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REVIEW

Research Progress of SGLT2 Inhibitors in Cancer Treatment

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Abstract: Sodium glucose co-transporter 2 (SGLT2) inhibitors represent a novel class of hypoglycemic drugs that have emerged in recent years. These inhibitors function primarily by blocking the reabsorption of glucose in the kidneys, specifically targeting the SGLT2 proteins in the proximal convoluted tubules. This inhibition results in the reduction of blood glucose levels through increased glucose excretion in the urine. Recent studies have identified SGLT2 expression in various cancer types, suggesting that SGLT2 inhibition can potentially suppress tumor growth. This article provides a comprehensive review of the role of SGLT2 in tumorigenesis and tumor progression, and explores the underlying mechanisms and potential therapeutic applications of SGLT2 inhibitors as anticancer agents.

Keywords: SGLT2 inhibitors, SGLT2, cancer, mechanism

Introduction

Cancer is a significant public health concern and ranks as the second leading cause of mortality worldwide, following cardiovascular disease. In 2020, approximately 19.3 million cancer cases were diagnosed, resulting in 10 million deaths globally.[1] Furthermore, tumors impose a substantial economic burden on patients' families, highlighting the imperative need to discover novel therapeutics that can effectively combat tumors. Nearly a century ago, the "Warburg effect" postulated that malignant cells consume more glucose than normal cells, helping them meet their biosynthetic demands and adapt to diverse microenvironments.[2] Glucose serves as an essential energy source for cancer cells to meet their biosynthetic demands and adapt to diverse microenvironments. Elevated glucose levels, or hyperglycemia, are a risk factor for cancer, potentially leading to tumor growth and an increase in tumor size within the body.[3] Epidemiological surveys have demonstrated that diabetic patients face more than twice the risk of developing liver cancer, pancreatic cancer, and endometrial cancer compared to non-diabetic individuals. Additionally, they exhibit 1.2–1.5 times higher risks of colorectal cancer, breast cancer, and bladder cancer than their non-diabetic counterparts.[4] Consequently, intervention studies targeting individuals with both diabetes and malignancies are gaining increasing importance. Given metformin's established anti-tumor effects, exploring whether other hypoglycemic drugs also possess therapeutic capabilities against tumors has become an active area of research interest.[5]

Sodium glucose cotransporter 2 (SGLT2) inhibitors are a novel class of oral hypoglycemic agents that have demonstrated potential anticancer properties based on numerous in vivo and in vitro animal studies. SGLT2 inhibitors, named after "agliflozin", encompass representative drugs such as dapagliflozin, empagliflozin, canagliflozin, and toagliflozin.[6] In humans and mammals, SGLT2 is localized in the brush border of the proximal tubule's S1 and S2 segments within the kidney. It plays a crucial role in reabsorbing approximately 90% of glucose filtered from the

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glomerulus. Unlike insulin-dependent mechanisms for hypoglycemia, SGLT2 inhibitors act on the SGLT2 transporters of renal proximal tubular epithelial cells to impede glucose reabsorption by increasing urinary excretion, thereby reducing blood glucose levels.[7] Furthermore, the anticancer activity of SGLT2 inhibitors has been confirmed across various cancers including liver cancer, prostate cancer, renal cell cancer, bowel cancer, lung cancer, breast cancer, pancreatic cancer and bladder cancer.[8–17] And combination treatments of SGLT2 inhibitors and metformin increase the anticancer effects in pancreatic cancer in vivo.[15] The objective of this review is to elucidate the involvement of SGLT2 in tumor occurrence and development while exploring the mechanism behind their potential application as anticancer agents. This aims to provide insights for further research into utilizing hypoglycemic drug class - specifically SGLT2 inhibitors- in the treatment of tumors.

SGLT2 Expression in Cancer Cells/Tissues

The expression and functional role of SGLT2 in cancer were initially reported by Ishikawa et al[18] who observed significant SGLT2 expression in liver and lymph nodes of metastatic lung cancer. This finding suggests that SGLT2 plays a crucial role in glucose uptake during lung cancer metastasis. Subsequently, Scafoglio et al[19] demonstrated the presence of SGLT2 expression in pancreatic and prostate cancers using the specific radioactive glucose tracer methyl-4-deoxy-4-[18F]-fluoro-α-D-glucoside (Me4FDG), which allowed visualization of glucose uptake by tumors. Additionally, increased expression of SGLT2 has been associated with poor prognosis and decreased overall survival in renal clear cell carcinoma.[20] In vitro Me4FDG uptake assays and immunocytochemical assays have also confirmed the presence of SGLT2 in human pancreatic and prostate adenocarcinomas.[21] Similar transporter expression has been observed in mouse models through Me4FDG micro-PET imaging, autoradiography, and immunocytochemistry. Furthermore, high-grade glioblastoma patients have exhibited Me4FDG uptake as well. However, the study by Du et al[22] showed that the expression level of SGLT2 in pancreatic ductal adenocarcinoma (PDAC) tumor cells was relatively low and not significantly higher than that in normal tissues. These results were validated through IHC analysis and bioinformatics databases (such as GEO and Oncomine), further supporting that SGLT-2 is not significantly overexpressed in pancreatic cancer cells. Collectively, these findings indicate that there is an overexpression of SGLT2 transporters in most tumors, presenting a potential therapeutic target for specific inhibitors against this protein.

Anticancer Mechanisms of SGLT2 Inhibitors

Inhibition of Wnt/β-Catenin Pathway

The Wnt/β-catenin pathway plays a pivotal role in the pathogenesis of liver cancer, thus garnering significant research attention. Within this pathway, Wnt ligands bind to coreceptors such as lipoprotein receptor-associated protein and coreceptor, inducing the dissociation of β-catenin from E-cadherin on the cell membrane. Consequently, free β-catenin translocates into the nucleus where it acts as a transcriptional regulator alongside downstream molecules including c-myc, cyclin D1, transient receptor potential cation channel subfamily c member 6 (TRPC6), among others.[23] However, in the absence of Wnt ligand stimulation, various kinase actions phosphorylate β-catenin leading to its proteasomal degradation. Furthermore, glucose entry into HCC cells also triggers the translocation of β-catenin from cytoplasm to nucleus where it functions as a transcription factor. The Wnt/β-catenin pathway is crucial for maintaining metabolic reprogramming in cancer cells.[24,25] Additionally, hepatocytes express high levels of glucose transporter 2 (GLUT2), which is involved in glucose influx and efflux across cell membranes, while HCC cells exhibit elevated expression levels of GLUT1, GLUT3 and SGLT2 along with GLUT2.[26]

Several in vitro studies have demonstrated the effective inhibition of β-catenin translocation from the cytoplasm to the nucleus by canagliflozin, an SGLT2 inhibitor (Figure 1). However, this effect is not solely attributed to SGLT2 inhibition, as other SGLT2 inhibitors such as dapagliflozin and empagliflozin do not induce similar changes.[27] This discrepancy may be due to canagliflozin's additional inhibitory effects on SGLT1 and GLUTs,[28] beyond its action on SGLT2 channels. Nevertheless, neither WZB117 (a GLUT1 inhibitor) nor short hairpin RNA (shRNA)-mediated gene knockdown of GLUT1 and GLUT3 exhibit comparable therapeutic effects against tumors as canagliflozin does. Furthermore, studies have confirmed that another mechanism through which canagliflozin exerts its anti-cancer effect is direct inhibition of

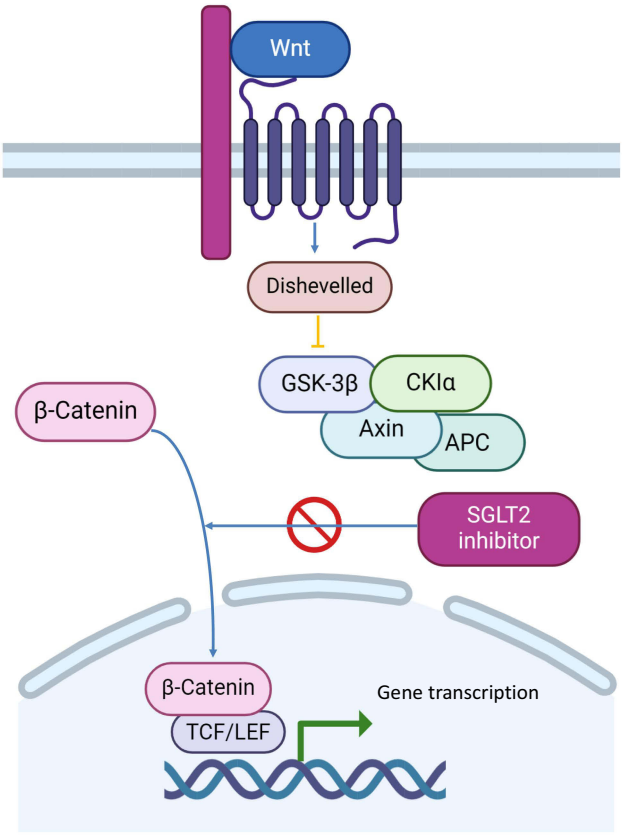

Figure 1 Inhibition of Wnt/β-catenin pathway.

protein phosphatase 2A activity, leading to enhanced proteasome degradation of β-catenin and impeding the occurrence and progression of hepatocellular carcinoma.[24]

Activation of the AMPK Pathway

The AMP-dependent protein kinase (AMPK) pathway is a crucial signaling mechanism that regulates cellular growth, survival, and metabolism. AMPK effectively inhibits tumor metabolism proliferation and restores normal liver function in diabetic patients. The primary activator of AMPK enhances the ratio of AMP/ATP by phosphorylating Thr172 within the activation loop in the α subunit.[28] Additionally, AMP can directly activate AMPK through binding to the γ subunit.[29] Canagliflozin impacts the electron transport chain in mitochondrial oxidative phosphorylation. Studies on various cancer cell lines, including prostate, lung, liver, and breast cells, have shown that it inhibits complex-I in the mitochondrial electron transport chain in a dose-dependent manner. This inhibition has significant antiadipogenic and antiproliferative effects in cancer cell therapy.[10] Multi-omics analysis on HCC cells revealed that canagliflozin administration down-regulates the alpha subunit of complex V within ATP synthase F1.[30] As a result, this alteration in the mitochondrial electron transport chain reduces ATP production and increases the AMP/ATP ratio, activating the AMPK pathway.[31] It also inhibits both the mammalian target of rapamycin (mTOR) pathway and acetyl-CoA carboxylase phosphorylation, thereby suppressing fatty acid synthesis as well as proliferation and survival among cancer cells.[32]

SGLT2 inhibitors also activate AMPK by inhibiting sterol regulatory element-binding protein 1 (SREBP1), which regulates genes encoding lipases involved in lipid synthesis. This inhibition also reduces the production of monounsaturated fatty acids and increases polyunsaturated fatty acids,[33] leading to lipid peroxidation and ferroptosis.[34] Canagliflozin downregulates SCD1 in HCC cells, inhibiting fatty acid synthesis and promoting cancer cell death.[30] Additionally, canagliflozin significantly downregulates ACAT1 (acyl-CoA: cholesterol acyltransferase 1), an enzyme that

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promotes liver cancer formation through regulation of fatty acid β-oxidation and ketone body formation.[35] Therefore, one anticancer effect of canagliflozin on HCC is its inhibition of ACAT1.

The activation of Canagliflozin-induced AMPK led to cell cycle arrest at the G2/M phase in Hep3B and HepG2 cells.[30] It has been demonstrated that AMPK induces G2/M phase arrest in HCC cells by regulating the levels of transcription factor p53 and protein p21.[36,37]

Inhibition of Angiogenesis

With the increasing metabolic demands of cancer cells, angiogenesis induced by multiple mechanisms plays a crucial role in carcinogenesis. This process is mediated, at least partially, through the PI3K/AKT/mTOR pathway due to elevated levels of vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and hypoxia-inducible factor-1α (HIF-1α). Studies on Huh7 and HepG2-derived tumors have demonstrated that canagliflozin administration resulted in down-regulation of key angiogenic factors such as angiopoietin, interleukin-8 (IL-8), tissue inhibitor of metalloproteinase-1 (TIMP-1), and matrix metalloproteinase-8 (MMP-8).[38,39] Although further preclinical and clinical investigations are needed to establish definitive conclusions regarding the impact of SGLT2 inhibitors on neovascularization in cancer, preliminary findings have shown promising potential for inhibiting this process.

Reduced Cancer Cell Adhesion

A key characteristic of cancer cells is impaired cell adhesion, both within and between cancer cells and surrounding tissues, thereby enhancing their invasive and metastatic potential. The impact of SGLT2 inhibitors on cell adhesion capacity has been investigated in various cancer cell lines, including HCT116 (colon cancer), H1792 (lung cancer), PANC-1 (pancreatic cancer), and HepG2 (hepatocellular carcinoma). Among these cell lines, HCT116 exhibits the highest sensitivity to dapagliflozin's anti-adhesive effect, which can be attributed to its elevated expression levels of SGLT2 and reduced expression levels of UDP-glucuronate transferase family 1 member A9 (UGT1A9). The higher ratio of SGLT2 to UGT1A9 expression in these cells allows dapagliflozin to remain active without being deactivated by UGT1A9, exerting a dose-dependent effect through SGLT2.[40] Exploring the related mechanism, it was found that dapagliflozin could selectively interfere with the adhesion of cells to collagen I and IV. Collagens I and IV bind discoidin domain receptor 1 (DDR1) to activate its intrinsic tyrosine kinase activity. Dapagliflozin induces DDR1 cleavage by upregulating the activity of a disintegrin and metalloproteinase domain-containing protein 10 (ADAM10). However, empagliflozin and tofogliflozin exhibit less pronounced anti-adhesive effects due to empagliflozin being metabolized not only by UGT1A9 but also by UGT2B7, UGT1A3, and UGT1A8; whereas cytochrome P450-related enzymes are responsible for the metabolism of tofogliflozin.[40] Further preclinical and clinical studies are warranted for a comprehensive understanding of the anti-adhesive effects exerted by SGLT2 inhibitors across different types of cancers.

Disruption of Glutamine Metabolism

Glutamate dehydrogenase (GDH) is a crucial enzyme involved in the conversion of glutamate to α-ketoglutarate, facilitating glutamate's entry into the tricarboxylic acid cycle. Elevated GDH activity has been linked to an unfavorable prognosis in colorectal cancer patients and serves as an independent prognostic factor, potentially due to the heightened adaptability of cells with increased GDH activity under metabolic stress conditions. Furthermore, overexpression of GDH promotes cell proliferation, migration, and invasion in vitro, while suppression of GDH activity significantly inhibits cancer cell proliferation.[41–43] Canagliflozin has demonstrated its ability to enhance cellular uptake of glutamine, which is converted into glutamate while concurrently suppressing GDH activity. This leads to an elevated ratio of glutamate / α-ketoglutarate by reducing α-ketoglutarate concentration within the tricarboxylic acid cycle and ATP production levels, thereby exerting an anti-proliferative effect on cancer cells. Additionally, supplementation with dimethyloxogglutarate in cell lines bypasses the step catalyzed by GDH and restores cellular α-ketoglutarate levels partially reversing canagliflozin's anti-proliferative effect.[44]

Inhibition of DNA and RNA Synthesis

Multi-omics analysis of cancer cell lines treated with canagliflozin revealed that administration of canagliflozin led to the down-regulation of nucleoside diphosphate kinase 1 (NME1) and up-regulation of nucleotide diphosphate (NDP), resulting in decreased DNA and RNA synthesis. In the mouse HCC model, canagliflozin was also found to down-regulate NME1, thereby inhibiting DNA and RNA synthesis and preventing the occurrence and progression of cancer.[30,45] Furthermore, canagliflozin administration suppressed the expression of DNA primase subunit 2 (PRIM2), a regulatory primase subunit involved in nucleotide formation, DNA replication, and mRNA transcription, thus exerting an inhibitory effect on cancer cells. However, it remains unclear whether these observed effects on HCC cells are specific to canagliflozin or if other SGLT2 inhibitors possess similar functions. The same experiments were conducted using dapagliflozin which did not demonstrate any inhibitory effect on Hep3B cell proliferation.[30] Apart from the Hep3B cell line, no studies have confirmed comparable effects of canagliflozin on other hepatocellular carcinoma cell lines. Therefore, further preclinical experiments and clinical studies are warranted for exploration and confirmation.

In summary, several pathophysiological mechanisms have been proposed to explain the potential anticancer effects of SGLT2 inhibitors in recent years. These include hindering cellular ATP production, activating the AMPK signaling pathway, inhibiting Wnt/β-catenin and mTOR signaling pathways, inducing apoptosis and ferroptosis, suppressing GDH activity, inhibiting DNA and RNA synthesis, as well as decreasing intercellular adhesion and angiogenesis (Figure 2). However, the heterogeneity within tumor types and variations among SGLT2 inhibitors hinder the generalizability of preclinical study outcomes. Nevertheless, SGLT2 inhibitors show promising therapeutic potential in oncology field that requires large-scale preclinical and clinical investigations.

Interactions of SGLT2 Inhibitors with Chemotherapeutic Agents

One potential clinical application of SGLT2 inhibitors in cancer patients is their interaction with anticancer chemotherapeutic agents.

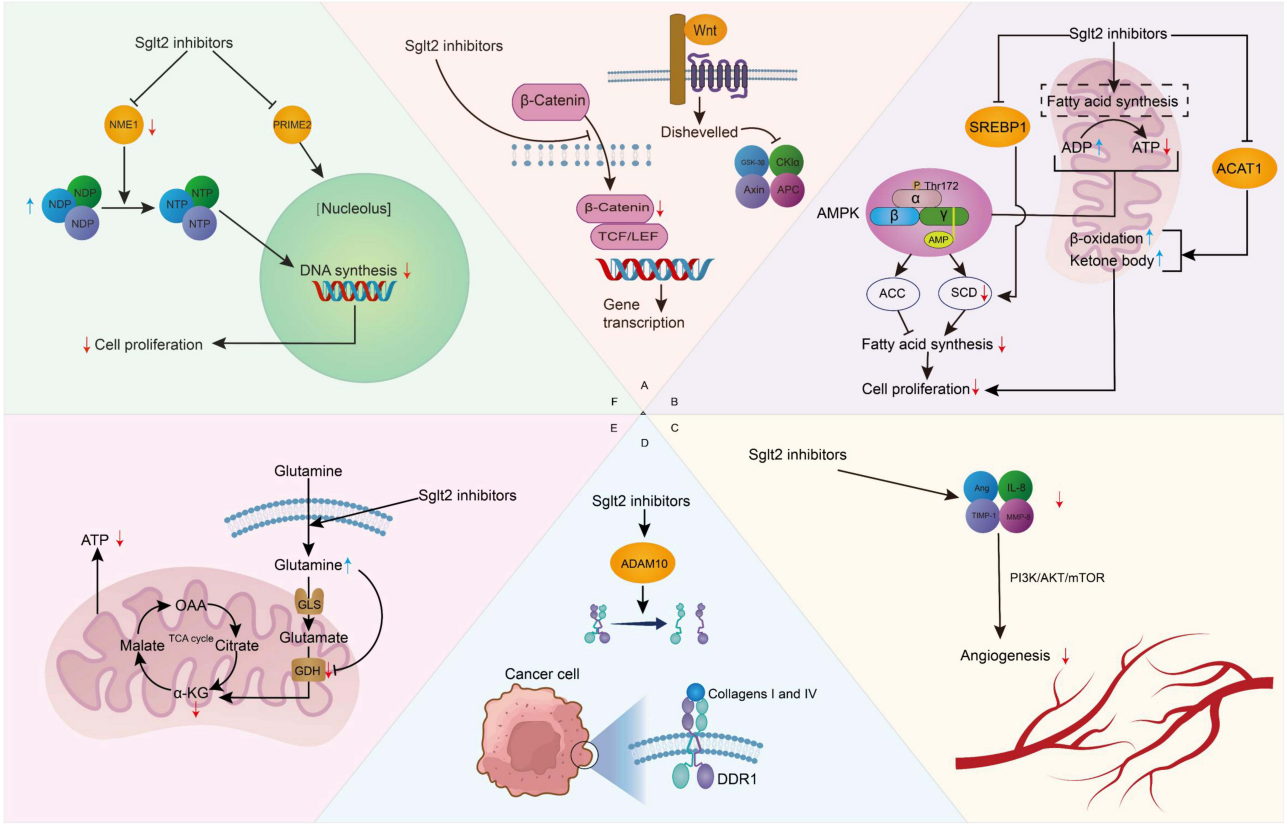

Figure 2 Anticancer mechanisms of SGLT2 inhibitors. Subfigures (**A**–**F**) delineate the six distinct mechanisms through which SGLT2 inhibitors exert their anticancer effects.

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Doxorubicin (Adriamycin) is an anthracycline chemotherapeutic agent that primarily exerts its effects through the generation of free radicals, intercalation into DNA, and inhibition of topoisomerase II activity. It has been extensively utilized in the treatment of lymphoma, gastrointestinal tumors, sarcoma, breast cancer, and bladder cancer. The principal dose-limiting adverse effect associated with doxorubicin therapy is cardiac toxicity. Co-administration of doxorubicin and empagliflozin has demonstrated a reduction in cardiotoxicity incidence compared to doxorubicin alone in mouse models, with the protective effect of empagliflozin appearing to be dependent on dosage.[46] The primary mechanism underlying doxorubicin-induced cardiotoxicity involves intracellular calcium and sodium overload mediated by SGLT1 activation, late sodium channel activation, and sarcolemmal sodium/hydrogen exchanger activation. SGLT2 inhibitors exhibit varying degrees of inhibition towards SGLT1 and sarcolemmal Na/H exchanger activity; thus they may potentially mitigate the cardiotoxic side effects induced by adriamycin.[47,48]

Sunitinib, a multitargeted tyrosine kinase inhibitor, is used to treat various malignant tumors including renal cell carcinoma, hepatocellular carcinoma, gastrointestinal stromal tumor. However, it has dose-limiting cardiotoxic side effects.[49] In vitro and in vivo studies have shown that sunitinib-induced cardiac adverse effects are mediated through AMPK signaling inhibition and mTOR pathway activation. Nevertheless, the administration of empagliflozin together with sunitinib can activate AMPK signaling while inhibiting the mTOR pathway and restoring cellular autophagy mechanism destruction. This effect has been confirmed in a mouse model.[50]

While SGLT2 inhibitors combined with sunitinib or doxorubicin have shown cardioprotective effects in vitro and animal experiments, further investigation is needed to understand their impact on the anticancer potential of this drug class. An in vivo study using a triple-negative breast cancer cell line (MDA-MB-231) revealed that empagliflozin enhanced the anticancer effect of doxorubicin by synergistically inhibiting the mTOR pathway and calmodulin.[51] Similar results were observed with canagliflozin on hepatocellular carcinoma or breast cancer cell lines.[52] Additionally, combining SGLT2 inhibitors with doxorubicin may reduce dose-limiting adverse reactions associated with chemotherapy drugs, enabling lower doses to achieve treatment goals. In conclusion, combining SGLT2 inhibitors with chemotherapeutic agents not only reduces cardiotoxic side effects but also achieves anticancer therapeutic effects at lower doses.

The Clinical Studies of SGLT2 Inhibitors on Cancer

Agents Undergoing or Having Undergone Clinical Trials

Recent advancements in the development of SGLT2 inhibitors have led to several agents being tested in clinical trials for their potential anticancer effects. Notable agents include:

Canagliflozin

Liver Cancer Model

In liver cancer models, Canagliflozin inhibits tumor cell growth by suppressing glucose uptake and activating the AMPK signaling pathway.[8–10]

Colorectal Cancer Model

Within colorectal cancer models, Canagliflozin demonstrates effects on inhibiting tumor cell proliferation and inducing apoptosis.[11]

Breast Cancer Model

Although direct applications of Canagliflozin in breast cancer models are not mentioned in search results, its mechanisms of action in other cancer models suggest potential inhibitory effects on breast cancer as well.[14,53,54]

Empagliflozin

Renal Cell Cancer Model

In renal cell cancer models, Empagliflozin suppresses tumor growth by inhibiting glucose uptake and influencing cellular metabolism.[11]

Breast Cancer Model

Empagliflozin shows enhanced anticancer activity in breast cancer models, likely due to its regulation of cellular metabolism.[14,53,54]

Dapagliflozin

Liver Cancer Model

In liver cancer models, Dapagliflozin inhibits tumor cell growth through the suppression of glucose uptake and activation of the AMPK signaling pathway.[55]

Colorectal Cancer Model

Within colorectal cancer models, Dapagliflozin exhibits effects on inhibiting tumor cell proliferation and inducing apoptosis.[12]

Lung Cancer Model

Although direct applications of Dapagliflozin in lung cancer models are not mentioned in search results, its mechanisms of action in other cancer models suggest potential inhibitory effects on lung cancer as well.[13]

The chemical structures and names of the above agents are shown in Figure 3.

Controversies and Research Outcomes in Clinical Application

Although the aforementioned series of preclinical experiments have validated the role of SGLT2 inhibitors in tumor progression, their clinical application in cancer patients remains a subject of debate. A recent meta-analysis indicates that in cancer patients, the use of SGLT2 inhibitors can significantly reduce the risks of all-cause mortality, heart failure hospitalization, clinically significant arrhythmias, and overall drug-related adverse events. These findings suggest that SGLT-2i may have potential protective effects in cancer patients, not only helping to control blood glucose levels but also potentially improving cardiovascular health and overall survival rates. This provides a significant basis for further

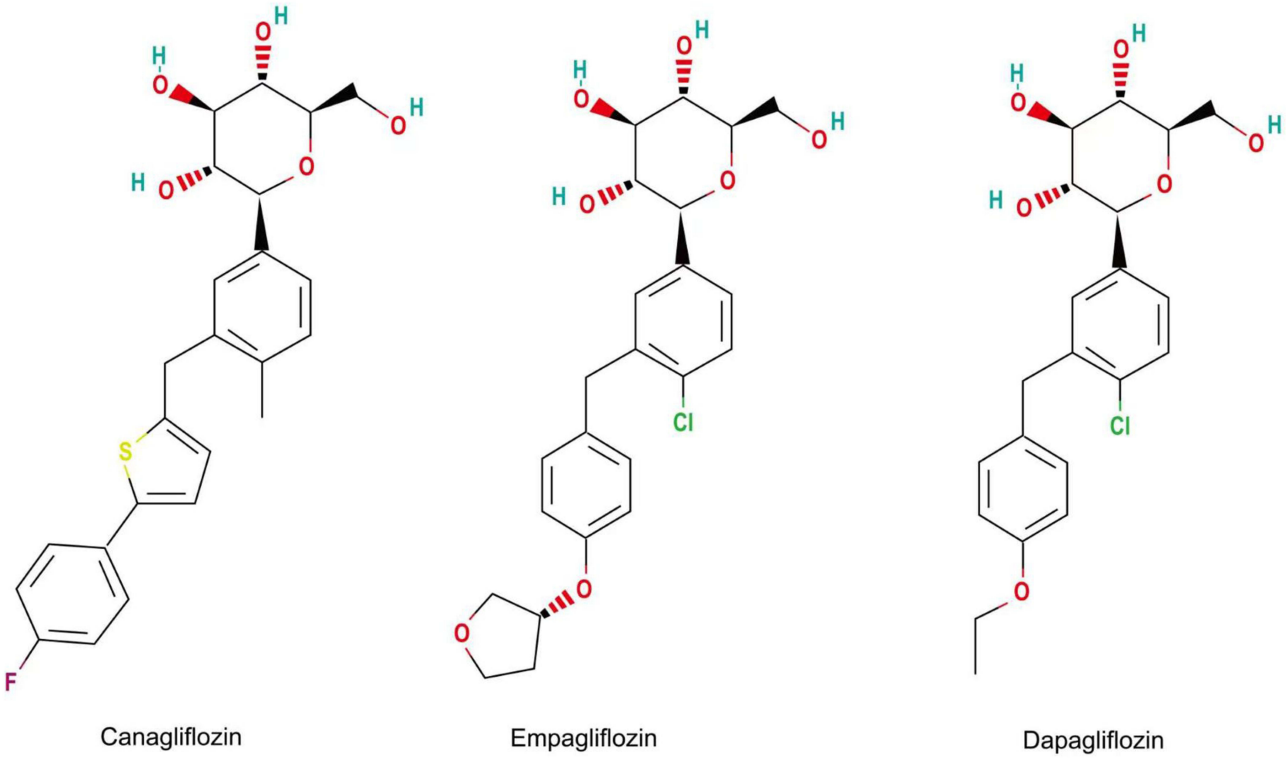

Figure 3 The chemical structures and names of the agents used in different cancer models.

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research into the application of SGLT2 inhibitors in cancer patients.[56] A retrospective cohort study found that SGLT2 inhibitors were associated with a higher rate of survival in type 2 diabetes mellitus patients with colorectal cancer.[57]

In the safety trials of SGLT2 inhibitors in diabetic patients, no significant increase in overall cancer events was observed. However, there was a notable increase in the incidence of bladder cancer in men and breast cancer in women in the SGLT2 inhibitors treatment group. These observations have led to systematic studies on the relationship between SGLT2 inhibitors use and cancer, but the results have been inconsistent.[58] Another research concluded that SGLT2 inhibitors did not significantly increase the overall risk of cancer or the risks of bladder and breast cancers. However, the higher risk of renal cancer associated with SGLT2 inhibitors warrants concern.[59] Lin et al tested the causal relationship between SGLT2 inhibition and three urological cancers (including bladder cancer, prostate cancer, and kidney cancer). They found no evidence that SGLT2 inhibition could increase the risk of these cancers. In vitro RNA-seq analysis also confirmed the study results, indicating that SGLT2 inhibitors do not induce upregulation of malignant markers ($P<0.05$).[60] In a large, population-based cohort study, no reduced short-term risk of lung cancer was observed among SGLT-2 inhibitor users.[61]

The controversy about cancer outcome in clinical application may be related to the heterogeneity of retrospective studies. With the widespread application of SGLT2 inhibitors, larger and longer follow-up is needed to verify.

Conclusion

SGLT2 inhibitors are a new class of oral hypoglycemic drugs that have shown positive outcomes in reducing cardiovascular risk, improving heart failure prognosis, and treating chronic kidney disease. Recently, there has been increasing interest in the potential anticancer effects of SGLT inhibitors. In vivo and in vitro experiments have proposed various mechanisms for their pathophysiological and tumor therapeutic effects, including inhibiting the Wnt/β-catenin signaling pathway, activating the AMPK signaling pathway, reducing angiogenesis and cancer cell adhesion, as well as inhibiting GDH activity and DNA/RNA synthesis. However, clinical studies have not yet confirmed SGLT2 inhibitors as an adjunctive treatment option for cancer management. Furthermore, animal studies have demonstrated that SGLT2 inhibitors can enhance the anticancer effects of certain chemotherapeutic agents while minimizing adverse effects at high doses. By summarizing existing research findings, it is clear that SGLT2 inhibitor therapy holds promising prospects for exploration in oncology. In addition to its beneficial effect on blood glucose control, this therapy is widely accessible and relatively cost-effective. Nevertheless, due to significant heterogeneity within or among tumor cells and types, further preclinical investigations and large-scale clinical trials involving patients with diverse cancer types at different stages are needed.

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. XY Miao, JN Zhang and WY Huang reviewed the literature, wrote drafts of the manuscript. YF Wang and AX Jin helped in evaluation of the literature and submit manuscript. ZZ Zhao and JP Cao designed and supervised the work. All authors contributed to the review and approved the submitted version.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Publisher's note All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

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