

Antidiabetic agents as potential cytotoxic candidates for cancer therapy

Research Article

Raniah I. Alnaser^{1,2*}, Fawaz A. Alassaf², Mohammed N. Abed³

¹Nineveh Health Directorate, Mosul, Nineveh province, Iraq

²University of Mosul, College of Pharmacy, Department of Pharmacology and Toxicology, Mosul, Nineveh province, 41002, Iraq

³University of Mosul, College of Pharmacy, Department of Clinical Laboratory Sciences, Mosul, Nineveh province, 41002, Iraq

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Abstract: **Purpose:** Hyperglycemia is an overlooked triggering factor for cancer, despite being critical to the survival and growth of cancer cells through a unique process known as the “Warburg effect.” Therefore, blocking glycolysis by using antidiabetic agents is an attractive approach for impeding cancer growth and enhancing their responsiveness to cancer treatments, while leaving healthy cells unaffected. This review aims to explore the potential of antidiabetics as cytotoxic agents for cancer treatment through their role as glucose deprivation candidates and the clinical considerations of using antidiabetics with their risk as carcinogenic in cancer therapy. **Methods:** PubMed, Cochrane Library, and Google Scholar were explored by applying the main topic-relevant keywords to consider articles that had been published up to February 2024 and which met our selection criteria. **Results:** The potential of antidiabetic agents to modify the risk of cancer is an exciting area of research in cancer therapy. Some classes of antidiabetics, such as biguanide, sulfonylureas, dipeptidyl peptidase 4 (DPP4) inhibitors, and sodium–glucose co-transporter 2 (SGLT2) inhibitors, have a direct cytotoxic effect on cancer cells, while others, such as glucagon-like peptide 1 (GLP-1) agonists and thiazolidinediones, have an indirect cytotoxic effect on cancer cells. **Conclusion:** Antidiabetic agents differ in their cytotoxic effectiveness toward cancer cells through several mechanisms. Apart from their potential effects on carcinogenicity, these medications hold promise for future cancer treatment. However, not all antidiabetic agents were good candidates for repurposing because of the well-documented carcinogenicity risk.

Keywords: Cancer • Diabetes Mellitus • Glucose Deprivation • Antidiabetics • Cytotoxicity

1. Introduction

Cancer is the second leading cause of death globally, and unfortunately, many triggering factors for different types of cancers have been overlooked, of which the critical one is hyperglycemia^[1]. Several studies explored the significant role of hyperglycemia in cancer development and mortality^[2–4]. Hyperglycemia is the elevation of blood glucose^[5] caused by different motives including diabetes mellitus, being obese, anxiety, medications such as estrogen and glucocorticoid, and pancreatic malfunction^[6,7]. Generally, high blood glucose plays a critical role in carcinogenesis risk, irrespective of diabetes or other related conditions^[8,9].

The main source of energy is glucose, and it is essential for normal cell functions. Normal cells typically

use various metabolic pathways to produce energy by converting glucose into pyruvate through glycolysis^[8]. Tumor cells have a unique glucose metabolism called the “Warburg” effect. This means that even under normal or low-oxygen situations, the cells convert glucose into lactic acid to produce energy by initiating glycolysis^[9]. However, due to the inadequate production of adenosine triphosphate (ATP) through glycolysis, cancer cells increase glucose uptake to support glycolysis for providing energy. High glucose levels can promote cancer progression through several mechanisms such as cancer cell proliferation, metastasis, invasion, resistance to apoptosis, and resistance to chemotherapy^[12].

It appears that cancer cells heavily depend on glucose metabolism to survive. This makes inhibition of glycolysis a highly attractive approach for selectively killing cancer

* E-mail: raniahimad@yahoo.com

cells and making them more sensitive to cancer therapy compared to normal cells^[12]. Glycolysis inhibition could be done by depriving cancer cells from glucose, thus, controlling the glucose level in blood brings forth insights into drug research and cancer management^[13,14].

The possibility of modifying the risk of cancer with certain types of antidiabetics could be an exciting area of research in cancer therapy. In addition to the potential effects of such medications on carcinogenicity through several mechanisms, it sheds light on the impact of antidiabetics beyond glycemic control. Several classes of antidiabetics have a direct cytotoxic action on cancer cells, such as biguanide, sulfonyleureas, dipeptidyl peptidase 4 (DPP4) inhibitors, and sodium-glucose co-transporter 2 (SGLT2) inhibitors, while others have an indirect cytotoxic action on cancer cells, such as glucagon-like peptide 1 (GLP-1) agonists and thiazolidinediones.

Therefore, this review aims to estimate the valuable actions of antidiabetics in managing cancer as direct or indirect cytotoxic agents, to provide a future viewpoint of using antidiabetics as therapeutic opportunities through glucose deprivation candidates, and the clinical considerations of using antidiabetics with their risk as carcinogenic in cancer therapy.

2. Role of glucose in tumor cell proliferation and progression

Normal cells usually use glycolysis to convert glucose into pyruvate in the cytosol. The pyruvate undergoes oxidative phosphorylation (OXPhOS) in the mitochondria via the tricarboxylic acid (TCA) cycle and the electron transport chain (ETC) to produce ATP^[10].

Cells can use anaerobic glycolysis under hypoxic conditions, converting pyruvate to lactate and producing less ATP at a quicker rate^[15]. Mitochondrial oxidation of one glucose molecule produces 36 ATP molecules, while its metabolism to lactate by glycolysis yields only two ATP molecules. Cells can use beta-oxidation or glutamine oxidation under aerobic conditions, depending on the availability of these metabolites^[16]. However, the process is not 100% efficient and can produce reactive oxygen species (ROS) like superoxide (O_2^-) and hydrogen peroxide (H_2O_2)^[17].

Cancer cells require a continuous supply of energy and raw materials for cell replication. Otto Warburg observed a metabolic adaptation known as the Warburg effect in 1920^[18]. This effect reveals that cancer cells consume more glucose and ferment it into lactate instead of undergoing mitochondrial oxidation, even

in the presence of oxygen. Warburg attributed this to dysfunctional mitochondria^[9]. Lactate is carried out of the cell by monocarboxylate transporters (MCTs). The exported lactate can be used by the surrounding cells' TCA cycle to provide energy. Lactate changes the pH of the tumor microenvironment and supports the growth of cancer cells. Cancer cells can withstand an acidic environment, which means that the presence of lactic acid can aid in the growth of tumors^[19].

Overall, faster glucose catabolism through glycolysis is essential for the uncontrolled growth of cells seen in cancer, as shown in Figure 2^[20]. Attractively, cancer cells prefer to convert glucose into lactate, even if there is a sufficient supply of oxygen, as seen in Figure 1. This process is known as aerobic glycolysis; it satisfies the biosynthetic and bioenergetic demands of the uncontrolled growth of cancer cells^[21].

Essentially, when glucose is available as an energy source, cancer cells focus almost entirely on reproducing and increasing their mass^[7]. Thus, by this explanation, hyperglycemia accelerates the proliferation of cells, but also could be stopped at fasting state^[23]. This concept attracted us to deprive the cancer cells of glucose and control cell proliferation and invasiveness by using antidiabetic agents.

In addition, inhibiting mitochondrial OXPhOS can prevent tumor invasion and reduce multidrug resistance in certain cancers^[24,25]. The OXPhOS of mitochondria and glutaminolysis contribute to cancer progression and metastasis^[26].

Cancer cells show aerobic glycolysis and efficient mitochondria, making tumor glycolysis a promising objective for cancer therapy. Controlling tumor glycolysis could be done by decreasing the available glucose and depriving the cells of glucose uptake.

Increased glucose uptake and lactate production (a process known as glycolysis) are seen in cancer cells. Oncogenic signaling controls this mechanism, enabling unchecked and fast cell division. Glycolytic intermediates, which are substrates for other biosynthetic routes like the pentose phosphate pathway and one-carbon metabolism, are used by cancer cells to maintain this process. They can provide the energy and building materials needed for cell division and growth by doing this. The metabolism of glutamine serves as an additional energy and biosynthetic source for cancer cells. Regulation of glutamine and glucose metabolism by oncogenic pathways allows cancer cells to develop tumors and adapt to various stressors. By lowering the amounts of ROS, a chemical that triggers apoptosis, this metabolic adaption aids cancer cells in avoiding^[20].

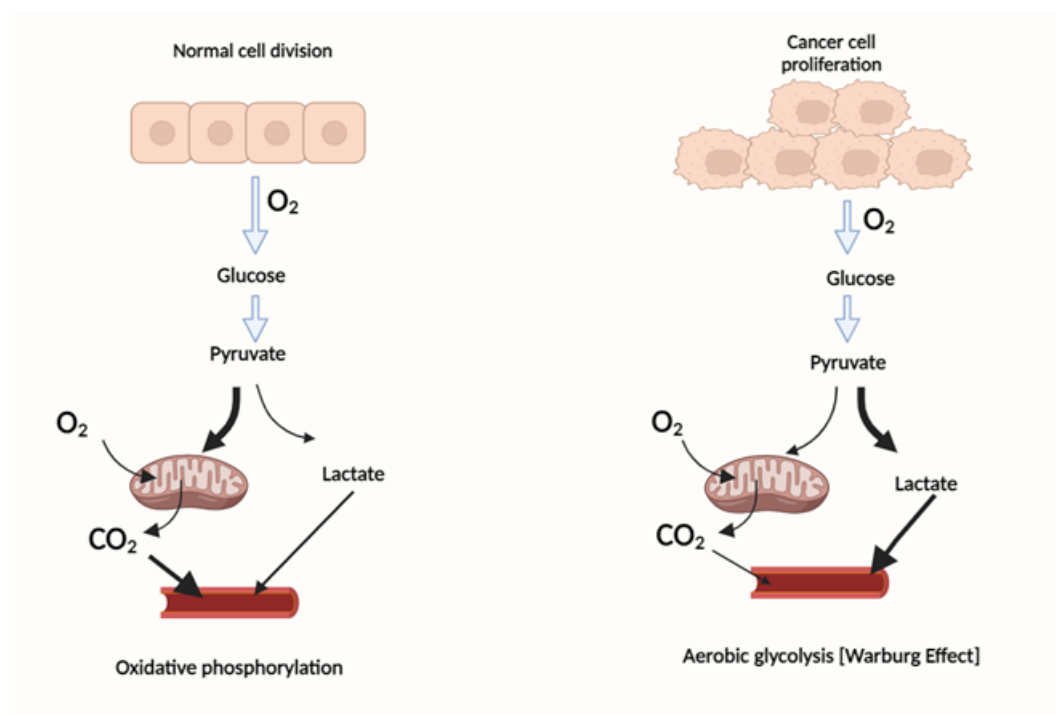


Figure 1: Difference in glucose metabolism between normal and cancer cells [22].

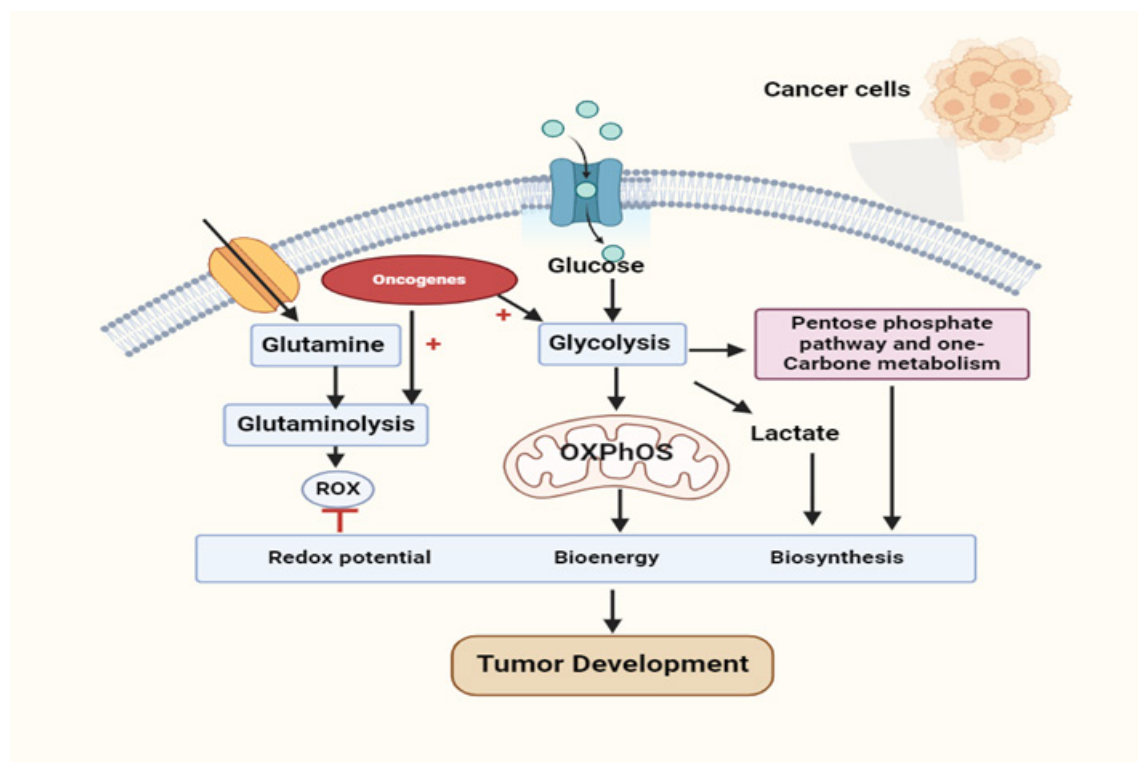


Figure 2: Internal metabolism of cancer cells.

3. Depriving cancer cells of glucose

It's widely accepted that cancer cells consume and process glucose more than normal cells. This results from adaptation of low energy yield from glycolysis. Cancer cells probably benefit from a high rate of glycolysis because it produces a large amount of ATP and provides different intermediates that are utilized in other metabolic pathways to produce amino acids, nucleotides, NADPH, and lipids. These substances are essential for fast cell proliferation^[17].

Several studies have shown that depriving cancer cells of glucose leads to their cytotoxicity through mechanisms that involve oxidative stress, which is not the case with normal cells^[27,28]. It is generally accepted that cancer cells are subject to persistent metabolic oxidative stress, which may cause them to enhance their glucose metabolism to generate more pyruvate and NADPH and fight away the toxicity caused by hydroperoxide. Glucose concentration in cancer cells is lower than in normal cells by 3- to 10-fold^[29]. Thus, deficiency of glucose leads to the reduction of ATP production and overproduction of ROS; this is called metabolic stress^[30].

Depriving cancer cells of glucose would, therefore, activate multiple pathways including adenosine monophosphate-activated protein kinase (AMPK), which is an energy sensor in the cell that reprograms the metabolic process^[31]. Activation of AMPK inhibits the biosynthesis process that consumes ATP, such as protein, fatty acid, and cholesterol synthesis.

The other pathway is Akt, which is a gene that is activated in several cancer cells and acts as an antiapoptotic factor to different stimuli such as hypoxia, chemotherapy, and radiation^[32]. Activation of the Akt pathway would not inhibit cell death, but render the cell more sensitive to oxidative stress as shown in several studies^[33–35]. The antiapoptotic activity of Akt is estimated to be linked to glucose metabolism. Thus, depriving cells of glucose could increase the ROS and amplify Akt activation, resulting in cell death^[33].

Therefore, it would be expected that depriving cancer cells of glucose would block the mechanisms that protect them from higher steady-state hydroperoxide levels, making cancer cells more susceptible to oxidative stressors and selectively lethal than normal cells^[13,37]. This underlies the principle of preclinical studies using some types of antidiabetics as cytotoxic agents to kill cancer cells. The concepts of the crucial roles of antidiabetics in lowering blood glucose and depriving the cancer cells of too much glucose uptake shed light on repurposing certain types of antidiabetics in cancer

therapy as direct cytotoxic agents or indirect cytotoxic agents through several mechanisms.

In addition, the overexpression of glucose transporters on the surface of the cancer cells that aids in high glucose uptake may be a good target for certain antidiabetics to prevent glucose entrances and promote their cytotoxic actions^[38].

Therefore, understanding the different mechanisms of antidiabetic agents as potential cytotoxic agents for different types of cancers gives more insights for using them in cancer therapy and this is explained subsequently.

4. The potential cytotoxic effects of antidiabetic agents

Recent clinical and preclinical studies have shown that antidiabetics may act as cytotoxic agents for cancer cells either directly or indirectly through different mechanisms, as discussed below (Table 1).

4.1. Metformin

Metformin is considered the first drug of choice for type 2 diabetes mellitus, and it has been shown to play an important protective role in cancer. It could act as a direct or indirect cytotoxic agent, as will be explored herein^[39]. Metformin has been studied in 1901 clinical trials for various types of cancer, with 216 ongoing. Its cytotoxic effects are confirmed in diabetic patients, but its therapeutic effects in nondiabetic cancer patients are less understood^[40].

Metformin is linked to a lower incidence of several cancers and longer survival rates in patients with colorectal, pancreatic, head and neck, lung, prostate, endometrial, and breast cancers^[39,41]. Metformin works as a direct cytotoxic agent by increasing the redox state at therapeutic concentrations and activating AMPK, which is necessary to inhibit complex I of the mitochondrial respiratory chain, which, in turn, inhibits the mechanistic target of rapamycin complex 1 (mTOR) signaling molecule at supratherapeutic dosages. Metformin also increases glucose utilization and lactate production in the gut, which helps maintain glucose^[42,43]. However, mTOR inhibition not only leads to the inhibition of gluconeogenesis in liver cells, but also decreases the production of protein and prevents cancer cell growth, promoting cancer cell apoptosis and death^[44]. Thus, by activation of the AMPK pathway, metformin plays a major role in different site-specific cancers such as breast cancer^[45], colorectal cancer^[46], and endometrial

Table 1: Summary of the cytotoxic effects of some antidiabetic drugs.

Antidiabetics class	Drug name	Tumor types	References
Biguanide	Metformin	Breast cancer	[45]
		Colorectal cancer	[46]
		Endometrial cancer	[47]
		Ovarian cancer	[183]
		Skin cancer	[184,185]
		Thyroid cancer	[186]
		Head and neck cancer	[175]
		Pancreatic cancer	[187]
		Lung cancer	[54]
Sulfonylurea	Glibenclamide	Gastric cancer	[76]
		Breast cancer	[69]
		Hepatocellular carcinoma	[70,73]
		Colon cancer	[75]
		Glioblastoma	[72]
Thiazolidinedione	Rosiglitazone	Neuroblastoma	[83]
Gliptins	Vildagliptin and sitagliptin		[96,102] [97]
	Vildagliptin, sitagliptin, and gemigliptin		[93,104,105]
	Vildagliptin, sitagliptin, and sitagliptin		[106,107]
	Sitagliptin	Vildagliptin	[103]
		Gastric cancer	[94]
		Breast cancer	[96]
		Endometrial cancer	[95]
		Cervical carcinoma	[99]
		Glioblastoma cancer in the brain	[100,101]
GLP-1 agonists	Exenatide-4	Hepatocellular carcinoma	[112,113]
		Breast cancer	[114]
		Prostate cancer	[115]
		Endometrial cancer	[116]
	Liraglutide	Endometrial cancer	[116]
SGLT2 inhibitors	Dapagliflozin	Pancreatic carcinoma	[38,123]
		Renal carcinoma (in humans)	[129]
		Human colon carcinoma	[188]
	Canagliflozin	Pancreatic cancer and early-stage lung cancer	[38,125,189] [130]
		Hepatocellular carcinoma (in humans)	[190]
		Lung cancer	[191]
		Breast cancer	[191,192]
		Prostate cancer	[192]
	Ipragliflozin	Thyroid cancer	[131]
		Breast carcinoma	[128]

cancer^[47]. In addition, by the same mechanism, metformin may suppress the breast metastasis that might be induced by DPP4 inhibitors^[48].

Metformin has been found to have an indirect inhibitory effect on cancer growth^[40]. It achieves this by reducing glucose production in the liver and increasing

glucose uptake by muscle cells. This, in turn, leads to a decrease in insulin release from the β cells of the pancreas and a reduction in the insulin level of plasma. As a result, the risk of proliferation of cancer cells is reduced^[44]. In addition, it has an action on the immune system; it promotes the production of immune cells and

prevents their apoptosis as seen in mice lymphoma^[49]. Recent studies have shown that metformin may promote the suppression of tumor microenvironment^[50,51]. Over 50 clinical trials have investigated metformin's use in human malignancies, with dosages ranging from 500 to 3000 mg/day^[52]. However, gastrointestinal toxicity has limited the use of metformin beyond 2500 mg/day, at which the anticancer effect occurs^[53]. It is recommended to aim for the maximum tolerated dose of 2500 mg/day in future trials and plan for dose increase and reduction of drug toxicity^[52].

In clinical practice, metformin has shown a cytotoxic efficacy against site-specific cancer, especially in combination with conventional anticancer agents, by decreasing the resistance of cancer cells to chemotherapy and improving their responsiveness^[54,55].

Several randomized clinical trials have provided valuable insights into the use of metformin in different solid cancers. The Metformin and Trastuzumab in Neoadjuvancy (METTEN) study reported the safety and tolerability of combining a standard antidiabetic dose of metformin with intricate neoadjuvant regimens involving targeted therapies like trastuzumab and anthracycline/taxane-based chemotherapy in women with early HER2-positive breast cancer^[56]. In addition, the MANSMED trial found that a combination of metformin with androgen deprivation therapy improves the prognosis of metastatic or locally advanced prostate cancer^[57]. Despite these promising outcomes, some trials did not reveal a role for metformin in improving cancer management. One such trial was MA.32, which observed minimal effectiveness for the addition of metformin to standard breast cancer treatment when compared to placebo in patients with high-risk operable breast cancer without diabetes. Nonetheless, this trial only focused on estrogen/progesterone receptor (ER/PgR+) breast cancer patients, so the findings might not be applicable to other types of breast cancer. Furthermore, because the study excluded patients with diabetes, who might respond differently to metformin, the results may not be generalized to other populations^[58].

In the NRG-LU001 clinical trial, the addition of metformin to concurrent chemo-radiotherapy and consolidation chemotherapy did not improve the survival results among patients with locally advanced non-small cell lung cancer. However, while this trial was not placebo controlled, only 39% of patients were able to continue with the recommended daily dose of metformin, without making any adjustment^[59]. Moreover, other clinical trials on endometrial cancer and metastatic pancreatic cancer did not reveal significant increase in the progression-free survival (PFS) and overall survival (OS) when metformin was added to paclitaxel and

carboplatin, where further studies are needed to expose the specific biomarkers in these cancers to maximize the response to metformin^[60,61].

4.2. Insulin

The widespread use of insulin in treating diabetes sheds light on its role as an anticancer agent. Unfortunately, the therapeutic insulin or its analog induces cancer risk by the same mechanism as endogenous insulin^[62]. Insulin and insulin analogs can stimulate cell proliferation via interaction with insulin growth factor-1 (IGF-1) and its receptors. Aspart insulin, an unusual human insulin analog, binds to hepatocytes, which leads to increased signaling of the mitogen-activated protein kinase (MAPK) pathway, promoting cancer progression^[63]. Insulin and insulin analogs are used for their positive effects such as antidiabetic action, despite the potential cancer risks, but they do not act as cytotoxic agents^[64].

4.3. Sulfonylurea derivatives

This class of antidiabetic agents binds to a specific receptor called sulfonylurea receptor that is located on the surface of pancreatic beta cells, resulting in insulin exocytosis from secretory granules^[65]. Thus, the endogenous insulin increases and may lead to cancer, as theoretical observational studies confirm the relationship between insulin and cancer risk^[66,67]. From the concept of glucose deprivation, the stimulation of insulin secretion could help in the uptake of glucose by the peripheral tissue, thus lowering blood glucose concentration^[65]. Sulfonylureas' effect on cancer risk in diabetic patients varies with the type of sulfonylurea used, based on clinical evidence. Differences in affinities for sulfonylurea receptors and off-target anticancer effects are the possible mechanisms^[68]. Many preclinical studies explored the direct cytotoxic effect of sulfonylureas on cancer cell growth, especially that of glibenclamide, a second-generation sulfonylurea drug that promotes apoptosis through blockage of potassium channels^[69–72]. When sulfonylurea binds with the sulfonylurea receptor, it inhibits the leakage of potassium ions and triggers the entry of calcium ions. This, in turn, promotes ROS production, and building up ROS can lead to apoptosis. Moreover, the increased inflow of calcium ions triggers insulin exocytosis^[68].

The types of cancer that glibenclamide might inhibit are breast cancer^[69], human hepatocellular carcinoma^[70,73], prostate cancer^[74], colon cancer^[75], gastric cancer^[76], and human glioblastoma^[72]. The

concentrations of sulfonylureas used in the reviewed *in vitro* studies appear to be higher than the therapeutic range achievable in patients^[68]. The potential cytotoxic effects of sulfonylureas described in preclinical studies are of interest from a mechanical point of view and warrant further investigation.

4.4. Thiazolidinediones

Thiazolidinediones (glitazones) are a group of antidiabetic agents that are peroxisome proliferator-activated gamma agonists. These drugs mainly target fat tissue, where they decrease the generation of proinflammatory cytokines and enhance insulin sensitivity^[77]. Glitazones increase insulin sensitivity in peripheral tissues, promoting glucose utilization in muscles, reducing glucose production in the liver, and promoting fat synthesis while inhibiting its decomposition. These actions help normalize metabolic disorders and lower the glycemic level indirectly^[78].

Glitazones (including pioglitazone and rosiglitazone) halt cancer growth by reducing S-phase kinase-associated protein 2 (Skp2) and increasing the upregulation of cyclin-dependent kinase inhibitor (p27kip1), inducing apoptosis via gene upregulation and antiapoptotic molecule downregulation, and inhibiting invasion via the MEK/extracellular signal-regulated kinase (ERK) pathway, which plays a crucial role in the development of cancer^[79]. Glitazone could inhibit cancer growth by activating the AMPK pathway. Several studies failed to observe the antiproliferative effects of glitazones, indicating inconsistent results^[80], whereas other studies showed the growth suppression effect of glitazones *in vivo* and *in vitro* cancer cell studies^[81–84]. Moreover, there is a study showing the reduction of pancreatic cancer risk among glitazone users^[85]. Rosiglitazone showed antiangiogenic activity by inhibition of cancer growth in a human neuroblastoma xenograft^[83].

4.5. Incretin mimetic

Incretin mimetic drugs include DPP4 inhibitors (gliptins) and GLP-1 agonists. These are classes of hypoglycemic agents used in diabetes mellitus.

4.6. Gliptins

The gliptins act by inhibiting the destruction of GLP-1 in the gut by dipeptidyl peptidase enzyme, thus enhancing insulin secretion, suppressing glucagon, and having a

beneficial effect on glucose homeostasis^[86]. Gliptin's class includes sitagliptin, vildagliptin, saxagliptin, alogliptin, and linagliptin.

The transmembrane glycoprotein DPP4 enzyme is expressed widely in various cell types including immune, epithelial, and endothelial cells. In addition, the soluble form is present in body fluids including blood plasma, seminal plasma, saliva, and cerebrospinal fluid^[87]. This enzyme is often disrupted in cancer and has a significant impact on several bioactive peptides that can influence the progression of cancer and the recruitment of immune cells. As a result, it could contribute to cancer development and can be a desirable therapeutic target^[88]. Gliptins represent a frequent option of choice in patients with diabetes because of their low side effect profile including minimal hypoglycemic risk effect, and weight neutral^[86]. Gliptins also have hepatoprotective, renoprotective, anti-inflammatory, and antioxidative effects. These actions make them a promising therapy in different pathological diseases that are linked to diabetes, including cancer^[89,90].

In addition, gliptins' role in lowering blood glucose levels and indirectly depriving cancer cells of numerous glucose uptake. Gliptins show direct cytotoxic action on cancer cells and act as anticancer agents by increasing immunity and promoting lymphocyte trafficking. Effector T cells are essential for antitumor immune responses, and chemokines guide T cells toward tumors. The DPP4 enzyme degrades the CXCL10 chemokine, which is responsible for guiding T cells into diseased tissues, thereby halting T-cell infiltration and tumor destruction. Inhibiting DPP4 activity improves immune efficacy, especially against tumors^[91]. Researchers observed that inhibiting DPP4 activity in mice using sitagliptin, a specific DPP4 inhibitor, preserved the CXCL10 chemokine's biological activity. This increased T cells in the tumor environment and inhibited tumor growth^[92].

In vitro study, sitagliptin was exposed to prevent the invasion, migration, at high doses, thyroid cancer development^[93]. Additional *in vitro* studies showed sitagliptins' ability to block the growth and clonogenicity of cancer cells in the stomach^[94]. Sitagliptin could also inhibit the growth of endometrial cancer cells with the invasiveness of colorectal tumor cells^[95,96]. In mammary tumorigenesis, sitagliptin showed the regulatory roles of DPP4 overexpression and controlling the transformation of epithelial cells through activation of apoptotic signals, decreased cell viability, and decreased colony formation in experimental animals^[97,98]. In cervical carcinoma, sitagliptin also showed a significant reduction in cell adhesion and viability^[99]. A recent study established the antitumor effect of sitagliptin in brain tumors, particularly glioblastoma, by inhibiting the survival and stemness of

glioblastoma cells both *in vivo* and *in vitro* and prolonging the longevity of mice with glioblastoma^[100,101].

One of the attractive points is that sitagliptin does not induce a hypoglycemic effect in patients with normal circulatory blood glucose or reduced body weight^[100]. These findings could establish its pharmacological safety profile as a cytotoxic agent in nondiabetic patients.

Vildagliptin decreases the growth of colorectal cancer cells *in vitro* and inhibits the growth of lung metastases in mice by boosting the apoptosis of cancer cells and decreasing autophagy^[102]. Moreover, vildagliptins inhibit lung cancer proliferation by increasing surfactant protein production in lung cancer cells. This drives macrophages toward a proinflammatory and anti-tumorigenic polarization, which enhances the cytotoxicity of natural killer cells within the cancer cell^[103].

Gemigliptin is a highly selective DPP4 inhibitor, and three *in vitro* experiments were conducted to assess its cytotoxic effects on thyroid cancer cells. Gemigliptin was found to have a cytotoxic effect that was dose and time dependent through different mechanisms^[104,105].

Gliptins could inhibit DPP4 enzyme in nanomolar concentrations, therefore, some data exploring the higher concentration of gliptins in cytotoxicity with their limited conclusions, applied a warning of using gliptins as a cytotoxic agent in high doses.

The aforementioned studies used millimolar concentration of gliptin, but a distinctive study explored the micromolar concentration of gliptins for decreasing the migration of leukemic stem cells from the stroma cell layer in chronic myeloid leukemia, but it had no effect on tumor growth^[106,107].

4.7. GLP-1 agonists

This is a class of hypoglycemic agents that bind to the GLP-1 receptors, which are expressed in different tissues including the pancreas, heart, gastrointestinal tract, and central nervous system^[108,109]. Thus, the abundance of the GLP-1 receptors and their multiple mechanisms of action promoted them as potential candidates for drug targeting in several diseases beyond diabetes. Few preclinical studies demonstrated the expression of GLP-1 receptors on rat and mice hepatocytes, which may aid in the elimination of hepatic glucose^[110,111]. Exenatide-4 is one of the GLP-1 agonists that has shown an antitumor effect against hepatocellular carcinoma^[112]. Exenatide-4 can prevent both obesity-dependent and obesity-independent liver cancer. It does this by reducing the activity of epidermal growth factor receptors and signals transducer and activator transcription 3 (EGFR-STAT3) signaling in a way that is dependent on both the dose of

exenatide-4 and the length of time it is taken for^[113]. It has been shown that exenatide-4 could inhibit breast cancer growth through the inhibition of the nuclear factor kappa B (NF- κ B) pathway^[114] and reduce the growth of prostate cancer by inhibition of ERK-MAPK phosphorylation^[115]. Liraglutide, another GLP-1 agonist, and exenatide-4 may be considered a potential treatment for endometrial cancer by targeting autophagy in cancer cells and through targeting GLP-1 receptors that are expressed highly in endometrial cells^[116]. Accordingly, the GLP-1 agonists have an indirect cytotoxic action on cancer cells, which also depends on the dose and the duration of usage.

4.8. Sodium-glucose co-transporter inhibitors

Another class of hypoglycemic agents called SGLT2 is used to treat diabetes mellitus by reducing circulating glucose through inhibiting renal tubular reabsorption and inducing renal extraction^[117]. This class includes dapagliflozin, empagliflozin, and canagliflozin and may be considered good candidates for cancer therapy^[118]. This finding resulted from studies that showed overexpression of SGLT1 and SGLT2 in certain types of malignancy (SGLT1 in brain, prostate, pancreas, ovaries, and head and neck cancer^[119–122] and SGLT2 in lung, brain, pancreas, and prostate cancer^[122–124]). So, direct blocking of glucose uptake in cancer cells via SGLT2 inhibitors leads to disruption of the energy production pathway.

Studies conducted in animals showed the role of dapagliflozin in mice with pancreatic cancer by inhibiting the SGLT transporter and preventing the uptake of glucose. In addition, the studies showed the decreased viability of pancreatic cancer and reduced cancer growth by inducing necrosis in xenograft mice models by canagliflozin and dapagliflozin^[123]. Moreover, inhibition of SGLT2 may be a good therapeutic target for early-stage lung adenocarcinoma. Canagliflozin is a selective inhibitor of SGLT2 and may act as a target for the prevention of lung carcinoma progression as observed in a mice model^[125]. In addition to some studies that focus on SGLT2 inhibition in the process of apoptosis^[126,127], some of the findings strongly suggested the role of SGLT2 inhibitors in the induction of apoptosis and their potential role as therapeutants in cancer therapy^[15,128]. For example, dapagliflozin reduces the renal cancer cell volume in humans by induction of apoptosis^[129] and canagliflozin promotes the apoptosis of both hepatocellular carcinoma in humans^[130] and thyroid tumor^[131]; in addition, canagliflozin has a direct effect on the activation of AMPK pathway and

inhibition of OXPhOS in the cancer cells of prostate, lung, breast, and liver cancers^[132]. Canagliflozin and empagliflozin activate the AMPK pathway and inhibit mTOR in pancreatic and breast cancer. Ipragliflozin may induce apoptosis in breast tumor cells^[128]. Thus, SGLT2 inhibitors have direct and indirect cytotoxic actions: firstly, by inhibiting mitochondrial complex-1 and secondly, by reducing glucose influx into cancer cells.

The usage of antidiabetic medications as cytotoxic agents against cancer has been the subject of previous sections. Scientists are still quite concerned about the safety of these medications since some studies have suggested that antidiabetic agents may raise the chance of developing specific cancers. Therefore, it is important to explore the risk of carcinogenicity of these agents, as will explained in the next section.

5. The risk of carcinogenicity with antidiabetics

5.1. Metformin

A risk of cancer with metformin is less common. Instead, it can lower the incidences of certain types of cancer, in addition to improving the survival of the patient suffering from cancer^[52]. However, gastric cancer may be associated with metformin users, which has been shown in studies of the elderly population^[133]. In comparison, other studies on diabetic patients explored the lower incidence of gastric cancer with metformin^[134,135]. Thus, these controversial studies on the relationship between metformin and gastric cancer need further investigation.

5.2. Insulin

Insulin has shown a considerable increase in the risk of pancreatic cancer through prompting cancer cell proliferation and angiogenesis^[136]. In addition, it has a significant effect on increasing the risk of liver, gastric, kidney, and respiratory cancer^[137]. Some studies have shown an increased risk of breast, prostate, and pancreatic cancers in individuals treated with insulin glargine^[136,138]. But other studies have shown no cancer risk with insulin users^[139–141].

5.3. Sulfonylurea derivatives

According to both personal observation and the largest systematic review, there is no association between cancer risk and the use of sulfonylureas compared

to its nonuse^[142–144]. However, some studies have shown that there is a higher risk of pancreatic cancer with sulfonylurea^[136]. The use of different sulfonylurea compounds in different studies may account for the contradictory results on the relationship between the usage of sulfonylureas and the risk of cancer. Variations in the compounds' affinity for the sulfonylurea receptor could account for the variation in cancer risk levels linked to various sulfonylurea compounds^[68]. A study in the elderly population showed that the risk of gastric cancer may be increased in sulfonylureas users^[133]. In addition, a study revealed a higher risk of lymphoma and leukemia in individuals with sulfonylureas, but no other associated cancer^[144]. The carcinogenicity risk from glibenclamide was found to be dose dependent; therefore, the drug should be used in the correct doses^[145].

5.4. Thiazolidinediones

According to a study, diabetic patients who were administered pioglitazone, insulin, and their analogs had a higher risk of developing hepatic cancer, pulmonary cancer, and pancreatic cancer compared to those who did not use them^[145].

A meta-analysis of both observational studies and randomized clinical trials revealed a link between pioglitazone and an increased risk of bladder cancer. In observational studies, this connection is dose and time dependent^[146]. The authors hypothesized that the bladder cells expressed many PPAR- γ , which are associated with cancer growth and progression^[147]. They suggest that a lower dose of pioglitazone has fewer side effects, while its favorable effects on insulin sensitivity, blood glucose, and cancer are maintained^[79].

5.5. Incretin mimetics

5.5.1. Gliptins

DPP4 inhibitors widely used as hypoglycemic agents, the high prevalence of cancer globally, and the controversial conclusions of the available data on the time- and dose-related effect of DPP4 inhibitors as cytotoxic agents attracted our attention to focus on the safety profile of DPP4 inhibitors in terms of cancer risk initiation and progression.

Firstly, in the case of cancer initiation, one of the most debated and disputed issues associated with the use of DPP4 inhibitors is the higher risk of pancreatic cancer. This is because pancreatic adenocarcinoma has elevated DPP4 expression, which may be related to the impaired regulation of glucose that is frequently observed

in this kind of cancer^[139,140]. In contrast, some studies found no significant pancreatic tissue abnormalities in diabetic patients receiving incretins compared to those not receiving them^[141,142]. There are conflicting reports on the relationship between pancreatic cancer and risk factors. Some studies showed a decrease or no increase in risk^[143–145], while others showed an increased risk, especially with long-term use^[155,156]. A cohort study found an increased risk of cholangiocarcinoma (cancer of the bile duct) in gliptin users, but the exact mechanism of this rare cancer type is lacking^[157].

Secondly, in the case of cancer progression in individuals with pre-existing cancer, a patient with a metastatic carcinoid tumor showed a double rise in serotonin levels after taking saxagliptin, as explored in a case study. This increase suggests tumor progression, but upon discontinuing the medication, the levels returned to normal, implying causality^[158]. Inhibiting DPP4 may promote the metastasis of breast cancer cells through the CXCR12–CXCR4 axis^[48], according to a mouse model study. Although the inhibitor used in the study was not potent and is not used clinically, it raises concerns that other DPP4 inhibitors may have the same effect^[150,151]. Sitagliptin administration in a mouse model of prostate cancer led to a faster restoration of tumor growth after castration, indicating that DPP4 inhibition may reduce the efficacy of androgen deprivation therapy^[161]. Saxagliptin and sitagliptin promoted cancer cell migration, invasion, and metastatic dissemination in animal models; for example, more lung invasiveness was seen in thyroid tumors^[162]. These drugs did not affect cell proliferation or sensitivity to chemotherapy. This result was associated with lower oxidative stress in cancer cells, which was brought on by decreased degradation and higher activation of the nuclear factor-E2 (Nrf2) antioxidative pathway^[163]. However, these studies lack the exact molecular mechanisms and data from clinical studies are limited. In addition, the studies of high-dose safety with long-term uses of gliptins are also limited.

Clinical studies show conflicting evidence on the influence of gliptins on cancer proliferation and progression, possibly due to the complex nature of tumor growth and the long period it takes for most malignancies to be diagnosed^[155,156]. Gliptins may help prevent the growth of some tumors, according to preclinical research, but there is a chance that DPP4 inhibition would accelerate the spread of pre-existing cancers^[166].

5.5.2. GLP-1 agonists

According to some preclinical and clinical studies, GLP-1 agonists have been associated with the risk of

medullary thyroid carcinoma and thyroid cancer^[167,168], so these drugs are contraindicated in patients with a family history of such types of cancer.

GLP-1 agonists may be associated with the risk of pancreatic cancer in long-term use due to their direct effects on the pancreas^[169]. However, the data that link pancreatic cancer with GLP-1 agonists are insufficient due to limited studies linking the relationship between the severity of the disease and the duration of the drug use^[112].

5.6. Sodium–glucose cotransporter inhibitors

At the start of SGLT2 inhibitor use, concerns arose regarding the higher risk of breast and bladder cancers. This resulted in the US Food and Drug Administration (FDA)'s refusal to approve dapagliflozin's usage in 2011^[1]. Moreover, a meta-analysis revealed that the prevalence of breast and bladder cancer was higher in individuals taking dapagliflozin compared to those who were not taking it^[170]. Although there were many concerns about a higher risk of bladder cancer, there were not enough cases to make any firm conclusions. It is noteworthy, therefore, that the usage of canagliflozin was linked to a decreased incidence of gastrointestinal malignancies, a finding not shared by dapagliflozin or empagliflozin^[171]. There was no significant difference in the incidence of cancer between SGLT2 inhibitors and placebo, according to a meta-analysis of 27 random clinical studies^[172].

In summary, the risk of carcinogenicity among antidiabetic agents is mainly associated with insulin users^[173], whereas the incidence of carcinogenicity with other antidiabetic agents is contradictory and suggests either no link with cancer or some positive or negative links with site-specific cancer, in addition to its dependence on the agents' used dose and duration of the treatment.

5.7. Clinical considerations of using antidiabetics in cancer therapy and one-sided questions

Understanding the cytotoxic efficacy of antidiabetic agents rising stars to use these agents in cancer therapy, in addition to exploring their risk in carcinogenicity gives a new candidate for researchers about the potential adjunctive effects of antidiabetics in managing cancer.

From the concept of Warburg's effects on the dependency of tumor on glucose, the interest of researchers to use certain types of antidiabetics in

cancer therapy has increased in recent years. Besides their hypoglycemic effects, several mechanisms such as cytotoxicity are being investigated. These mechanisms are diverse and sometimes depend on direct glucose deprivation from the cell or could be an indirect action, and could give a new perspective to treat cancer in the future.

Moreover, due to the potential cytotoxic effect of antidiabetics, the repurposing strategies of antidiabetics focus on their role of controlling glucose levels, giving a promise of synergistic and co-adjunctive effects with conventional anticancer agents and minimizing their side effects^[174].

Metformin is linked to a lower incidence of several cancers and longer survival rates in patients with colorectal, pancreatic, lung, prostate, endometrial, and breast cancers^[39,41]. In addition, it has beneficial roles when combined with other conventional cytotoxic agents to improve their chemotherapeutic actions and overcome treatment resistance^[55,175]. A synergistic action of metformin when combined with other antidiabetic agents such as gemigliptin and pioglitazone attracted endocrinologists to suggest the combinational therapy of antidiabetics to be prescribed by oncologists for targeting specific types of cancer such as thyroid^[167,168]. Despite the effectiveness of metformin in different cancers, the use of metformin in patients with gastric cancer is not favorable until a definitive safety of metformin in this type of cancer is provided^[178]. Thus, among the reported studies of the different actions of metformin on several cancer cells, it could be relevant for repurposing metformin for cancer treatment. Metformin shows little adverse effects and supports the observed data in preclinical and clinical models.

In addition to metformin, DPP4 inhibitors and SGLT2 inhibitors showed supporting results and could be advantageous for controlling specific types of cancers, but also intentions should be assessed in using DPP4 inhibitors in patients with pre-existing pancreatic cancer^[166], and using SGLT2 inhibitors in patients pre-existing bladder cancer^[170].

In this review, we highlighted that not all antidiabetic agents seem to be proper candidates in cancer therapy, given their risk of carcinogenicity in the considerations. Sulfonylureas, thiazolidinediones, and GLP-1 agonists are examples of antidiabetic classes that need to be assessed specifically for each drug within the class for potential action. For example, glibenclamide exhibits cytotoxic action on different types of cancer, while other drugs in the sulfonylureas class may have carcinogenic effects. The effect of pioglitazone differs from rosiglitazone in cancer cells; pioglitazone could promote the carcinogenicity of specific cancer, while

rosiglitazone could have a cytotoxic effect on cancer cells. Moreover, exenatide-4 and liraglutide showed a potential cytotoxic effect, while there is limited data about other drugs in the GLP-1 class.

Despite the carcinogenic risk of some antidiabetic agents, the risk can be eliminated by combining therapy with metformin, which has a favorable toxicity profile, low cost, and a good impact on metabolic parameters^[52,179]. Thus, the collaboration between endocrinologists and oncologists can improve cancer therapy by using certain antidiabetics as cytotoxic agents for specific types of cancer as illustrated in Table 1 and giving a future perspective of including antidiabetic agents in the guidelines of cancer therapy. In addition, the accurate choice of antidiabetic agents to treat diabetic patients with a family history of cancer will promote their efficacy and prolong the longevity of life by controlling cancer development and progression^[180].

Recent advancements in cancer treatment with immunotherapy are outstanding. Nevertheless, it is unknown if immunotherapy is impacted by antidiabetic medications. In 2016, Scharping and his colleagues showed that using metformin to adjust the oxygen tension in the tumor microenvironment produced a significant impact on PD-1 blockade immunotherapy's effectiveness^[181]. In addition, studying the impact of six common antidiabetic drugs (metformin, acarbose, glimepiride, sitagliptin, pioglitazone, and insulin) on anti-PD1 immune checkpoint inhibitors in diabetic patients with colon cancer revealed the effectiveness of adding acarbose and sitagliptin to anti-PD1. However, diabetes patients treated with anti-PD1 for melanoma respond better to immunotherapy when glimepiride or metformin is added to the treatment plan^[182]. Nonetheless, in future research, it is advised to assess the safety and efficacy behind combining antidiabetics with immunotherapies for enhanced outcomes in different types of cancer.

Although the abovementioned finding gives hope for repurposing antidiabetic agents for cancer therapy, several one-sided questions are still unanswered and further investigations are needed to clarify them. The first one is the dose of antidiabetic agents used in preclinical studies; unwanted side effects, mainly hypoglycemia, could occur when using a dose higher than the therapeutic range. Thus, additional studies are needed to assess the safety of potential cytotoxic doses on normal cells. Second, the duration of the drug used also needs further assessment. Third, the selectivity to redox reaction or glucose metabolism needs further investigation, and the last one is the route of administration. Most antidiabetics are taken orally; what will be the extent of inhibition if administered

parenterally? Therefore, further studies on animals are suggested to assess their cytotoxic actions after they are administered parenterally.

In conclusion, antidiabetic agents vary in their cytotoxic efficacy and risk of cancer. Some of them have potential direct or indirect cytotoxic action and significantly impede cancer growth, while some others aggravate the condition due to their carcinogenic risk. These differences result from their abilities to impede intracellular glucose entry and deprive cancer cells of it, increase ROS production, and promote apoptosis, in addition to their direct cytotoxic effects on cancer by trafficking the immune cells toward cancer.

Therefore, antidiabetic agents have the potential in cancer therapy to impede cancer progression and metastasis, overcome chemotherapy resistance, and alleviate the side effects of traditional treatments. Ongoing preclinical investigations and possible new clinical trials indicate promise for their future use.

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Author contributions

These authors contributed equally to this work.

Conflict of interest

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