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Anti-Diabetic Drugs as Novel Avenues in Cancer Management

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Abstract

The International Diabetes Federation has highlighted the global rise in diabetes, impacting 463 million people, or 9.3% of the population, with projections indicating an increase to 700 million by 2045. There is a significant connection between diabetes, particularly type 2, and cancer risk due to impaired insulin signaling promoting abnormal cell growth. Antidiabetic medications regulating insulin show promise as adjuvants in cancer therapy, sparking growing interest in this area. This review provides a comprehensive overview of the complex relationship between antidiabetic drugs and cancer through epidemiological data, preclinical studies, and clinical trials examining the potential anti-cancer properties of drugs like metformin and SGLT-2 inhibitors. It also addresses controversies surrounding the effects of biguanides and SGLT-2 inhibitors on cancer treatment while identifying research gaps to promote extensive exploration into this topic and foster innovative treatment approaches. However, using antidiabetic drugs to fight cancer presents challenges such as optimizing dosing and managing side effects; thus, emphasizing continuous research for developing effective personalized treatment strategies (Figure 1).

Keywords: Diabetes; Cancer; Anti-Diabetic Medications; Metformin; SGLT-2 Inhibitors; Insulin; Molecular Pathways; Epidemiology

Introduction

Diabetes and cancer are interrelated diseases that have a significant impact on morbidity and mortality. Type 1 diabetes results from autoimmune destruction of pancreatic β-cells, requiring early insulin therapy due to absolute insulin deficiency [1,2]. Type 1 diabetes affects approximately 6% of patients. The most common form is Type 2 Diabetes (T2D), which accounts for more than 90% of cases. T2D is primarily caused by impaired insulin secretion and insulin resistance, which is often associated with genetic factors and obesity. It is a chronic, lifelong metabolic disorder and a growing global public health problem [3]. According to the latest data from the International Diabetes Federation in 2021, 537 million adults worldwide have diabetes, with projections of 783 million by 2045 [4]. Both types of diabetes enhance the chance of fatal complications, including cancer, with common risk factors such as aging, sex, obesity, physical inactivity, diet, alcohol, and smoking [5]. The metabolic and hormonal consequences of diabetes and its treatment may also influence cancer risk. The primary objective of T2DM treatment is to attain optimal glycemic control, with a target Hemoglobin A1C (HbA1C) level below 7% to prevent micro- and macro-vascular complications [1].

Cancer is a major health challenge worldwide, leading to high mortality rates and significant healthcare expenditure each year. Which is characterized by abnormal cell growth, loss of cell cycle regulation, and the ability to metastasize to other parts of the body [6]. Carcinogenesis, a multifaceted process begins with a normal cell undergoing various genetic changes before it transforms into a neoplastic cell, invades, and spreads. Oncogenesis goes through various stages - initiation, promotion, and progression, which means the emergence of a more aggressive phenotype in the promoted cells [6], and common treatment modalities include radiotherapy, surgery, and chemotherapy, either individually or in combination [3]. Radiotherapy is used for localized cancers in conjunction with surgery, while chemotherapy targets rapidly dividing cells but is hampered by limitations such as toxicity to healthy cells and drug resistance [6]. Alternative approaches, including specific antidiabetic agents such as sulfonylureas, biguanides, and thiazolidinediones, have shown potential in cancer treatment by addressing the problems of drug resistance and

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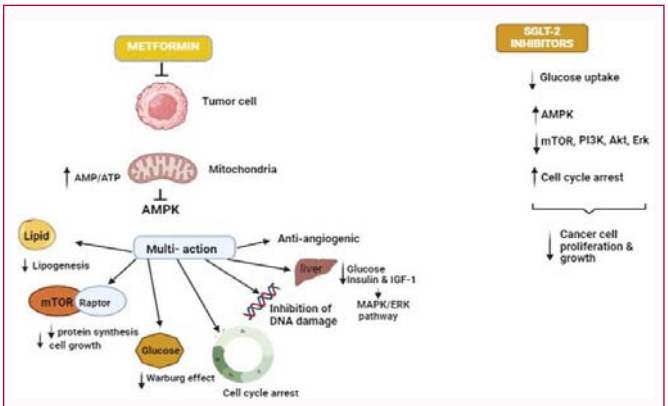

Figure 1: Graphical Abstract.

toxicity [3]. There are also metabolic links between cancer and T2D that increase susceptibility to certain cancers such as bladder, colon, pancreatic, ovarian, breast, and endometrial in people with diabetes [7]. However, due to the shared risk factors and pathways, there is growing interest in research into repurposing antidiabetic drugs for cancer treatment and prevention [8]. The repurposing of drugs, *i.e.* the discovery of new utilization of approved drugs, is becoming increasingly important in cancer treatment due to its effectiveness compared to the development of new drugs [9]. Repurposed drugs have the advantage that they interact with multiple targets or pathways, have established pharmacokinetics and pharmacodynamics, and thus simplify the drug development process [7]. The use of existing drugs can have a significant impact on cancer treatment.

The precise links between cancer and diabetes are not fully understood. Still, common risk factors for both conditions include high blood sugar levels leading to Advanced Glycated End products (AGEs) and oxidative stress, as well as high levels of insulin due to insulin resistance or exogenous insulin use. Inflammation and obesity are also contributing factors [3]. Despite diabetes being a risk factor for cancer, some antidiabetic medications may have benefits in managing cancer. Type 1 diabetes is treated with insulin, while type 2 diabetes is managed with antidiabetic drugs and lifestyle changes to control blood sugar levels and complications. Interestingly, these medications also have anti-cancer properties that can slow disease progression [5]. While some studies suggest a potential risk of cancer with antidiabetic drugs, their anti-cancer effects generally outweigh any risks [9]. This highlights the metabolic connections between cancer and diabetes and the potential for repurposing antidiabetic drugs for cancer management.

Most studies have explored the potential of anti-diabetic drugs for the treatment of various cancers [3,9,10]. However, there are still gaps in our understanding of how these drugs work in cancer treatment. Therefore, this review aims to analyze the complex mechanisms of action of these drugs and summarize recent advances in their molecular effects, preclinical studies, and clinical trials for cancer treatment. It highlights their central role in biology and medicine. It emphasizes the need to consider both the advantages and disadvantages and to explore strategies such as drug combinations and personalized treatment plans to improve the effectiveness of cancer treatment.

Anti-Diabetic Drugs & Cancer Risk

Both hyperglycemia and hyperinsulinemia are known risk factors for cancer development [11,12]. While certain anti-diabetic medications portray anti-cancer properties, others may raise the risk of cancer. The fundamental reason for the difference most likely comes from the different ways these medications work to regulate blood sugar levels [2,13]. Metformin & Thiazolidinediones (TZD) can lower insulin concentration whereas sulfonylureas & exogenous insulin can raise it. Additionally, TZD & metformin can reduce insulin resistance [12,14]. Numerous evidence supports the fact that metformin- an anti-diabetic drug has potential anti-cancer properties. Multiple findings support utilizing anti-diabetic medications as prospective candidates for drug repositioning in anti-cancer therapy. It is well-recognized that having T2D enhances the chance of getting many cancers, including, pancreatic, liver, endometrial, and colorectal cancers [15]. Additionally, untreated diabetes mellitus-related hyperinsulinemia, hyperglycemia, and chronic inflammation are menacing factors causing the onset and/or progression of cancer [16,17]. Therefore, treating these conditions with anti-diabetic medications may provide indirect therapeutic benefits. Furthermore, some anti-diabetic medications potentially interfere with the control of intracellular metabolism, for instance by activating AMPK or inhibiting the uptake of glucose, thereby promoting apoptosis [18] (Table 1).

Metformin & Its Anti-Cancer Properties

Biguanides are oral medications for lowering blood sugar levels that were initially created for T2D treatment. They originate from the *Galega officinalis* plant & contain guanidine's & galectins as their active ingredients. Metformin, a dimethyl biguanide, was the first of these drugs to be studied in human trials [18]. Metformin is commonly prescribed as the first line of treatment for T2D and is found to have potential anti-cancer effects in various cancer types associated with T2D [35,36] (Figure 2); it was approved by the FDA for T2D treatment in 1994. Several epidemiological studies have directed that metformin has the potential to decrease the likelihood of developing breast, colon, pancreatic, and liver cancers. Additionally, it may also contribute to enhancing cancer prognosis [37]. According to certain clinical studies; metformin may have a synergistic impact when used in addition to other anticancer therapies [38] (Figure 3).

Metformin exercises its anti-diabetic effects *via* varied mechanisms like- suppressing hepatic gluconeogenesis, reducing insulin resistance, and enhancing peripheral glucose uptake by the skeletal muscle, while not affecting glycogenolysis [18,39]. Metformin lowers glucose levels entering the bloodstream by increasing intestinal absorption & utilization of glucose by the intestinal cells [39]. Metformin is introduced into the cell through OCT-1 & OCT-3 (Organic Cation Transporter 1/3) [20,40]. The liver is contemplated as the primary site of action of metformin. Metformin improves glucose absorption by increasing the movement of Glucose Transporters (GLUT), such as GLUT-1, to the cell plasma membrane. It also causes the activation of

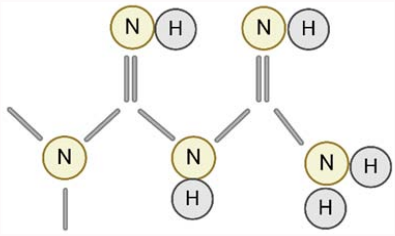

Figure 2: Molecular structure of metformin.

Table 1: Anti-diabetic drugs and their potential anti-cancer effects.

Antidiabetic Drug Class	Drugs	Mechanism of Action in Antidiabetic Therapy	Potential Effects on Cancer	References
Biguanides	Metformin	↓glucose production by liver cells ↑ insulin sensitivity ↑ peripheral glucose uptake	- AMPK activation - modulation of insulin signaling pathways - mTOR inhibition - targets respiratory complex 1 of ETC - ↓cell energy consumption - anti-proliferative - pro-apoptotic - modulation of chemokines	[18-20]
Renal glucose transporter inhibitor - SGLT-2	Canagliflozin Dapagliflozin Empagliflozin	↓Glucose reabsorption ↓Blood glucose concentration ↓hyperinsulinemia	- Cell cycle arrest -anti-proliferative effect - DNA damage repair - inhibition of glucose uptake in various cancerous cells - inhibit mitochondrial complex-I supported respiration - pro-tumorigenic chemokines	[18,21,22]
Thiazolidinediones (TZD)	Pioglitazone	↑insulin sensitivity PPARα & PPARγ agonist Hypoglycemic activity	- ↓Cell proliferation - inhibit angiogenesis promoting factors – IL-8 & COX-2 mRNA expression in pancreatic cancer - promote CEA mRNA expression in BxPC-3 cells - ↑pancreatic cancer cell differentiation - block MAPK cascade & TGFβ/SMAD signaling - activate PPARγ induced cell cycle G2 arrest, PPAR-γ activation inhibits growth of tumor cells - inhibit bladder cancer cell proliferation by inhibition of PI3K-Akt pathway *in vitro*	[23-25]
Insulin Analogues	Glargine Human insulin Aspart Lispro Glulisine Detemir Degludec	glucose-lowering ↑insulin ↓excessive glucose production by the liver ↑glucose uptake ↑glucose storage in muscle tissues ↑glucose oxidation	- potentially carcinogenic - overexpression of insulin receptor - pro proliferative - hyperinsulinemia - ↑IGF-1 synthesis - anti-apoptotic - ↓SHBG levels - aberrant IGF signaling	[18,26,27]
Sulfonylureas	Glibenclamide Gliclazide Glimepiride	attach to the pancreatic beta cells' ATP-sensitive potassium channels (K) & block them. ↑insulin secretion leading to ↑ plasma insulin concentration ↓insulin metabolism in the liver causes ↓ serum glucose levels ↓glucagon secretion ↑sensitivity to insulin in peripheral tissues	- ↑risk of pancreatic & breast cancers	[28-30]
DPP-4enzyme inhibitors	Sitagliptin Saxagliptin Vildagliptin Gempigliptin Linagliptin Alogliptin	inhibit enzyme DPP-4 ↑levels of incretin hormones inhibit decomposition of incretins, Glucagon-Like Peptide-1 (GLP-1) & Glucose-dependent Insulinotropic Peptide (GIP)	- ↑growth, metastasis, of cancer & resistance to chemotherapy - ↑risk of cholangiocarcinoma - ↑breast cancer metastasis by inducing EMT through C-X-C motif chemokine 12 (CXCL12)/C-X-C receptor 4 (CXCR4)-mediated mTOR activation - ↓the apoptosis of breast cancer cells by inducing autophagy - induced autophagy leads to angiogenesis	[31-34]

Insulin Receptor & Insulin Receptor Substrate 2. Metformin thereby improves the inhibition of gluconeogenesis mediated through insulin. Moreover, it also inhibits the peptide hormone glucagon's gluconeogenic activity. Metformin increases insulin sensitivity & insulin-mediated skeletal muscle glucose absorption. This effect is mediated by increased tyrosine kinase activity of the insulin receptor as well as increased activity & glucose transporters' relocation to the plasma membrane, including GLUT-4 [40]. Various clinical & pre-clinical studies have indicated that the main method by which metformin works is through decreasing liver glucose production. This results from its capacity to block gluconeogenesis *via* a variety of mechanisms [41,42] (Figure 4).

It is well known that metformin has pleiotropic effects. Its multiple possible pharmacologic effects include anti-cancer actions. It's been observed that metformin has anti-cancer attributes due to its insulin-lowering action, which may reduce tumor growth in insulin-resistant people. The mitochondria is target action-site for metformin. Metformin inhibits the respiratory complex I of the electron transport chain in the mitochondria of preneoplastic & neoplastic cells, thereby lowering the energy consumption of a cell [14,43]. Metformin increases muscle glucose uptake, lowering plasma insulin levels and assisting in the decrease in the proliferation of both

Table 2: Metformin pre-clinical studies for various cancer type.

PRE-CLINICAL TRIAL	OBSERVED EFFECTS OF METFORMIN	REFERENCES
MCF-7 Breast cancer cell lines	- ↓ phosphorylation of ribosomal protein S6, S6 Kinase & eIF4E binding protein - ↓ HER2 expression by inhibiting p70S6K1 - Inhibit mTOR - ↓ translation initiation as a result of AMPK activation	[46]
Ovarian cancer cell line & nude mice	- Anti-cancer effect of metformin due to the regulation of S1P & SPHK1 expression	[47]
Animal models of pancreatic cancer	- inhibit insulin like growth factor 1 (IGF-1) & mTOR - ↑ phosphorylation of AMPK & tuberous sclerosis complex 1& 2 (TSC1 & TSC2)	[46]
Endometrial cancer cell lines HEC1B & HEC265	- ↓ PP2A expression - ↓ PP2A expression: leading to antiproliferative effects of Metformin	[48]
Xenograft model with breast cancer (MCF-7 nude BALB/c mice)	- ↓ tumor progression - delays the tumor growth	[49]
Ovarian cancer cell lines (UWB1.289, UWB1.289. BRCA, SKOV3, OVCAR5, A2780 & C200)	- metformin & olaparib combination reduced cell proliferation & colony formation - cell cycle S-phase arrest - olaparib & metformin combination inhibited A2780 & SKOV3 in ovarian tumor xenografts - Olaparib activates AMPK - Metformin does not affect DNA damage signaling	[50,51]
Nude mice having Acute Myeloid Leukemia (AML)	- ↓ proliferation of AML cells -activate LKB1/AMPK/TSC pathway, which leads to mTOR inhibition & further suppress translation of mRNA	[46]
Colorectal cancer cell lines	- stimulate cell cycle arrest in G0/G1 phase - ↓ c-Myc expression & causes IGF-1R downregulation - up-regulation of the adenosine A1 receptor induces apoptosis - ↑ the activity of the Sprouty2 gene, which suppresses colon cancer growth	[52]
MIA PaCa & PANC-1 cells	- ↓ cell survival by ↓ ROS production - downregulation of NOX 2 & NOX4 protein expression.	[53]
Transgenic p48Cre/+; LSL-KrasG12D/+ mice	- Inhibit PanIN Lesion Progression & Carcinoma Spread - mTOR/pAMPK Signaling modulation - Cancer Stem Cell Markers (CD24 & CD44) downregulation - Induces Apoptosis	[45]
AML cells	- ↑ apoptosis - induces cell cycle arrest - inhibit cell proliferation via mitochondrial respiration inhibition	[54]
Tobacco-induced lung cancer mice	- inhibit insulin like growth factor 1 receptor/insulin receptor (IGF-1R/IR) - ↓ mTOR activation in lung cells; leading to 72% ↓ in tumor	[46]
Acute lymphoblastic leukemia (ALL) cell line 697	- notable cell damage & ↓ mitochondrial membrane potential - caspase-3 activation - induce apoptosis	[54]
4 breast cancer cell lines (MDA-MB-468, BT20, HCC70 & MDA-MB-231)	- Metformin suppresses downstream signaling & P-Stat3 activation at Tyr705 & Ser727	[55]
2 Renal cancer cell lines (A498 & GRC-1) & BALB/C nude mice	- Antiproliferative effects of metformin depend on the glucose concentration in the extracellular environment	[56]
MM cell lines	- inhibit proliferation - induce G0/G1 cell cycle arrest; through inhibition of HIF-1 signaling - activate AMPK & inhibited p-4EBP1, mTORC1, mTORC2 & p-AKT expression in the mTOR signaling pathway - inhibit DNA damage repair in tumor cells.	[54]
Hela Cells & *C. elegans*	- Anticancer activity of metformin is due to mitochondrial complex I inhibition	[57]
Triple-negative MDA-MB-231 breast cancer cells	- antiproliferative effect attained via AMPK-dependent mechanism	[30]
in vivo study using Genetically Modified (GM) mice (oncogenic Kras-mediated PDAC) mice models	- anti-angiogenic effects of metformin are believed to be through AMPK &/or STAT3	[58]

cancerous & precancerous cells [35].

Metformin can activate AMPK in a manner dependent on Liver Kinase B1 (LKB-1) [25]. In the direct pathway (insulin-independent); Metformin acts by inhibiting Electron Transport Chain I (ETC I), reduces oxygen consumption rates and NADH oxidation. Thus, AMPK is triggered by a drop in ATP, surge in cellular AMP, and a rise in the AMP/ATP ratio. Moreover, oxidative phosphorylation activates AMPK, and inhibiting ETC complex 1 further inhibits this process [39,40,44]. By inhibiting mitochondrial function, metformin can cause a metabolic transition to glycolysis from OxPhos, which reduces levels of glucose available to cancer cells [39]. AMPK activation reverses ATP depletion, generates more ATP, inhibits gluconeogenesis, transforms the anabolic to the catabolic state of the cell, & returns cellular balance, all of which results in antiproliferative & energy-saving strategies. Additionally, mTOR signaling inhibition–a key regulator of cell growth–occurs when AMPK is activated [12,44,45].

The indirect (insulin-dependent) route involves inhibiting insulin levels to prevent the growth of cancerous cells through the insulin/IGF-1 pathway. Both pathways activate AMP-activated protein kinase which suppresses carcinoma cell growth by targeting the mTOR and inducing apoptosis & cell-cycle arrest [35]. Because of its capacity to increase insulin sensitivity and hence stimulate the absorption and use of glucose by peripheral tissues, metformin is also widely used

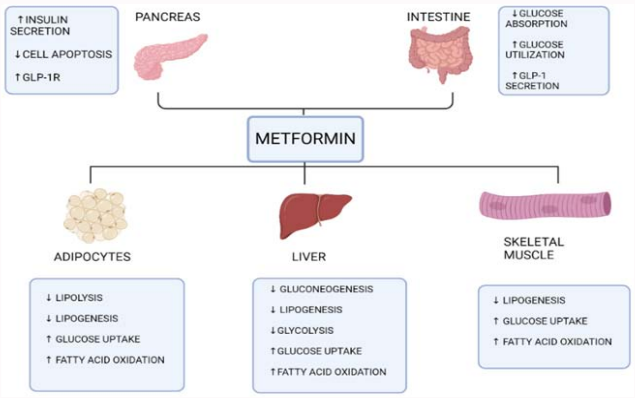

Figure 3: Metformin action on various organs.

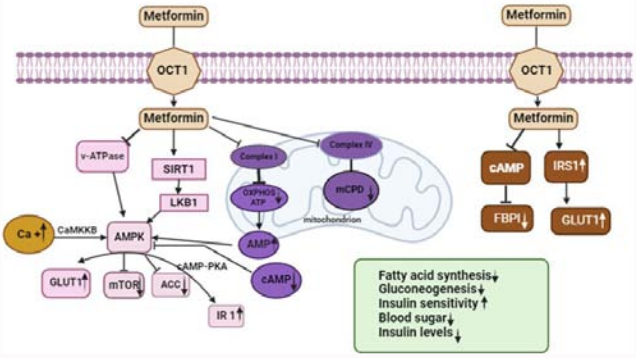

Figure 4: Glucose lowering mechanism of Metformin.

as an "insulin sensitizer" in the treatment of diabetes. Metformin activates AMPK and promotes the insulin-dependent consumption of glucose by peripheral tissues such as the liver, muscle, and adipose tissues [41] (Table 2, 3).

SGLT–2 Inhibitors & Cancer

Glucose acts as the primary metabolic form of energy in mammalian cells. There are two ways in which cells absorb it: 1) facilitated by glucose transporters without sodium, 2) sodium-glucose cotransporters (symporter) through secondary active transport [68]. SGLT2, also known as sodium-glucose cotransporter 2, plays a vital role in the delivery of glucose across epithelial cells & is part of the SLC5A gene family responsible for transporting solutes [69]. The SGLT2 functions as a transporter for both sodium & glucose molecules, moving them across the cell membrane in a 1:1 ratio [70,71]. Recently, the FDA sanctioned SGLT2 inhibitors such as canagliflozin, dapagliflozin, & empagliflozin as a novel category of glucose-lowering drugs (referred to as gliflozins) for managing type 2 diabetes mellitus [18,69] (Figure 5).

SGLT2 inhibitors are a novel category of antidiabetic medication that doesn't affect insulin resistance or insufficiency. In the proximal tubules, SGLT1 & SGLT2 reabsorb glucose that has been filtered *via* the kidneys & back into the bloodstream. Only 10% of reabsorbed glucose by the kidneys is accounted for by SGLT1, rest 90% by SGLT2. The renal cortex expresses SGLT2 primarily [41] the Small Intestines, Heart, Trachea, & Plasma Membranes are the organs where SGLT1 is mostly expressed in addition to the kidney. Diabetes patients' blood glucose levels may be lowered by blocking these kidney transporters, which reduces renal glucose reabsorption [72]. Several pathways connect SGLT2 inhibitors to cancer risk. Cancer cells' survival primarily relies on glucose as their energy source & they utilize glucose transporters such as GLUT1 for cellular entry. Hence, Glucose Transporter 1 (GLUT1) expression is upregulated in most cancer cells. Research has shown that heightened expression of SGLT2 in cancer cells strongly contributes to enhanced proliferation, migration & invasion capabilities in various tumors due to its role in glycolysis & glucose uptake. Consequently, suppressing SGLT2 expression can substantially hinder tumor advancement [73]. While GLUT1 inhibition appears to be a promising cancer treatment, this strategy is challenging since normal cells also express GLUT1, as it is expected to induce some harmful consequences on healthy tissues. However, because SGLT2 expression is somewhat restricted compared to the widely expressed GLUT1, it may be possible for SGLT2 inhibitors to decrease tumor growth safely [74]. SGLT2 inhibitors reduce blood glucose by blocking kidney glucose reabsorption, thereby reversing the harmful effects of insulin resistance. Recent research indicates that SGLT2 inhibition may also have a suppressive effect on cancers that express SGLT2, such as Breast cancer, Cervical cancer, Hepatocellular cancer, Prostate cancer & Lung cancer [71]. The anti-tumor & anti-angiogenic effects of SGLT2 inhibitors are due to their ability to inhibit glucose uptake [52]. SGLT2 inhibitors also have an advantageous influence on malignancies by reprogramming metabolism, reducing inflammation & reducing oxidative stress [75]. A research team originally led by Scafoglio et al. demonstrated the expression of SGLT2 in pancreatic & prostate adenocarcinomas. Significantly, it demonstrated that SGLT2 inhibitor therapy (canagliflozin & dapagliflozin) reduced tumor development & triggered tumor necrosis [73,75,82]. An oral selective SGLT2 inhibitor is canagliflozin. When taken orally, it is quickly absorbed & reaches its maximal plasma concentration in one to two hours. Lower postprandial blood glucose is a result of canagliflozin's dual actions of boosting urine glucose excretion & slowing intestinal glucose absorption [18]. In anaerobic conditions, glycolysis is the primary energy source in healthy cells. Under aerobic conditions, glucose is fully oxidized into CO_2 through oxidative phosphorylation in mitochondria and the citric acid cycle in the cytosol. Tumor cells utilize both aerobic and anaerobic glycolysis to produce energy when their mitochondria are obstructed. They achieve this by upregulating

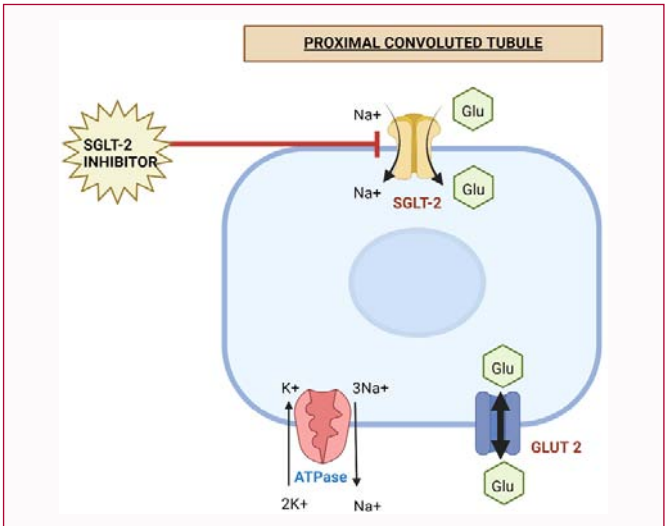

Figure 5: The process by which SGLT-2 Inhibitors limit the absorption of glucose.

Table 3: Metformin clinical studies for various cancer types.

Cancer type	Study design & population	Inclusion criteria	Main findings	Reference
Colorectal cancer	Case-control study. Cases-controls: 2088:9060	Cases: DM2 with CRC. Controls: DM2 without CRC Metformin user *vs.* non-user	OR: 0.83 (0.68-1.00)	[59]
Breast cancer	Phase II 850 mg/m^2 metformin is combined with anthracyclines, platinum, taxanes, or capecitabine Given Twice a day for 9 weeks to 78 women with metastatic breast cancer		this combination improved survival & tumor response via changing factors like insulin, glucose & Homeostatic model assessment (HOMA)	[60]
Gastric cancer	Retrospective Cohort, Taiwan. 287971 DM2 with metformin. 16217 DM2 without metformin	DM2 patients newly treated with antidiabetic drugs Metformin user *vs.* non-user	HR: 0.45 (0.36-0.56)	[61]
Pancreatic ductal adenocarcinoma	Retrospective cohort study. n = 62.809 DM2. Comparison between treatments: 1. Metformin alone; 2. Sulfonylureas alone; 3. metformin along with sulfonylurea; insulin	DM2 developed >40 years of age; United Kingdom residents Metformin *vs.* Sulfonylurea Metformin *vs.* Insulin	HR: 0.20 (0.11-0.36). HR: 0.22 (0.12-0.38)	[62]
Hepatocellular carcinoma	Clinic-hospital based case control. Cases-controls: 190:359	Cases: HCC patients. Controls: Liver cirrhosis patients & normal healthy individuals Metformin *vs.* sulfonylureas Metformin *vs.* insulin	OR: 0.39 (0.22-0.73). OR: 0.21 (0.11-0.42)	[63]
Intrahepatic cholangiocarcinoma	Clinic-hospital based case-control. Cases-controls: 612:594	Cases: ICC patients. Controls: Non-cancer patients Metformin user *vs.* nonuser	OR: 0.40 (0.20-0.90)	[64]
Colorectal cancer	Retrospective cohort. 482 local rectal cancer patients	Locally advanced rectal adenocarcinoma treated with chemoradiation & surgery Metformin user *vs.* nonuser	PCR: OR: 16.8 (1.6-181.1). OS at 5 & 10 years (metformin vs non-metformin users): 81% & 79% *vs.* 56% & 39% (P=0.022)	[65]
Colorectal cancer	Clinical Trial, 40 patients of Stage III CRC	FOLFOX 4 12 cycles plus metformin 500 mg thrice a day	Neuropathy grade 2-3 (metformin *vs.* non): 60% *vs.* 95% (P=0.009)	[66]
Pancreatic ductal adenocarcinoma	Single-arm phase II Number of individuals = 20	Locally advanced or metastatic. 2nd line treatment. Single center. Brazilian Metformin 1750 mg/d + paclitaxel (80mg/m2 D1, 8, 15 every 28d)	DCR at 8 weeks 31, 6%	[67]

DCR: Dacryocystorhinostomy; OS: Overall Survival; OR: Origin Recognition Complex; HR: Hazard Ratio; PCR: Polymerase Chain Reaction

glucose absorption systems and altering the expression of metabolic enzymes to adapt to aerobic glycolysis.

Anticancer drugs may target metabolic enzymes & glucose absorption systems. As can be seen in the core of solid tumors, the Na+-D-glucose cotransporters SGLT1 & SGLT2 are interestingly expressed in a variety of malignancies & offer an efficient means of raising glucose concentrations in malignant cells at reduced external glucose concentrations, therefore inhibiting glucose uptake can be beneficial in tumor suppression [70] (Table 4).

Insulin & Cancer

When blood glucose levels rise, the β pancreatic cells in the islets of Langerhans release a hormone known as insulin [83,84]. Insulin is an endocrine peptide hormone that acts on target cells' receptors bound to the plasma membrane to synchronize an anabolic reaction to the accessibility of nutrients. Insulin has direct actions on skeletal muscle, liver & white adipocytes representing its involvement in glucose steady state. Insulin is also widely recognized for its mitogenic effects by enhancing the anabolic state necessary for cell growth, which stimulates the growth of both healthy & unhealthy cells. Insulin's biological effects rely on how it interacts with the cell surface receptors in the complicated insulin/IGF-1 family [85] (Figure 6).

Functionally, insulin primarily triggers two cell signaling pathways: the insulin receptor substrates PI3K protein kinase B pathway; and the extracellular signal-regulated kinase 1/2-MAPK pathway [55]. In addition to controlling glucose metabolism, the PI3K pathway primarily initiates the metabolic effects of insulin, which also affect cell cycle arrest/proliferation & death. The MAPK pathway has

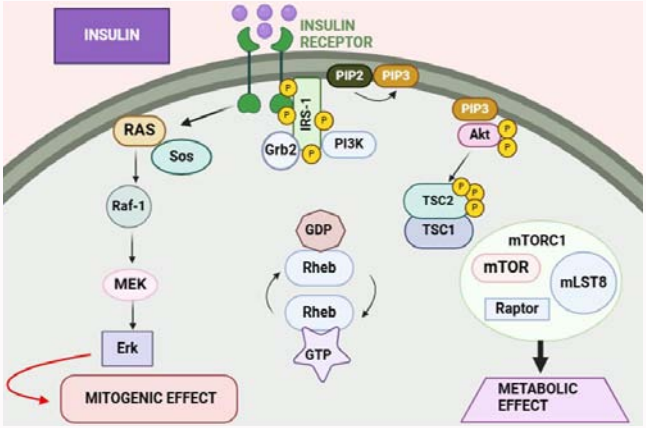

Figure 6: Insulin signaling under normal insulin levels.

no metabolic consequences, but it promotes cell division & prevents apoptosis [86]. The complex IGF organization comprises the ligands - insulin, IGF-1 & IGF-2; their receptors, Insulin Receptor (IR), Insulin-like Growth Factor 1 Receptor (IGF-1R), Insulin-like Growth Factor 2 Receptor (IGF-2R) respectively & Insulin-like Growth Factor Binding Proteins (IGFBPs). IGF-1R in addition to IR was discovered to be overly expressed in cancerous cells & the IR-A isoform is seen to be predominant [87]. Insulin predominantly interacts with its receptor at normal physiological conditions. Once this receptor is phosphorylated, it triggers a variety of intracellular signaling pathways that promote mutual metabolic & mitogenic effects. The cognate IGF-1R and these pathways are comparable and partly shared [85]. The

Table 4: SGLT-2 inhibitors impact on several cancer types.

CANCER TYPE	SGLT-2 INHIBITOR	MAIN FINDINGS	REFERENCES
Thyroid cancer	Canagliflozin	- ↓ glycolysis levels - interfere with glucose uptake - ↑ activation of ATM/CHK2 leading to initiation of DNA damage repair - activate AMPK, by inhibiting complex I of the respiratory chain - inhibits AKT/mTOR pathway - ↓ secretion of pro-tumorigenic CXCL8 & CCL2 - hinders the G1 to S phase transition of the cell cycle - down-regulate cyclin D3, cyclin D1, cyclin E1, cyclin E2, & E2F1	[76,77]
Colorectal cancer	Canagliflozin & Dapagliflozin	- inhibit cancer through inhibition of SGLT2-mediated glucose uptake	[18]
Liver tumorigenesis	Tofogliflozin	- ↓ liver tumorigenesis by ↓ levels of glucose & free fatty acid	[74]
Breast cancer	Ipragliflozin	- anti-proliferative effect observed due to inhibition of glucose & sodium influx - induces hyperpolarization of the cell membrane & mitochondrial membrane instability by blocking the sodium influx	[75]
Oral squamous cancer	Canagliflozin & Dapagliflozin	- at concentrations of 250 µg/ml & 400 µg/ml; loss of cell viability in KB cell lines - number of cells exhibiting positive cytotoxic activity ↓, as a result of glucose absorption limitation & inhibition of mitochondrial intracellular ATP generation, which in turn limited the cancer cells' life cycle.	[78]
Lung cancer	Canagliflozin & Ipragliflozin	- at IC50 & Sub-IC50 concentrations, these ↓ colonies' number, migration & size in A-549 lung cancer cell lines. - canagliflozin also induces apoptotic effects in A-549 cells	[79]
Prostate cancer	Canagliflozin & Ipragliflozin	- therapy of Du-145, prostate cancer cell line, with canagliflozin or ipragliflozin, induced cell death in a concentration- contingent manner	[79]
Hepatocellular carcinoma (HCC)	Canagliflozin	- inhibits glucose uptake & glycolytic metabolism - ↓ HCC cell growth by triggering cell cycle arrest & apoptosis - suppress angiogenic activity	[52]
Cervical cancer	Empagliflozin	- ↓ migration of cervical cancer cells & ↑ apoptosis in HeLa & C33A cell lines - & ↑ AMPK/FOXA1 pathway & ↓ expression of Shh	[80]
Breast cancer	Canagliflozin & Dapagliflozin	- ↓ proliferation of breast cancer cell lines (MCF7, SKBR3 & BT-474, NT2197) - ↓ Mitochondrial respiration & total ATP production ↓ Glutamine metabolism	[81]

Shh: Sonic hedgehog signaling molecule; FOXA1: forkhead box A1

extracellular domain of transmembrane Tyrosine Kinase IR interacts with insulin. The structural makeup of IR contains 2 transmembrane β subunits & 2 additional cellular α-subunits which are bound together by disulfide connections. Alternative splicing produces two isoforms of IR: Isoform A (IR-A) which deficits exon 11 & Isoform B (IR-B) which consists of exon 11 [83,87]. While IR-B primarily exhibits metabolic influences and is primarily expressed in insulin-target tissues (liver, muscle & fat), IR-A exhibits higher mitogenic effects & is primarily expressed in fetuses & cancerous cells [85]. Insulin and IGF-1 act as growth factors that play a role in glucose metabolism and initiate cell signaling pathways responsible for cell propagation, diversity & persistence. The downstream process activated by insulin and IGF-1 includes various molecules like the IR substrate proteins as well as pathways such as the PI3K & MAPK. PI3K triggers the protein kinase B pathway which along with the MAPK pathway supports cell growth while also exhibiting anti-apoptotic effects, both of which contribute significantly to tumorigenesis. IR plays a primary part in maintaining glucose concentrations [87]. IGF-1 signaling through the IGF-1 receptor demonstrates a greater impact on cell proliferation and survival compared to insulin. Increased expression of IGF-1 may encourage tumor development associated with higher susceptibility to prostate, breast, colon, & lung cancers. Insulin is efficient in binding to and activating the IGF-1 receptor; thus, high levels of insulin in the blood may induce cell proliferation and survival using this pathway [86]. IR is mainly found in fat tissue, liver & muscle tissues, while IGF-IR is present in nearly all bodily tissues. In fetal tissue, IR-A exhibits high expression levels and mediates anti-apoptotic & mitogenic effects; while IR-B mainly has metabolic outcomes. IR-A binds to both insulin & IGF-2, while IR-B has limited responsiveness to IGF-2. Additionally, IGF-2 strongly stimulates cell proliferation. Insulin & IGF-1 have the highest affinity for their respective receptors. Due to their close similarity, IGF-1R & IR can combine to form hybrid receptors with characteristics more similar to IGF-1R than IR. These hybrid receptors demonstrate a greater binding preference for IGF-1 over insulin, potentially enhancing cell sensitivity to IGF-1 through additional binding sites provided by the hybrids [87]. Raising insulin levels can also indirectly stimulate cell development by decreasing the liver's synthesis of IGF-1-binding proteins. This raises the amounts of physiologically active unrestricted IGF-1, a powerful mitogenic &

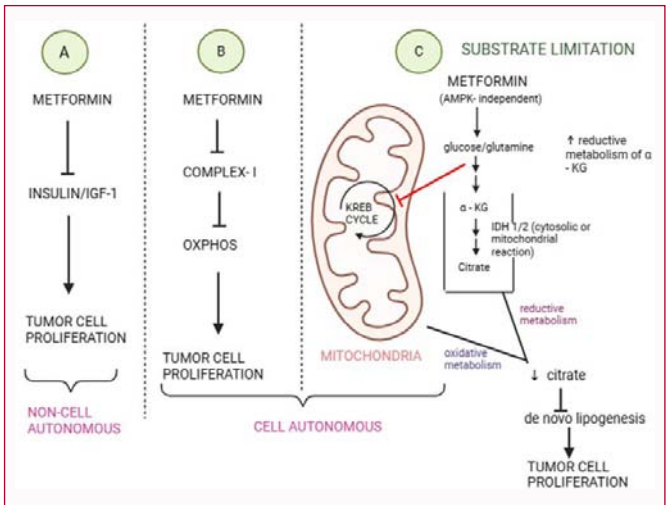

Figure 7: Metformin anti-cancer mechanism.

Table 5: Synergistic effect of antidiabetic drugs with chemotherapeutic treatments.

Cancer type	Anti-diabetic drug	Chemo-therapeutic drug	Observed results	Reference
Breast cancer	Metformin	Paclitaxel (PTX)	- BALB/c mice were inoculated with 4T1 cells - Co-delivery of PTX with metformin ↓ cell proliferation & ↑ apoptosis *via* the Toll-Like Receptor (TLR) signaling through the modification of TLR-MyD88-ERK pathway (which is liable for growth, progression, metastasis, & drug resistance in tumors)	[92]
Non-small cell lung carcinoma	Metformin	EGFR-TKI	- administration of metformin led to an increased median progression-free survival (PFS) in NSCLC patients undergoing both initial & subsequent EGFR-TKI therapies - use of Metformin was associated with an increased Objective Response Rate (ORR) & Disease Control Rate (DCR).	[93]
Pancreatic cancer	Rosiglitazone & Metformin	Gemcitabine	- rosiglitazone + gemcitabine ↓ proliferation of MiaPaCa2 cells - combination of either rosiglitazone or metformin with gemcitabine ↑ apoptosis - rosiglitazone ↑ PTEN & ↓ levels of phosphorylated AKT - metformin ↑ phosphorylation of AMPK - both metformin & rosiglitazone induced ↓ level of BCL-2 in MiaPaCa2 cells - each rosiglitazone & metformin ↓ levels of phospho-mTOR kinase (Ser2448). However, did not ↓ level of total mTOR proteins - levels of phospho-S6 & phospho-4EBP1 also ↓ by treatment of rosiglitazone & metformin in MiaPaCa2 cells	[94]
CT26 (colon cancer) B16F10 (melanoma) A549 (lung cancer) E6E7Ras (tonsil cancer) MCF7 (breast cancer) DU145 (prostate cancer)	Phenformin	Oxamate	- Both of the drug's function in term in inhibiting complex I & LDH at the same time - Phenformin inhibits mitochondrial complex I leading to ↑ ROS production - When phenformin is present, oxamate's inhibition of LDH causes ↓ ATP levels & ↑ ROS generation due to ↑ electron transport through complex I	[95]
Pancreatic cancer	Metformin	Boswellic acid nanoparticle	- significant cytotoxic action in (MiaPaCa-2) with a constant concentration of metformin & 0.3 mg/ml & 0.4 mg/ml of boswellic acid nanoparticles - ↑ restriction of cell proliferation through cytotoxicity & ↓ cell growth - inhibit cell migration of MiaPaCa-2 cells - induces apoptosis leading to fragmented DNA	[96]
Breast cancer	Metformin	Vitamin D3	- in MDA-MB-231 cells combined treatment of metformin along with vitamin D3 inhibited cell proliferation & activated apoptosis - Mechanisms include AMPK activation, Bax upregulation, caspase 3 cleavage, & inhibition of pBcl2, c-Myc, pIGF-IR, pmTOR, pP70S6K, & pS6	[43]
Lung cancer	Canagliflozin & ipragliflozin	Raloxifene	- this combination of 3 drugs ↓ cell survival & resulted in mutually beneficial effects comparing to monotherapy with each drug	[79]
Caco 2 & MCF-7 cell lines	Canagliflozin & ipragliflozin	Doxorubicin	- ↑ intracellular doxorubicin level by reducing the P-glycoprotein (P gp) activity - P-gp efflux is an ATP-dependent pump & combining canagliflozin with doxorubicin may reduce	[79]
Ovarian cancer	Canagliflozin	Paclitaxel	- in ES-2 cell lines canagliflozin ↑ paclitaxel-induced apoptosis & DNA-damaging effect - paclitaxel disrupts microtubule dynamics & canagliflozin damaged SAC (spindle assembly checkpoint) activity, together they trigger premature mitotic exit, accumulation of aneuploid cells with DNA damage, & cause apoptosis	[97]
Human endometrial carcinoma (snu-1077 & hec-1 cell lines)	Metformin & SGLT2 inhibitor	Carboplatin or Cisplatin	- metformin & SGLT2 inhibitor combination with carboplatin or cisplatin caused more robust apoptosis compared to each agent alone in both cell lines - SGLT2-inhibitor with carboplatin had better apoptotic effects than metformin & carboplatin in hec-1 & snu-1077 cell lines - When used with platinum-based chemotherapy, metformin & SGLT2 inhibitors show synergistic anti-proliferative effects for endometrial cancer.	[98]

anti-apoptotic substance that is shown to support the proliferation of cancerous cells [85]. This excess IGF-1 hyperactivates IGF-1R & IR/IGF-1R and their proliferative and anti-apoptotic effects in both pre-malignant and malignant tissues [49]. Furthermore, the binding of an IGR ligand can activate the MAPK & JAK/STAT pathways [83]. Both *in vivo* and *in vitro* evidence indicate that hyperinsulinemia can promote and progress cancer by stimulating cell proliferation. By employing this mitogenic potential, hyperinsulinemia may act as a stimulus for the growth of preneoplastic & neoplastic cells, leading to more violent tumors that were previously present but undetected. Both endogenous hyperinsulinemias owing to insulin resistance and exogenous hyperinsulinemia for diabetes treatment

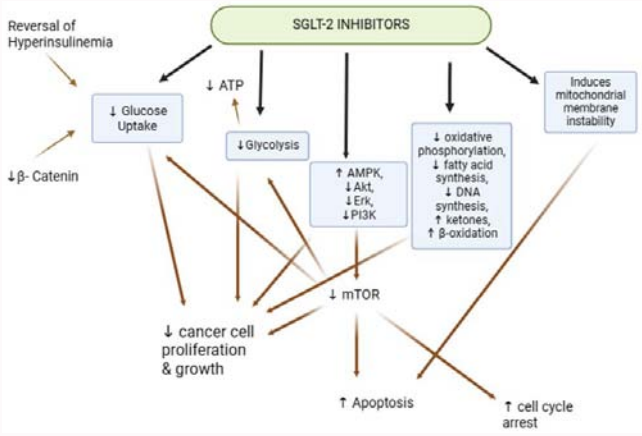

Figure 8: SGLT-2 inhibitor anti-cancer mechanism.

possibly will have damaging penalties [85]. Insulin has been shown to have a carcinogenic effect in individuals with an extended history of T2D, even when it is exogenous [88,89]. Furthermore, abnormal insulin signaling may facilitate the spread of cancer by augmenting the production of hyaluronan, which is an extracellular matrix constituent that stimulates the growth & progression of tumors, along with the Epithelial to Mesenchymal Transition (EMT) [85,90].

Combination Therapy

The majority of cancers are now treated with surgery, chemotherapy, and radiation treatment, with great success in slowing tumor growth and enhancing the prognosis and quality of life of those afflicted. However, the problem is that using a single treatment modality or solo strategy results in toxicity, resistance development, metastasis, and disease recurrence. Employing tailored therapeutic combination regimens results in (1) increased treatment efficacy and better overall result and prognosis, with reduced metastasis and relapse incidence; (2) united results of the drugs, necessitating much lower dosages of the combination drugs for the highest efficiency; (3) reduced drug-induced toxicity and undesirable consequences due to lower doses of the medications are used in combination; and (4) prevention of development of resistance compared to when the drugs are used in combination [91] (Table 5).

Mechanism of Action

Compelling evidence supports an exact link between T2D & cancer. As a result, many medications used to treat diabetes are being repurposed for treating cancer. The majority of available evidence indicates that metformin exhibits anti-proliferative properties in various cancer types. Metformin functions by activating AMPK, which negatively controls the mTOR, an important factor influencing tumorigenesis & energy balance. It is believed that AMPK and its upstream activator, the LKB1 tumor suppressor, occupy a vital role in metformin's anticancer effects [99,100]. When metformin is administered; AMPK is activated, which inhibits the gene that causes glycogenesis in hepatocytes from transcribing. During this process, muscle cells absorb more glucose as a result of a decrease in glycogenesis. Insulin levels are then decreased as a result of muscle cells' absorption of glucose. High blood insulin levels have mitogenic effects & may lead to tumor growth & proliferation because cancer cells have many insulin receptors, lowering blood insulin levels lowers the risk of malignancy & inhibits the growth of cancer cells. AMPK activation causes mTOR inhibition [20]. By triggering translation & protein synthesis *via* its primary downstream target, S6 kinase, the mTOR acts as the master regulator of protein synthesis [4]. Hence, prevention of mTOR causes a decrease in levels of 4E-BPs (4E-Binding Proteins) & S6Ks (ribosomal protein S6 kinase) factors & decreases protein synthesis & proliferation. This prevents cancer growth & proliferation [20]. Additional pathways *via* which Metformin functions include mitochondrial Glycerophosphate Dehydrogenase (mGPDH), Adenosine Monophosphate-activated Protein Kinase (AMPK), mammalian Target of Rapamycin (mTOR), & Nuclear Factor kB (NF-kB) [18]. The mTOR pathway encourages rapid progression of the cell cycle by regulating the synthesis of proteins which are crucial in the proliferation & continued existence of cancer cells. Moreover, the mTOR pathway's activation encourages the spread of tumors & an increase in chemotherapy & radiation resistance. Thus, targeted mTOR pathway inhibition can aid in the therapy of cancer. Metformin's anti-neoplastic properties result in the reduction of protein synthesis & cell proliferation by activating AMPK through mTORC1 inhibition. Nevertheless, metformin-mediated, AMPK-independent mTOR impedance is also documented *via* REDD1, a target gene of Hypoxia-Inducible Factor 1 (HIF-1) associated with the control of cell survival [101]. However, metformin may also activate pathways that are not dependent on AMPK, leading to the cessation of cancer cell growth. Alternatively, it could employ an AMPK-dependent/LKB1-independent pathway to inhibit the multiplication of malignant cells [99,102] (Figure 7).

New evidence points to a "substrate limitation" theory as the explanation for metformin's capacity to obstruct the development of tumor cells according to this model, the antineoplastic metformin action is attributed to lipogenic citrate production inhibition through the oxidative metabolism pathway in mitochondria due to drug-stimulated reduction of Krebs cycle intermediates in an LKB1- & AMPK-independent manner. This inhibition of lipogenic processes, which are fundamental for the formation of membranes & tumor cell multiplication, leads to lagging functional mitochondria in tumor cells, making them insensitive to metformin. However, by silencing ATP Citrate Lyase (ACL), the susceptibility to the cytostatic outcomes of metformin can be reestablished in these cells. This suggests the potential for future therapeutic strategies employing metformin in combination with ACL activity inhibition. Additionally, Metformin increases citrate production via reductive carboxylation of α-ketoglutaric acid, but this is insufficient to support tumor cell proliferation in its presence [99]. Metformin also limits the spread of cancer and its invasion by eliminating cancer stem cells that may transition from Epithelial to Mesenchymal Transition (EMT). Through EMT, stem cells can migrate from the epithelium to the circulatory system & spread throughout the body. EMT is a process that allows the stem cell to self-renew & commence tumor growth; it is linked to aggressiveness & a poor prognosis [12]. The EMT signaling pathway is subdued by metformin through many mechanisms, such as blocking COX-2-mediated Prostaglandin E2 (PGE2) production, reducing the expression of Snail protein, inhibiting the B-cell-specific Moloney murine leukemia virus integration region 1 (Bmi-1), & lowering IL-6. Furthermore, metformin reduces the signaling of Platelet-Derived Growth Factor B (PDGF-B) & PDGF-receptor β, prevents angiogenesis & reduces tumor movement by reducing angiogenic stimulus, minimizing VEGF expression & preventing HIF-1α-induced angiogenesis-related factor expression [39].

SGLT-2 inhibitors are another well-researched family of anti-

diabetic medications. The effectiveness of SGLT2 inhibitors in eliminating malignant cells has also been supported by emerging data. In many *in vitro* & *in vivo* models reduced glucose absorption is widely linked to their anti-proliferative action [75]. It has been shown that Canagliflozin inhibits mitochondrial complex I which disrupts cellular respiration & significantly increases AMPK activity, resulting in anti-lipogenic & anti-proliferative actions [76,103]. Also, Canagliflozin inhibits glutamine metabolism, which disrupts the citric acid cycle. This results in decreased proliferation & decreased cellular respiration [91]. Research has shown that canagliflozin administration inhibited the antagonistic effects of cisplatin-induced p53 phosphorylation, Mitogen-Activated Protein Kinase (MAPK) pathway activation, DNA repair, angiogenesis & autophagy. Canagliflozin activates the PI3K, which enhances Akt activation & prevents cisplatin-induced cellular death [79]. Several studies have shown that repression of glutamine metabolism & interference with multiple signaling cascades (*e.g.*, PI3K/AMPK) may be important mechanisms behind the anticancer properties of SGLT2 inhibitors [75] (Figure 8).

The main way SGLT-2 inhibitors work against cancer is by activating AMPK, which they do indirectly. They reduce ATP synthesis & raise the AMP/ATP ratio, leading to AMPK activation. Additionally, they impact oxidative phosphorylation & decrease ATP synthase F1, inhibiting mitochondria complex-I & decreasing ATP synthesis in cancer cells. The consequences are an increased AMP/ATP ratio & a rapid increase in AMPK activity. Their impact on glutamine metabolism correspondingly influences the elevated AMP/ATP ratio [75]. Glutamine is converted to glutamate, which serves as a carbon source for the TCA cycle. SGLT-2 inhibitors decrease intracellular alpha-ketoglutarate concentration by inhibiting GDH activity. This reduction results in decreased incorporation into the TCA cycle & subsequently lower creation of NADH & NADPH. Lower concentrations lead to diminished ATP production, activating AMPK & impaired mitochondrial antioxidant defense due to lower levels of NADPH. The rise in AMPK activity brought by SGLT-2 inhibitors has various effects on cancer cells including significant ACC phosphorylation & inhibition of mTOR. ACC phosphorylation leads to its inhibition; hence, the inhibitors quickly suppress fatty acid production in cancerous cells, ultimately inhibiting their proliferation. Inhibition of mTOR is also believed to partly account for suppressed proliferation & induction of apoptosis in cancer cells. SGLT-2 inhibitors activate AMPK, leading to the inhibition of SREBP1 & subsequently SCD1. This causes a reduction in MUFA production & increased PUFAs, which can lead to lipid peroxidation & ferroptosis. The activation of AMPK also inhibits the malignant cell cycle at the G2/M phase. Furthermore, SGLT-2 inhibitors affect NME1 & NDP expression in cancerous cells, impacting RNA/DNA synthesis as well as DNA replication/mRNA transcription through PRIM2 downregulation [104].

Conclusion

The interaction of genetic, environmental, and lifestyle factors significantly impacts the global burden of diabetes mellitus and cancer. Diabetes presents challenges to healthcare systems and individual well-being, while cancer remains a significant threat that requires coordinated efforts in prevention and treatment. Understanding the fundamental processes related to the pathophysiology of both diseases has led to innovative therapeutic approaches like drug repurposing. Specifically, antidiabetic drugs such as metformin and SGLT-2 inhibitors have demonstrated potential anticancer activity; however, their specificity and underlying mechanisms are not fully understood. Careful dose adjustment and monitoring are necessary for balancing the antidiabetic and anticancer effects to minimize potential side effects and drug resistance. Despite challenges, ongoing research supports exploring different classes of antidiabetic agents for cancer therapy either alone or combined with established treatments. Future studies should concentrate on identifying molecular targets & optimizing treatment plans to enhance efficacy & reduce adverse effects. Overall, repurposing antidiabetic drugs for cancer therapy offers a promising way forward in personalized medicine aimed at improving patient outcomes.

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