocarcinoma, GnP has demonstrated a limited ORR of 23% and an overall survival of less than one year. The results indicated that the addition of dapagliflozin to GnP therapy allowed patients to preserve muscle mass while reducing fat mass, a factor that correlated with improved efficacy in solid tumors, as assessed by the RECIST 1.1 criteria. This suggests a potential link between the muscle-to-fat ratio and tumor growth. Furthermore, during dapagliflozin combination therapy, some patients showed slowed tumor progression. After 8 weeks of treatment, dapagliflozin was discontinued, and follow-up at 3 months revealed an increase in tumor size or the

development of new metastases. These findings further suggest that the combination of dapagliflozin with GnP may suppress pancreatic ductal adenocarcinoma growth, and the addition of dapagliflozin was well-tolerated by patients, without inducing additional toxicity.[105]

Compared to other classes of antidiabetic medications, the clinical advantage of SGLT2 inhibitors lies in their anti-tumor proliferative effects and relatively low side-effect profile.[17,133] An analysis of the DAPA-CKD trial highlighted that infections and malignancies were the most common causes of non-cardiovascular death. Compared to placebo, dapagliflozin was associated with a reduced risk of death related to malignancies.[134] Additionally, a retrospective cohort study using a large-scale epidemiological database found that the use of SGLT2 inhibitors was associated with a reduced risk of incident cancer, particularly CRC, with a risk reduction hazard ratio of 0.71 (CI 0.50–0.998).[135] In addition to randomized controlled trials and retrospective analyses, clinical trials are currently recruiting or have completed recruitment to confirm the combination of SGLT2 inhibitors with anticancer agents.

At present, clinical trials of combination with SGLT2 inhibitors are ongoing continuously. We have identified 20 clinical trials that are actively recruiting participants to evaluate the efficacy and safety of SGLT2 inhibitors in combination with other anticancer agents until June 2025 (Table 4). Results can be found in the ClinicalTrials.gov website. These encompass a diverse range of tumor types, including breast cancer, prostate cancer, or and pancreatic cancer, from early to advanced stages. Among them, 1 trail combine surgery therapy, 1 trail combine neoadjuvant therapy, and 11 trails combine CT. A study (NCT05025735) aims to evaluate the relationship between glucose reduction and breast cancer incidence by combining dapagliflozin with alpelisib and letrozole for the treatment of $HR^+/HER2^-$ PIK3CA-mutant metastatic breast cancer. The trial assesses whether dapagliflozin can enhance the therapeutic efficacy of alpelisib by reducing the incidence of hyperglycemia. If dapagliflozin can mitigate alpelisib-induced hyperglycemia and the subsequent rebound hyperinsulinemia, it may improve the treatment outcomes of alpelisib. Additionally, clinical trials are also investigating the link between SGLT2 inhibitors and tumor immunity. A prospective randomized controlled trial (NCT05903703) evaluating the combination of canagliflozin with gemcitabine for pancreatic cancer treatment shows that canagliflozin may enhance gemcitabine efficacy by reducing PD-L1 expression and restoring $CD8^+$ T cell activity. The primary endpoints include partial and complete tumor response, as well as progression-free survival, with the trial scheduled for completion by March 2027.

Interestingly, a trial (NCT04887935) is investigating whether SGLT2 inhibitors can be used as neoadjuvant therapy in prostate cancer patients undergoing surgery. The study plans to administer dapagliflozin daily for six weeks before surgery and four weeks after surgery. The evaluation will include adverse events (CTCAE v5.0), changes in prostate tumor size measured by MRI, assessment of tumor necrosis or atrophy, as well as changes in blood glucose and insulin function-related markers, providing preliminary evidence for the potential application of SGLT2 inhibitors in prostate cancer treatment. Another longitudinal, dose-exploration Phase Ib study (NCT05521984) aims to assess the safety and tolerability of dapagliflozin combined with carmustine CT in children with recurrent primary brain tumors. Additionally, a Phase 1b/2 clinical trial (NCT04073680) plans to recruit 60 patients with advanced solid tumors to receive combination therapy of selumetinib and canagliflozin. The study will explore the safety and efficacy of the treatment by evaluating the incidence of adverse events, clinical tumor assessments, pharmacokinetic parameters (Cmax, Tmax, and AUC), and determine the optimal dosing for advanced solid tumor patients with PI3Kα mutations.

During CT treatment in cancer patients, a common adverse effect is cardiotoxicity. Therefore, many clinical studies have focused on whether SGLT2 inhibitors can reduce cardiac toxicity and have potential cardioprotective effects in cancer treatment. A prospective randomized controlled trial (NCT06711185) plans to assess whether dapagliflozin can alleviate drug-induced myocardial fibrosis during anthracycline CT in breast cancer patients. The study will examine whether dapagliflozin can reduce heart dysfunction, prevent heart failure, and attenuate cardiac remodeling, with the primary endpoint being left ventricular ejection fraction (LVEF). Similarly, another clinical trial (NCT06491680) will measure N-terminal pro-B-type natriuretic peptide (NT-pro BNP) to determine if dapagliflozin can prevent and delay anthracycline-induced cardiac toxicity. Another study (NCT05271162) is focusing on the efficacy of empagliflozin in preventing left ventricular dysfunction caused by high-dose DOX or epirubicin, investigating whether SGLT2 inhibitors can prevent LVEF reduction after high-dose anthracycline treatment and improve patient survival and quality of life.

Table 4 Ongoing Clinical Trials of SGLT2i in Cancer Patients

Study Object	Phase	SGLT2i	Treatment Combination	Duration	Main Results	NCT
Breast cancer	PHASE2	Dapagliflozin (10 mg)	Dapagliflozin +Anthracyclines	Baseline, 3 months, 6 months, 12 months and 18 months.	**Primary outcomes** Left Ventricular Ejection Fraction Global Longitudinal Strain **Secondary outcomes** Difference in CTRCD The changes in NT-pro-BNP, hsTnI, CKD-EPI eGFR, and hsCRP	NCT06341842
Prostate cancer	PHASE1	Dapagliflozin (10 mg)	Dapagliflozin + Prostatectomy	6 weeks	**Primary outcomes** Frequency and severity of toxicities related to dapagliflozin. Successful completion of dapagliflozin treatment. **Secondary outcomes** Changes in tumor size, necrosis degree, plasma glucose, C-peptide, HbA1c, and glucagon levels.	NCT04887935
Pancreatic cancer	PHASE1	Dapagliflozin (5 mg daily for 2 weeks, then 10 mg daily for 6 weeks)	Dapagliflozin +Nab-paclitaxel and gemcitabine	8 weeks	**Primary outcomes** Tolerability measured by related adverse events over 30 days post-treatment. **Secondary outcomes** Changes in plasma glucose, ketones, HbA1c, CA19-9, body composition metrics, tumor size, and necrosis.	NCT04542291
Pediatric brain tumor	PHASE1	Dapagliflozin (5 mg daily for 2 weeks, then 10 mg daily for 10 weeks)	Dapagliflozin + Carmustine	12 weeks	**Primary outcomes** Adverse events graded by CTCAE (version 5.0) from treatment start to 30 days post-treatment. **Secondary outcomes** Changes in blood glucose, ketones, HbA1c, tumor response rates, feasibility of enrollment, and changes in fructosamine, c-peptide, and glucagon over the treatment period.	NCT05521984
Chemo-naive patients with a first diagnosis of cancer	PHASE2/3	Empagliflozin (10 mg)	Empagliflozin +Doxorubicin	3 months	**Primary outcomes** Cardiac troponin T Echocardiography (ECHO)	NCT06103279
Advanced solid tumors	PHASE 1/2	Canagliflozin (300 mg)	Serabelisib + Canagliflozin	6 months	**Primary outcomes** Safety evaluated by adverse events; laboratory abnormalities and tumor assessments by RECIST **Secondary outcomes** Pharmacokinetics of serabelisib (Cmax, Tmax, AUC)	NCT04073680
Breast cancer	PHASE4	Dapagliflozin (10 mg)	Dapagliflozin +Anthracyclines	0 and 2 to 3 months from baseline	**Primary outcomes** Changes in serum N-terminal pro-B-type natriuretic peptide (NT-pro BNP) **Secondary outcomes** Changes in left ventricular ejection fraction (LVEF)	NCT06491680

(*Continued*)

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Table 4 (Continued).

Study Object	Phase	SGLT2i	Treatment Combination	Duration	Main Results	NCT
$HR^+/HER2^-$ metastatic breast cancer	PHASE2	Dapagliflozin (10 mg)	Dapagliflozin + Alpelisib + Fulvestrant	1 year	**Primary outcomes** Incidence of all-grade hyperglycemia as assessed by CTCAE v5.0. **Secondary outcomes** Incidence of Grade 3/4 hyperglycemia as assessed by CTCAE v5.0. Overall response rate (ORR) Progression-free survival.	NCT05025735
HER2-negative breast cancer	PHASE1	Dapagliflozin (10 mg)	Dapagliflozin +Standard of care neoadjuvant chemotherapy	Baseline, post paclitaxel treatment at week 12, and 2 weeks post neoadjuvant therapy.	**Primary outcomes** Change in Homeostasis Model Assessment-Insulin Resistance **Secondary outcomes** Changes in fasting glucose, insulin concentrations, and IHC for PKB/AKT, insulin receptor, IGF1R, IRS1, and SGLT2	NCT05989347
Breast cancer	PHASE3	Dapagliflozin (10 mg)	Dapagliflozin +Anthracycline	12 months	**Primary outcomes** Primary efficacy composite endpoint at 12 months. **Secondary outcomes** Secondary efficacy composite endpoint at 6 months Changes in left ventricular ejection fraction and diastolic function Quality of life assessments, and safety endpoints including Cardiovascular events and occurrences of hypoglycemia.	NCT06304857
Breast cancer	PHASE2	Dapagliflozin (10 mg)	Dapagliflozin + Doxorubicin	3 months	**Primary outcomes** Change in ejection fraction using echocardiography **Secondary outcomes** Changes in Cardiac Troponin T and NT-pro-BNP levels	NCT06427226
Breast cancer	PHASE3	Empagliflozin (10 mg)	Empagliflozin + Anthracyclines	24 months	**Primary outcomes** Number of participants with left ventricular systolic dysfunction **Secondary outcomes** All-cause death, CV death, myocardial infarction, ischemic stroke, changes in GLS, structural myocardial alterations, and cardiac biomarkers	NCT05271162
Non-diabetic glioma	PHASE3	Dapagliflozin (10 mg)	Dapagliflozin +Levetiracetam	2 weeks	**Primary outcomes** Magnetic resonance imaging of the brain with contrast Optic nerve sheath diameter for assessment of intracranial tension **Secondary outcomes** Tumor necrosis factor alpha Interlukin-6	NCT06750458

Breast cancer	PHASE2	Canagliflozin (100 mg for the first week, starting week 2 and onward to 300 mg)	Canagliflozin +Alpelisib +Fulvestrant	12 weeks	**Primary outcomes** Hyperglycemia-free rate for participants	NCT05090358
Urinary tract malignancies	N/A	Empagliflozin	Empagliflozin+DPP-4 inhibitors	60 months	**Primary outcomes** Occurrence of urinary tract cancers, including bladder and renal cancers.	NCT03464045
Solid tumors with platinum chemo	PHASE2	Dapagliflozin (10 mg)	Dapagliflozin + Platinum-based chemotherapy	4 weeks	**Primary outcomes** Urinary KIM-1/Creatinine (uKIM-1/Cr) expression at 72 hours **Secondary outcomes** uEGF/Cr, uNAG/Cr, AlbU/Cr, uβ2-m/Cr at baseline, 72 h, 168 h. Incidence of AKI at 72 h and Day 7 (KDIGO criteria). eGFR (CKD-EPI 2021) at 72 h and Day 7. Electrolyte disturbances (Na, Mg, P) at 72 h and Day 7. Safety & tolerability (CTCAE v5.0) through 4-week follow-up.	NCT07018622
Breast cancer	PHASE2/3	Dapagliflozin (10 mg)	Standard anthracycline-based and/or trastuzumab-based chemotherapy + Dapagliflozin	26 weeks	**Primary outcomes** Change in Left Ventricular Ejection Fraction **Secondary outcomes** Changes in cardiac biomarkers (Troponin I, NT-proBNP, Galectin-3, CA 15–3) Changes in kidney function (serum creatinine and BUN) Changes in hematologic profile (CBC) Changes in liver function (ALT, AST, ALP, bilirubin)	NCT06888505
Breast cancer	Phase 2	Empagliflozin (10 mg)	Carvedilol + empagliflozin	6 months	**Primary outcomes** Feasibility of HER2HEART as measured by the number of patients enrolled over a 6-month period **Secondary outcomes** Tolerability as measured by treatment adherence via self-report Tolerability as measured by incidence of serious adverse events Tolerability as measured by incidence of adverse events of special interest	NCT06844669
Pancreatic cancer	N/A	Canagliflozin (400mg)	Canagliflozin +Gemcitabine	18 weeks	**Primary outcomes** Clinical responses, including complete response (CR), partial response (PR), stable disease (SD), and disease progression (PD), are evaluated at 6-week intervals.	NCT05903703
Breast cancer	PHASE3	Dapagliflozin (10 mg)	Dapagliflozin + Anthracyclines	36 weeks	**Primary outcomes** Change in left ventricle ejection fraction	NCT06711185

Abbreviations: AUC, area under the concentration–time curve; AKT, protein kinase B; CA19-9, carbohydrate antigen 19–9; CKD-EPI eGFR, Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; ECHO, echocardiography; GLS, global longitudinal strain; HbA1c, glycated hemoglobin A1c; hsCRP, high-sensitivity C-reactive protein; hsTnI, high-sensitivity troponin I; IHC, immunohistochemistry; IGF1R, insulin-like growth factor 1 receptor; IL-6, interleukin-6; IRS1, insulin receptor substrate 1; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-B-type natriuretic peptide; ORR, overall response rate; PD, progressive disease; PK, pharmacokinetics; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SGLT2, sodium-glucose cotransporter 2; SD, stable disease; Tmax, time to reach maximum concentration; TNF-α, tumor necrosis factor alpha.

Additionally, a clinical trial (NCT06427226) is designed to evaluate whether dapagliflozin can provide cardioprotection by improving energy metabolism and reducing oxidative stress. The hypothesis is that dapagliflozin may lower cardiac troponin T levels and improve LVEF, thus offering potential cardiovascular protection, particularly in mitigating anthracycline-induced cardiotoxicity. Lastly, a Phase III study (NCT06304857) will assess the effectiveness of dapagliflozin in preventing cardiac toxicity in breast cancer patients receiving anthracycline treatment. Patients will take 10 mg of dapagliflozin daily, and cancer therapeutics-related cardiac dysfunction will be measured at 6 and 12 months of treatment, with the study evaluating the impact of dapagliflozin on the incidence of cardiac dysfunction in breast cancer patients. This study is expected to complete by December 2027. As more clinical trial results emerge, the potential role of SGLT2 inhibitors in cancer patients will continue to unfold. The combination of SGLT2 inhibitors with other cancer treatments may provide new insights into cancer therapy, improving treatment efficacy, reducing adverse effects, and offering great promise in the field of oncology by ultimately enhancing patient survival and quality of life.

Discussion

Therapeutic and Translational Potential of Combination Therapies Involving SGLT2 Inhibitors in Cancer

SGLT2 inhibitors combination therapies represent a promising treatment approach in oncology, as the integration of multiple therapeutic strategies offers an effective means of combating cancer. Targeted therapies function by specifically targeting cancer cells or the critical pathways necessary for tumor growth,[136] while immunotherapies aim to stimulate or enhance the body's immune system to recognize and eliminate cancer cells.[44] Chemoradiation, which combines CT with radiation therapy, remains a cornerstone of treatment for advanced cancers. When used in combination, these therapies can complement each other's mechanisms of action, leading to more sustained tumor control and potentially greater survival benefits compared to their use in isolation. Additionally, combination therapies offer significant advantages in overcoming drug resistance. As a newly discovered anticancer agent, SGLT2 inhibitors have been shown to exert anticancer effects across a variety of malignant tumors. They not only influence metabolic processes but also exert both direct and indirect anticancer effects through various mechanisms.[44,52] The combination of SGLT2 inhibitors with other cancer treatments could help modulate the TME, potentially enhancing the sensitivity of tumors to both CT and immunotherapy.[26] The integration of SGLT2 inhibitors with multiple treatment modalities, including targeted therapies, immunotherapy, and conventional chemoradiation, has the potential to provide more sustained control of tumor growth in cancer patients compared to conventional therapies alone. Additionally, combination therapies may help overcome drug resistance and enhance the effectiveness of monotherapy, offering patients more durable and effective treatment options, particularly in advanced-stage cancer.[92]

Currently, research is focused on exploring the preclinical and clinical applications of SGLT2 inhibitors as part of combination therapies for cancer treatment, both in vitro and in vivo. SGLT2 inhibitors, such as empagliflozin, dapagliflozin, canagliflozin, and tofogliflozin, enhance anticancer efficacy through mechanisms such as metabolic reprogramming, immune modulation, and the regulation of key signaling pathways. By reducing glucose uptake in tumor cells, these inhibitors amplify the effects of CT and RT.[137] Additionally, through the activation of AMPK and inhibition of mTOR, these inhibitors promote cell cycle arrest and apoptosis, enhancing the sensitivity of tumor cells to chemotherapeutic agents such as paclitaxel, cisplatin, and anthracyclines.[82] Dapagliflozin also improve the TME by increasing immune cell infiltration and reducing pro-inflammatory cytokines, such as TNF-α and IL-1, which enhances the effectiveness of Anthracyclines therapies.[138] Empagliflozin and dapagliflozin reduce inflammation and oxidative stress by inhibiting inflammasomes and activating AMPK.[64,139] Canagliflozin, in addition to these effects, enhances chemosensitivity by modulating the tumor immune microenvironment and inhibiting glycolysis.[93]

Several ongoing clinical trials are currently investigating the safety and efficacy of SGLT2 inhibitors in combination with established cancer therapies. These trials range from phase 1 and 2 to Phase 3 studies. The clinical studies aim to comprehensively evaluate the safety, efficacy, and potential protective effects of SGLT2 inhibitors. They are crucial for determining optimal dosing regimens, identifying biomarkers that may predict response, and assessing the long-term

benefits of combination therapies for patients with advanced-stage cancers, particularly those with metabolic disorders or heart and kidney dysfunction.

Current Challenges and Perspectives

Research on the combination of SGLT2 inhibitors with cancer therapies represents a promising and emerging direction in oncology.[27] Although numerous preclinical studies support the potential of these agents to enhance antitumor efficacy when used alongside established therapies, most of the current evidence is derived from in vitro experiments and animal models. Clinical data remain limited, primarily stemming from early-phase exploratory trials, and large-scale randomized controlled studies evaluating their efficacy, safety, and long-term survival benefits in cancer patients are still lacking.[105,140] Moreover, drug tolerance and individual variability remain major obstacles to achieving precise clinical application. Differences in patients' metabolic status, tumor molecular subtypes, and genetic backgrounds may significantly influence the pharmacological response to SGLT2 inhibitors.[29] For instance, in tumor cells with high glucose metabolic dependence such as pancreatic and liver cancers, the inhibitory effects may be more pronounced, whereas in tumors characterized by high metabolic heterogeneity or weak glucose uptake dependence, the therapeutic efficacy may be limited.[93,141] Therefore, the development of predictive molecular biomarkers and the optimization of patient stratification strategies will be key directions for future research. In addition, existing research has predominantly focused on classical agents such as dapagliflozin, empagliflozin, and canagliflozin, with insufficient exploration of other types of SGLT2 inhibitors and non-selective targets within the SGLT2 family. Looking ahead, SGLT2 inhibitors are expected to play an increasingly important role in cancer combination therapies, particularly in conjunction with metabolic-targeted agents, immune checkpoint inhibitors, and epigenetic modulators to achieve multilayered antitumor synergy. The combinations of diverse therapeutic modalities can provide a systematic understanding of how SGLT2 inhibitors regulate key nodes within metabolic, signaling, and immune interaction networks, offering a theoretical foundation for precision combination therapy.[23,99,142] At the same time, the acceleration of multicenter, prospective clinical studies is essential to validate their long-term safety, sustained efficacy, and translational feasibility.

In summary, the challenges and future prospects of SGLT2 inhibitors in cancer therapy coexist. With ongoing mechanistic exploration and progressive clinical validation, their therapeutic position within the oncology landscape will become increasingly clear. These efforts are expected to promote a paradigm shift in metabolic anticancer strategies, from single target interventions to systemic metabolic reprogramming, thus providing new avenues for precision cancer therapy.

Conclusion

SGLT2 inhibitors have emerged as promising agents with anticancer effects. Acting at the intersection of metabolism, inflammation, oxidative stress, and immune regulation, they suppress tumor proliferation, invasion, and metastasis while enhancing therapeutic sensitivity and protecting normal tissues. Preclinical studies have consistently shown that agents such as empagliflozin, dapagliflozin, and canagliflozin exert potent antitumor effects across diverse solid tumors, including liver, breast, gastric, and brain cancers. Beyond their direct cytotoxicity, their cardioprotective and nephroprotective properties alleviate chemotherapy-induced toxicity, offering an additional therapeutic advantage. When combined with radiotherapy, chemotherapy, targeted therapy, or immune checkpoint blockade, SGLT2 inhibitors synergistically enhance treatment efficacy through metabolic reprogramming and immune microenvironment modulation. With further elucidation of underlying mechanisms and the advancement of high-quality clinical trials, SGLT2 inhibitors are expected to become an integral component of anticancer therapy. Their synergistic potential across radiotherapy, chemotherapy, targeted therapy, and immunotherapy opens new avenues for precision and individualized oncology treatment.

Abbreviations

ADAM10, a disintegrin and metalloproteinase domain 10; AKT, protein kinase B; α-SMA, α-smooth muscle actin; AMPK, AMP-activated protein kinase; ATM, ataxia telangiectasia mutated; BAK, Bcl-2 antagonist killer 1; BOK, Bcl-2-like protein 13; CAT, catalase; CD98hc, CD98 heavy chain; CDK1, cyclin-dependent kinase 1; CDK2, cyclin-dependent kinase 2; CDK4, cyclin-dependent kinase 4; CDK6, cyclin-dependent kinase 6; CKD, chronic kidney disease; CLS, crown-like structures; CPT, cisplatin; CRP, C-reactive protein; CRC, colorectal cancer; CT, chemotherapy; CXCL1,

chemokine (C-X-C motif) ligand 1; CXCL8, chemokine (C-X-C motif) ligand 8; CXCL10, chemokine (C-X-C motif) ligand 10; DCR, disease control rate; DDR1, discoidin domain receptor 1; DPP4, dipeptidyl peptidase-4; DOX, doxorubicin; EMT, epithelial-mesenchymal transition; ER, endoplasmic reticulum; FOXP3, forkhead box P3; FOXA1, forkhead box A1; GBM, glioblastoma; GSH, glutathione; GSK-3β, glycogen synthase kinase 3 beta; HbA1c, glycated hemoglobin; HCC, hepatocellular carcinoma; HIF-1α, hypoxia-inducible factor 1-alpha; HUVECs, human umbilical vein endothelial cells; ICIs, immune checkpoint inhibitors; IL-1, interleukin-1; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-12, interleukin-12; IFN-β, interferon-β; IFNγ, interferon gamma; JNK, c-Jun N-terminal kinase; LDH, lactate dehydrogenase; M-CSF, macrophage colony-stimulating factor; MDA, malondialdehyde; MMP, mitochondrial membrane potential; MMP-9, matrix metalloproteinase-9; NA, not available; NASH, non-alcoholic steatohepatitis; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NLR family pyrin domain containing 3; NAD+, nicotinamide adenine dinucleotide; Nrf2, nuclear factor erythroid 2-related factor 2; ORR, objective response rate; OTUD5, OTU deubiquitinase 5; PI3K, phosphoinositol-3 kinase; PKM2, pyruvate kinase M2; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; RIRR, ROS-induced ROS release; ROS, reactive oxygen species; RT, radiotherapy; SCID, severe combined immunodeficiency; SGLT2, sodium-glucose cotransporter 2;SHH, Sonic Hedgehog; Snai1, snail family transcription factor 1; SIRT-1, sirtuin 1; SIRT3, sirtuin 3; SP1, specificity protein 1; TCA, tricarboxylic acid; TFR, transferrin receptor; TME, tumor microenvironment; TNF-α, tumor necrosis factor-alpha; Tgfb1, transforming growth factor β1; TZM, Trastuzumab; UGT1A9, uridine diphosphate glucuronosyltransferase 1 family member A9; YAP1, yes1 associated transcriptional regulator.

Data Sharing Statement

No data was used for the research described in the article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflict of interest.

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