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REVIEW

# Unraveling Diabetes Mellitus-Driven Tumorigenesis: From Pathophysiological Mechanisms, Therapeutic Drugs to Tailor-Made Nanosystems

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**Abstract:** Diabetes mellitus (DM) and cancer are two major global public health challenges. Growing evidence shows that the core features of DM, including hyperactivated insulin/IGF-1 signaling axis, chronic hyperglycemia, and a persistent inflammatory microenvironment, are important factors driving tumorigenesis and progression. Currently available clinical antidiabetic drugs, such as chemically synthesized drugs, biological and natural products, have been proven to achieve a dual therapeutic effect of controlling blood glucose and regulating the tumor microenvironment (TME). However, these drugs face practical difficulties such as poor oral bioavailability, off-target side effects, and low drug accumulation at tumor sites in clinical application. To overcome these challenges, nanotechnology offers a highly promising solution. Thus, this review elucidates the mechanisms of DM-driven cancer development and the anti-tumor therapeutic mechanisms of current anti-diabetic drugs. Then, we highlight how tailor-made nanosystems overcome traditional delivery barriers, offering unique advantages in targeted delivery, integrated diagnostics, and the oral administration of fragile biologics. Finally, the clinical translatability, disadvantages, and future prospects of these nanosystems will be briefly discussed.

**Keywords:** diabetes mellitus, nano-delivery systems, cancer development, hyperglycemia, therapeutic agents

## Introduction

Diabetes mellitus (DM) and cancer are two major global public health challenges with high mortality rates, and the prevalence of both conditions continues to rise worldwide. According to the International Diabetes Federation (IDF), the global prevalence of DM was an estimated 537 million cases in 2021, and this number is projected to increase to 783 million by 2045.[1] Meanwhile, the World Health Organization (WHO) has reported a significant increase in cancer burden, predicting a rise from 14 million cases in 2012 to 22 million by 2032.[2] This upward trend is expected to continue, with global cancer cases estimated to reach at least 592 million by 2035.[3] Studies have shown a strong correlation between DM and carcinogenesis, with the most evident correlation reported with type 2 DM (T2DM).[4] Indeed, elevated blood glucose levels have been identified as a key factor in this relationship, as they are known to stimulate the proliferation and progression of cancer cells, thereby increasing cancer incidence.[5] For instance, the pancreatic cancer incidence rate among diabetic patients is 54% higher than that in the general population.[6] These statistics highlight the critical intersection of DM and cancer, demanding coordinated strategies to manage both diseases effectively.

Recent evidence further elucidates the mechanisms behind this relationship, suggesting that hyperglycemia promotes tumorigenesis in solid malignancies (eg, pancreatic, liver, and breast cancers (BC)).[7,8] This is driven by several key mechanisms. Firstly, hyperglycemia drives cancer progression through chronic hyperinsulinemia and activation of the insulin-like growth factor-1 (IGF-1) signaling pathway, which promotes cellular proliferation and suppresses apoptosis.[9] Secondly, long-term hyperglycemia generates harmful reactive oxygen species (ROS) and pro-inflammatory cytokines (eg, IL-6, TNF-α), which can damage DNA and create a cancer-friendly environment.[10] Additionally, hyperglycemia

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promotes the "Warburg effect" of cancer cells by increasing glucose supply, which drives preferential reliance on glycolysis for energy production even under aerobic conditions.[11,12] This process releases lactic acid (LA), which accumulates in the tumor microenvironment (TME). This accumulation exacerbates the formation of acidic TME and induces resistance to anti-cancer therapy.[13]

The relationship between DM and cancer is complex and bidirectional. Not only does DM increase cancer risk, but some cancer treatments can also impact blood glucose levels. Certain cancer therapies, such as radiation, biological agents, and chemical agents, may lead to transient or permanent diabetes, with this risk particularly associated with mTOR inhibitors, immune checkpoint inhibitors, and tyrosine kinase inhibitors.[14,15] Conversely, preclinical and clinical studies have also found that antidiabetic drugs could reduce cancer-related risk and mortality in diabetic populations, but the precise mechanisms underlying this phenomenon still require further exploration.[16,17]

In this review, we will first elaborate on the potential mechanisms by which hyperglycemia contributes to cancer development in DM patients. We will then discuss feasible drugs and their clinical treatment options for this specific patient population. Notably, we will provide a detailed discussion of nanodelivery systems tailored to the unique pathological characteristics of DM patients with cancer. Finally, we will briefly explore future prospects and potential breakthroughs for these therapeutic strategies.

## Pathophysiological Mechanisms of DM Contributing to Cancer Initiation and Progression

DM is categorized into T1DM and T2DM. Epidemiological evidence indicates that patients with T2DM face a substantially higher cancer risk compared to those with T1DM. This disparity is primarily attributed to dysregulation of the insulin/IGF-1 signaling axis, chronic hyperglycemia, and an inflammatory microenvironment.[18] As illustrated in Figure 1, this section will elaborate on the pathophysiological mechanisms through which DM contributes to cancer initiation and progression.

### Insulin/IGF-1 Signaling Axis

The Insulin/IGF-1 system (IIS) comprises three ligands (insulin, IGF-I, IGF-II), six binding proteins (IGFBP1-6), and two receptors—the insulin receptor (IR) and IGF-1 receptor (IGF-1R).[19] Under physiological conditions, IIS plays essential roles in metabolic homeostasis, tissue development, and immune responses.[20–22] However, its dysregulation drives cancer progression via enhanced proliferation, metastasis, and stemness maintenance. As shown in Figure 1A, IGF-1R activates the PI3K/AKT/mTOR pathway through insulin receptor substrates (IRS-1/2). This activation promotes the expression of cell cycle proteins, such as Cyclin D1, thereby accelerating the cell cycle process. Simultaneously, IGF-1R also activates the Ras/Raf/MEK/ERK cascade, which drives the expression of cell proliferation genes, including c-Fos and c-Myc, ultimately promoting DNA synthesis and mitosis.[23–25] Furthermore, the crosstalk between IIS and sex hormones (eg, estrogen) has been reported to cooperatively drive the progression of hormone-dependent cancers. In $ER^+$ BC, estrogen upregulates the expression of IGF-1, IGF-1R, and IRS-1, thereby synergistically activating the PI3K signaling pathway. This activation, in turn, suppresses the production of sex hormone-binding globulin (SHBG), a protein with high affinity for testosterone and estrogen. Consequently, estrogen bioavailability increases, amplifying its oncogenic effects.[26] Cancer stem cells (CSCs), a subpopulation of cancer cells endowed with self-renewal and pluripotent properties, play pivotal roles in cancer initiation and metastasis. IIS supports CSCs plasticity by blocking differentiation via the IRS2-PI3K/GSK3β/MYC signaling pathway and by mediating marker upregulation (eg, CD44/ALDH1) through NF-κB/IGF2 signaling.[27,28] Furthermore, IGF-1R also enhances invasiveness by activating migration-related pathways such as integrin and IGF-1R/AKT/S6 signaling cascade.[29,30]

### Hyperglycemia

DM is a metabolic disorder characterized by chronic hyperglycemia, resulting from impaired insulin secretion or insulin resistance. As shown in Figure 1B, sustained hyperglycemia facilitates cancer progression through key mechanisms such

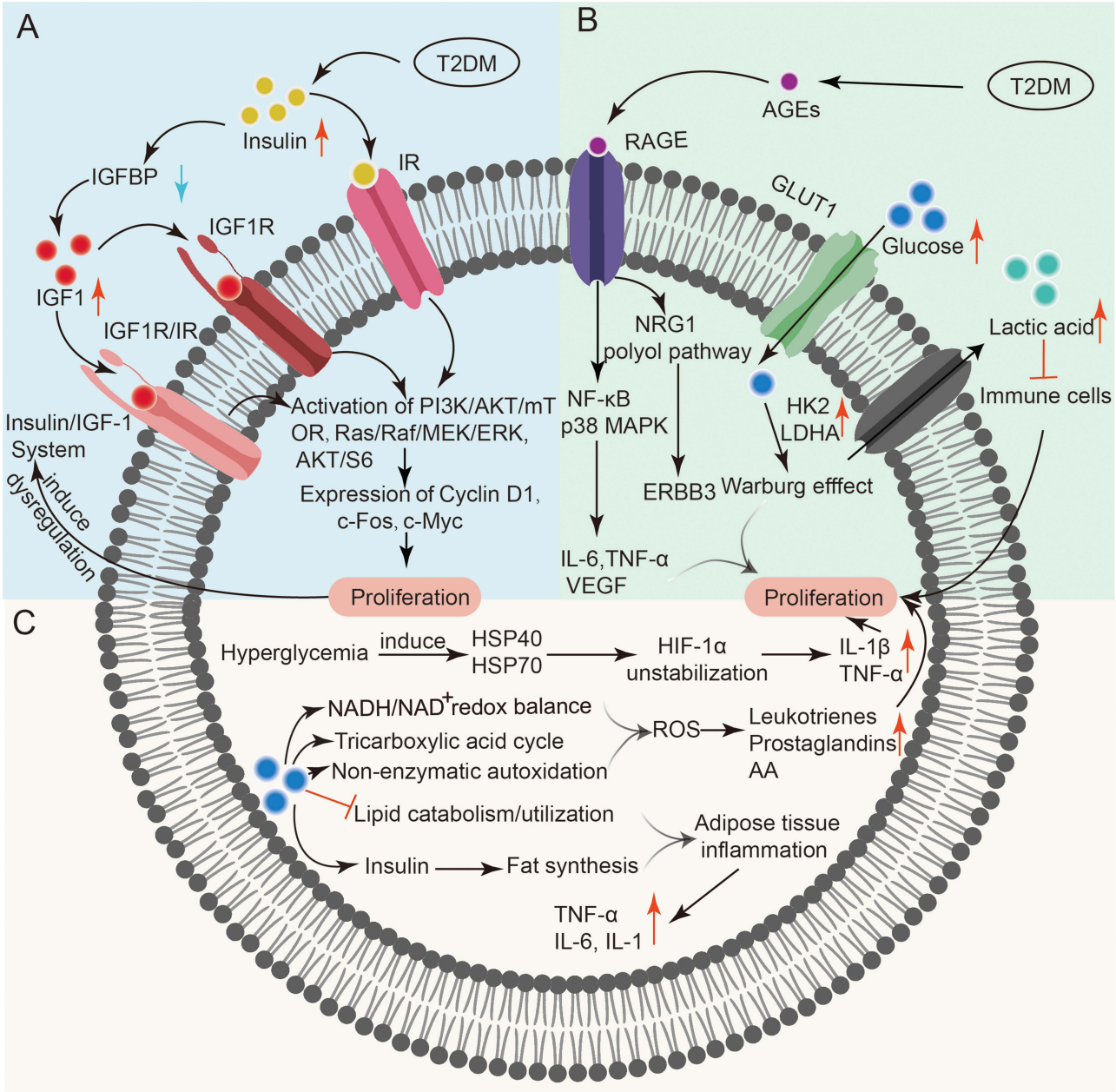


**Figure 1** The mechanisms of diabetes mellitus-driven tumorigenesis. (**A**) The imbalance of insulin/IGF axis drives cancer progression via promoting the expression of cell cycle proteins and cell proliferation genes; (**B**) hyperglycemia facilitates cancer progression through metabolic reprogramming of cancer cells, TME modification, and epigenetic alterations; (**C**) DM-induced inflammatory microenvironment fosters cancer progression by activating pro-oncogenic signaling, and inducing oxidative stress. The red arrows indicate upregulated expression, the blue arrows indicate downregulated expression, and the black arrows represent direction indicators.

as hypoxia-inducible factor (HIF) activation, metabolic reprogramming of cancer cells, TME modification, and epigenetic alterations.

## Metabolic Reprogramming and Lactate-Mediated Immunosuppression

Specifically, elevated glucose levels induce metabolic adaptation in malignant cells through upregulation of glucose transporter 1 (GLUT1) and key glycolytic enzymes, including hexokinase 2 (HK2) and lactate dehydrogenase A (LDHA).[31,32] This metabolic shift enhances glucose uptake and promotes lactate overproduction, thereby accelerating the "Warburg effect" and formation of an acidic peritumoral microenvironment. Accumulated lactate within this microenvironment exerts multiple immunosuppressive effects. Firstly, lactate inhibits the activation and proliferation


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of T cells, induces the M2-like polarization of tumor-associated macrophages (TAM), and upregulates the expression of PD-L1. Secondly, lactate stimulates the secretion of immunosuppressive cytokines such as IL-10 and TGF-β, collectively suppressing the overall anti-tumor immune response.[33–35]

### Extracellular Matrix (ECM) Modification and Epigenetic Alterations

Hyperglycemia induces ECM stiffening via non-enzymatic glycation of collagen and elastin fibers. This biomechanical change activates the integrin-adhesion plaque kinase (FAK) signaling pathway in cancer cells and promotes the activation of tumor-associated fibroblasts (CAFs), ultimately enhancing cell migration and invasion.[36] Furthermore, hyperglycemia-derived advanced glycation end products (AGEs) bind to the receptor (RAGE) on the cell surface. This binding activates the NF-κB pathway and the p38 MAPK pathway, leading to the release of key mediators. Specifically, this cascade upregulates pro-inflammatory factors (such as IL-6 and TNF-α) and pro-angiogenic factors (such as vascular endothelial growth factor, VEGF), thus promoting inflammation and angiogenesis in the TME.[37,38] Finally, persistent hyperglycemia promotes cancer progression by inducing cancer epigenetic alterations, including abnormal histone modifications and DNA methylation regulation. In detail, hyperglycemia upregulates the expression of NRG1 by enhancing the acetylation of histone H3K27 in the enhancer region of the NRG1 gene, thereby activating the ERBB3 signaling pathway and promoting the progression of BC.[39,40] Additionally, hyperglycemia depletes NADPH by activating the polyol pathway, reducing the synthesis of S-adenosylmethionine (SAM) and affecting the activity of DNA methyltransferase (DNMT), which further disrupts methylation homeostasis.[41]

### HIF Activation and Cancer Progression

Excess glucose exacerbates the hypoxic TME and induces the abnormal activation and upregulation of HIF-1α in cancer cells in a PI3K/Akt signaling pathway-dependent manner.[42] As a key transcription factor, HIF-1α drives multiple malignant biological processes of tumors through a series of downstream regulatory effects. First, HIF-1α upregulates the expression of pyruvate dehydrogenase kinase-1 (PDK-1) to inhibit mitochondrial oxidative phosphorylation, remodel cellular energy metabolism homeostasis, and increase intracellular ATP content, which provides sufficient energy for cancer cell proliferation, invasion, and migration.[43] Second, HIF-1α mediates the upregulation of matrix metalloproteinase-9 (MMP-9) expression to directly enhance the invasive and migratory abilities of cancer cells and facilitate distant metastasis. Moreover, HIF-1α induces the secretion of chemokine CCL2 to recruit monocytes and macrophages, and further activates pancreatic stellate cells to promote the formation of tumor-specific desmoplastic stroma.[44] It also upregulates the expression of vascular endothelial growth factor (VEGF) to induce abnormal angiogenesis in tumors, which in turn further exacerbates hypoxia in the TME.[45] Collectively, these effects form a self-reinforcing positive feedback loop of "hyperglycemia-HIF-1α activation-cancer progression", continuously driving cancer development and deterioration.

## Inflammatory Microenvironment

DM is recognized as a chronic inflammatory disorder that fosters cancer progression by establishing a pathologically sustained inflammatory microenvironment, activating pro-oncogenic signaling, and inducing oxidative stress. As shown in Figure 1C, the synergistic effect of persistent insulin resistance and chronic hyperglycemia leads to the increased synthesis and storage of fat while simultaneously suppressing lipid catabolism. This resulting lipid accumulation triggers robust inflammatory responses, particularly in adipose tissue. Evidence demonstrates that adipose tissue inflammation triggers an increase in immune cell populations (such as macrophages and lymphocytes) and promotes the release of inflammatory cytokines, including cancer necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 (IL-1), which collectively stimulate cancer cell proliferation.[46]

Furthermore, hyperglycemia-driven accumulation of methylglyoxal promotes the interaction between hypoxia-inducible factor-1α (HIF-1α) and heat shock protein (HSP40 and HSP70), which disrupts HIF-1α stabilization and transcription through the carboxyl terminus of the E3 binding enzyme of the HSP70 interacting protein. This mechanism compromises cellular hypoxia adaptation capacity, aggravating tissue oxygen deprivation.[47,48] Tumor hypoxic microenvironment induces abnormal polarization of macrophages (such as an imbalance between M1 and M2 phenotypes) by

activating the HIF signaling pathway, promotes the release of inflammatory cytokines (such as IL-1β and TNF-α), and drives the proliferation of inflammatory cells. In turn, inflammatory factors can enhance the expression of HIF through oxygen-independent pathways to form immunosuppressive microenvironment, ultimately promoting cancer progression.[49,50]

Finally, long-term hyperglycemia in DM patients serves as the initial trigger for excessive ROS production, laying the foundation for ROS to act as a central hub. Persistent high glucose levels disrupt cellular metabolic homeostasis, mainly inducing ROS overproduction through three major pathways: i. High glucose increases the flux of nutrients into the tricarboxylic acid cycle, leading to overproduction of ROS in the mitochondrial electron transport chain, which is the main source of intracellular ROS;[51] ii. High glucose undergoes non-enzymatic autoxidation to generate dicarbonyl compounds (eg, methylglyoxal), which further react with cellular components to produce ROS;[52] iii. High glucose converts $NAD^+$ to NADH via the polyol pathway, disrupting the NADH/$NAD^+$ redox balance and promoting superoxide generation via complex I, thereby inducing oxidative stress.[53] These three pathways synergistically lead to sustained elevation of ROS levels in the comorbid microenvironment, triggering chronic inflammation. Subsequently, accumulated ROS activates proinflammatory transcription factors such as (nuclear factor-κB, NF-κB), thereby mediating the release of pro-inflammatory cytokines (eg, TNF-α, IL-6, IL-1β).[54] These cytokines not only exacerbate insulin resistance to further enhance ROS production but also recruit tumor-associatedTAMs, neutrophils, and other immune cells to the tumor site. These immune cells secrete additional growth factors, proteases, and ROS, forming a positive feedback loop that sustains the pro-inflammatory microenvironment.[55] Moreover, accumulated ROS also oxidizes arachidonic acid (AA) to pro-inflammatory leukotrienes and prostaglandins by activating the isomer of phospholipase A2, ultimately accelerating cell cycle progression.[52]

## Therapeutic Potential of Antidiabetic Agents in Modulating Cancer Development

The pharmacotherapeutic regimens for DM patients with cancer require dual optimization of glycemic control and anti-cancer efficacy, while avoiding the exacerbation of drug interactions and metabolic disorders. Current therapeutic drugs with dual anti-cancer and antihyperglycemic properties can be classified into chemically synthetic drugs, biological products, and natural drugs, which exert the DM-cancer bidirectional regulation. As shown in Table 1, this section summarizes the representative drugs that influence the DM-cancer axis, and emphasizes the prospects of combination therapy targeting the interaction between DM and cancer.

**Table 1** The Effect of Antidiabetic Drugs on Cancer

| Anti-Diabetic Drug Class | Scientific Name | Anti-Cancer Mechanism | Ref. |
|---|---|---|---|
| Biguanides | Metformin | AMPK phosphorylation<br>mTORC1 expression ↓<br>ATP depletion and ROS overproduction | [56–58] |
| Sulfonylurea agents | Glibenclamide | KLF4 expression ↓<br>p70S6K activity ↓<br>$K_{ATP}$ channels suppression | [59,60] |
| SGLT2 inhibitors | Canagliflozin | Suppressing glucose uptake ↓<br>GLDH and mitochondrial respiratory chain complex I blockade<br>mTORC1 expression ↓ | [61–63] |
| | Empagliflozin | Cyclins and cyclin-dependent kinases ↓ | [64] |
| GLP-1 RA | Liraglutide | GLP-1R expression ↓<br>EMT suppression<br>Akt/STAT3 phosphorylation↓ | [65–67] |

**Note**: The symbol "↓" represents a down-regulation or reduction of the corresponding parameter.


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## Chemically Synthesized Drugs

Metformin, a first-line therapeutic agent for T2DM, exerts its antihyperglycemic effect primarily through promoting the phosphorylation of adenosine monophosphate-activated protein kinase (AMPK) in the liver. This activity enhances insulin sensitivity and attenuates the oncogenic drive of hyperactivated insulin/IGF-1 (insulin-like growth factor-1) axis commonly observed in diabetic condition.[68] Furthermore, metformin exhibits significant capacity to inhibit cancer progression through both AMPK-dependent and AMPK-independent signaling cascades, contributing to a demonstrable reduction in overall cancer incidence.[56] Mechanistically, metformin selectively inhibits mitochondrial complex I in cancer cells. This inhibition elevates the AMP/ATP ratio, thereby activating AMPK via LKB1-mediated phosphorylation at Thr172. This activation cascades further suppress the mammalian target of rapamycin complex 1 (mTORC1), thereby impeding protein synthesis and cell proliferation.[57] Notably, tumor-selective accumulation of metformin induces a bioenergetic crisis, characterized by ATP depletion and ROS overproduction, which ultimately triggers oxidative stress and apoptosis.[58] Furthermore, multiple clinical trial data have demonstrated that metformin can improve survival rates in cancer patients via combining with radiotherapy and chemotherapy. For instance, a retrospective study enrolling 2592 patients with early or locally advanced BC revealed that among diabetic patients receiving neoadjuvant chemotherapy, those concomitantly treated with metformin achieved a pathological complete response (pCR) rate of 24%, which was significantly higher than that in diabetic patients not receiving metformin (8%) and non-diabetic patients (16%).[69] A Phase II single-arm clinical trial showed that oral administration of metformin at 2500 mg/day combined with intravenous irinotecan resulted in prolonged median progression-free survival (3.3 months, 95% CI 2.02–4.55 months) and median overall survival (8.4 months, 95% CI, 5.9–10.8 months) in colorectal cancer patients with DM.[70] Although metformin shows both anti-diabetic and anti-cancer potential, its anti-tumor efficacy is relatively modest as a single agent, especially in advanced tumors. High concentrations are required to exert significant anti-cancer effects, which are difficult to achieve via standard clinical oral administration.

Sulfonylurea agents (eg, glibenclamide) exert their insulinotropic effect primarily by stereospecifically binding to the sulfonylurea receptor 1 (SUR1) on pancreatic β-cells. This binding inhibits ATP-sensitive potassium (KATP) channels and consequently activates voltage-dependent calcium channels (VDCCs).[71] Beyond their role in glycemic control, SUR1 blockade therapy upregulates Krüppel-like factor 4 (KLF4) via phosphorylating 70 kDa ribosomal S6 kinase (p70S6K), thereby inhibiting cell growth, epithelial-mesenchymal transition (EMT), and migration.[59] Additionally, sulfonylureas have been reported to enhance the anti-cancer efficacy of chemotherapeutic agents such as doxorubicin.[60] Unfortunately, their anti-cancer effects are highly cell-type dependent and inconsistent across studies. Moreover, they carry the risk of hypoglycemia, which may limit their long-term use in cancer patients.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors function as antidiabetic agents by selectively blocking the SGLT2 receptor in the kidney, thereby impeding glucose reabsorption and promoting its excretion in the urine to decrease plasma glucose levels.[72] Substantial evidence demonstrates that SGLT2 inhibitors (eg, canagliflozin and empagliflozin) exhibit anti-cancer properties in both in vitro and in vivo models, primarily by suppressing glucose uptake in cancer cells.[61] Specifically, canagliflozin inhibits cancer cell proliferation by blocking glutamine dehydrogenase (GLDH) and mitochondrial respiratory chain complex I, leading to disruption or interruption of cellular respiration.[62,63] Additionally, empagliflozin suppresses BC cell proliferation and induces cell cycle arrest by downregulating cyclins and cyclin-dependent kinases (CDKs).[64] Notably, when used as adjunctive therapy, SGLT2 inhibitors synergistically enhance the efficacy of chemotherapy, radiotherapy, or surgical interventions, while also mitigating chemotherapy-induced adverse effects such as myelosuppression and nephrotoxicity.[73–75] While they improve both glycemic control and cancer outcomes, the long-term safety in cancer patients remains to be further validated. In addition, preclinical and clinical evidence remains insufficient to establish the safety and efficacy of SGLT2 inhibitors as anticancer agents. To date, only two clinical trials (NCT06818305, NCT05903703) are actively investigating the potential antitumor effects of these agents.

## Biological Products

Incretin-based drugs, which include glucagon-like peptide-1 receptor agonists (GLP−1 RAs) and dipeptidyl peptidase-4 (DPP−4) inhibitors, constitute a major class of antidiabetic agents for second- or third-line T2DM treatment. These drugs leverage the physiological actions of incretin hormones. Specifically, GLP-1 RAs (eg, liraglutide and semaglutide) bind to and enhance the GLP-1 receptors (GLP-1R) on the membrane of pancreatic β cells. This activation increases intracellular cyclic adenosine monophosphate (cAMP) levels, initiating protein kinase A (PKA) and cAMP-activated guanine nucleotide exchange factor 2 (Epac2) pathways, thereby promoting glucose-dependent insulin secretion.[76] DPP-4 inhibitors enhance the half-life of endogenous incretin hormones, specifically GLP-1 and GIP, by inhibiting the DPP-4 enzyme, thereby sustaining their effects on stimulating insulin secretion and inhibiting glucagon.[77]

GLP-1 RAs demonstrate significant anti-oncogenic properties. Liraglutide, for instance, has been shown to inhibit cancer cell proliferation, migration, and invasion through multiple mechanisms, including the downregulation of GLP-1R expression and the suppression of epithelial-mesenchymal transition (EMT), as well as Akt and STAT3 phosphorylation.[65–67] DPP-4 inhibitors exhibit indirect anti-cancer effects by prolonging the half-life of endogenous GLP-1 and SDF-1α, which enhances anti-inflammatory effects and regulates T-cell function to inhibit cancer immune escape.[78] Clinical trials indicate that GLP-1RAs significantly reduce the risk of multiple cancers such as gallbladder, hepatocellular carcinoma (HCC) and ovarian.[79] In T2DM patients, GLP-1RAs do not increase BC risk (RR = 0.99, 95% CI 0.48–2.01), but long-term use (>7 years) may elevate pancreatic cancer incidence.[80,81] Notably, GLP-1RAs show superior protection against colorectal cancer (CRC) compared with other antidiabetic drugs, such as insulin (HR = 0.56, 95% CI 0.44–0.72), metformin (HR = 0.75, 95% CI 0.58–0.97).[82] These data substantiate GLP-1RAs as effective anticancer agents, particularly for individuals with obesity-associated cancer risk. Despite these therapeutic benefits, the clinical utility of incretin-based drugs is constrained by potential safety concerns. Preclinical data indicate that long-term use of incretin-based drugs may carry potential risks of tumorigenesis. For example, GLP-1 RAs may be associated with an increased incidence of thyroid cancer, while DPP-4 inhibitors have been linked to an elevated risk of pancreatitis.[83]

The insulin-like growth factor-1 receptor (IGF-1R) exhibits a high degree of homology (approximately 60%) with the insulin receptor (IR). Due to this similarity, both receptors can form heterodimeric receptors (IGF-1R/IR), leading to cross-activation of downstream signaling pathways.[84] A major concern with IGF-IR inhibitors is their metabolic side effects. Studies have reported that they can promote glucagon secretion by activating the hypothalamic–pituitary–adrenal axis and exacerbate insulin resistance by disrupting normal insulin signaling.[25,85] Furthermore, although IGF-1R-targeted therapies were among the earliest developed anti-cancer strategies, current clinical trials have demonstrated that the therapeutic efficacy of IGF-1R inhibitors against cancers is unfortunately limited.[86,87]

## Natural Products

Natural bioactive components have attracted considerable attention in the field of DM-cancer prevention and treatment, attributed to their diverse biological functions and favorable safety characteristics. Consequently, natural compounds are being explored as promising candidates for DM-cancer treatment. Table 2 summarizes different natural extracts and molecules with dual regulatory functions in "DM-cancer", detailing the specific molecular targets underlying their anticancer efficacy and the mechanistic pathways mediating their antidiabetic effects.

Resveratrol, a natural polyphenol belonging to the stilbene family, possesses diverse biological activities, including antioxidant, anti-inflammatory, and anti-cancer properties. It is reported that resveratrol can exert anti-proliferative and pro-apoptotic effects on human cervical cancer cells by stimulating caspase-3 and caspase-9, inducing p53 expression, and upregulating the Bcl-2 protein.[91] Furthermore, it can prevent the proliferation of colon cancer cells and induce cell apoptosis by inhibiting the AKT/STAT3 signaling pathway. In pancreatic cancer, resveratrol limits metastasis by regulating the expressions of N-cadherin and TNF-α.[92,93] Beyond its anti-cancer capabilities, resveratrol improves insulin sensitivity by activating AMPK and sirtuin (SIRT).[88] Moreover, it enhances glucose absorption in skeletal muscle cells by rapidly stimulating endogenous GLUT4 translocation and increasing the phosphorylation of the PI3K/Akt or AMPK/Akt-dependent signaling pathways.[89,90]

**Table 2** Natural Products with Dual-Modulatory Effects DM-Cancer

| Natural Products | Therapeutic Mechanism of DM | Anti-Cancer Target |
|---|---|---|
| Resveratrol | Activating AMPK and sirtuin (SIRT)[88]<br>stimulating endogenous GLUT4 translocation and enhancing the phosphorylation of the PI3K/Akt or AMPK/Akt-dependent signaling pathway[89,90] | Caspase-3 and caspase-9, p53 expression, Bcl-2 protein[91]<br>AKT/STAT3, N-cadherin and TNF-α expressions[92,93] |
| Curcumin | Activating peroxisome proliferator-activated receptor gamma (PPARγ), and key enzymes involved in gluconeogenesis, glycolysis, and lipid metabolism[94,95] | COX-2 and EGFR expression, ERK 1/2[96]<br>cyclin D expression and p21-activated kinase 1 (PAK1)[97]<br>cell cycle and apoptosis[98] |
| Epigallocatechin Gallate | Forming reversible and non-competitive inhibitory complexes with α-glucosidase[99] | VEGF/VEGFR and activator protein-1 (AP-1) and VEGF promoters[100]<br>reactive oxygen species (ROS), Nrf2, STAT3, and PI3K/Akt, and down-regulate, EGFR, AP-1, Bcl-2, and NF-κB[101] |
| Quercetin | Promoting Akt phosphorylation and GLUT4 receptor translocation[102]<br>scavenging ROS and increasing the AMP/ATP ratio in β-cells.[103] | EGFR expression and caspase-3/-9 along with pro-apoptotic Bcl-2 family members[104,105]<br>cyclin E/D, PCNA, and Cdk-2 proteins expression[106] |
| Berberine | Reducing glycated HbA1c and triglyceride levels, decreasing leptin and resistin production, upregulating adiponectin mRNA expression[107] | p53 and p21 expression, pro-apoptotic proteins (eg, Bax), E-cadherin and MMPs expression, ERK/MAPK, NF-κB, and AP-1[108] |

Curcumin (CUR), a natural polyphenolic compound of dihydroxy-diphenylheptane derived from *Curcuma longa*, exhibits diverse biological activities, including anticancer, antidiabetic, antioxidant, and anti-inflammatory effects. As an established anticancer agent, CUR modulates multiple oncogenic signaling pathways and has been reported for the treatment of various solid tumors.[109] For instance, it demonstrates anticancer activity in lung adenocarcinoma by inhibiting the expression of cyclooxygenase-2 (COX-2) and epidermal growth factor receptor (EGFR), alongside suppressing the activity of extracellular signal-regulated kinase (ERK) 1/2.[96] Additionally, CUR significantly reduces cyclin D expression and inhibits p21-activated kinase 1 (PAK1) activity, thereby suppressing gastric cancer cell proliferation.[97] Notably, CUR has been reported to prevent colorectal cancer proliferation by blocking the cell cycle and accelerating apoptosis.[98] As for DM management, CUR exerts hypoglycemic effects through dual mechanisms: i. promoting insulin secretion by the activation of peroxisome proliferator-activated receptor gamma (PPARγ), ii. enhancing hepatic metabolic function by activating key enzymes involved in gluconeogenesis, glycolysis, and lipid metabolism.[94,95]

Epigallocatechin Gallate (EGCG), a catechin flavonoid compound, exhibits remarkable biological activities such as antioxidant, anti-inflammatory, and anticancer effects. For example, EGCG not only directly antagonizes the VEGF/VEGFR axis but also suppresses VEGF transcription by interfering with the DNA-binding activity of activator protein-1 (AP-1) and VEGF promoters, thereby inhibiting angiogenesis of BC.[100] Furthermore, ECGG promotes the accumulation of ROS and activates Nrf2 signaling pathways to inhibit the expression of NAF-1 in pancreatic cancer, ultimately enhancing the sensitivity of pancreatic cancer cells to gemcitabine.[110] It also has been reported to prevent various solid tumors (such as cervix cancer, ovarian cancer, etc) via activating apoptotic signaling pathways (such as STAT3, and PI3K/Akt), and down-regulating proteins associated with cancer cell anti-apoptosis (eg, EGFR, AP-1, Bcl-2, and NF-κB).[101] As for the anti-DM effect, EGCG reduces glucose absorption by forming reversible and non-competitive inhibitory complexes with α-glucosidase, thereby reducing postprandial glucose absorption.[99]

Quercetin (Qu), a prominent polyphenolic flavonoid compound, exhibits diverse biological activities, notably anti-oxidant, anti-inflammatory, antibacterial, and anti-cancer effects. For example, Qu has been reported to induce apoptosis in CRC by decreasing the expression of ErbB2 and ErbB3 proteins and directly activating caspase-3/-9.[104] In addition, it

also induces apoptosis, downregulates EGFR expression, and pro-apoptotic Bcl-2 family members in hepatoma cells.[105] Furthermore, Qu arrests cancer cell cycle progression by suppressing the expression of key regulatory proteins, including cyclin E/D, proliferating cell nuclear antigen (PCNA), and cyclin-dependent kinase 2 (CDK2), while concurrently increasing the expression of the inhibitory proteins p21 and p27.[106] As bioflavonoids are recognized as potential therapeutic agents for diabetes and its complications, quercetin enhances glucose metabolism via dual pathways: i. enhancing cellular glucose uptake by promoting Akt phosphorylation and GLUT4 receptor translocation;[102] ii. promoting mitochondrial biogenesis and insulin secretion by scavenging ROS and increasing the AMP/ATP ratio in β-cells.[103]

Berberine (BBR), an isoquinoline alkaloid extracted from *Coptis* species, exhibits diverse biological activities, including antibacterial, anti-inflammatory, and anti-cancer effects. In detail, BBR suppresses non-small cell lung cancer (NSCLC) cells growth by enhancing the protein expression of p53 and p21 and activating pro-apoptotic proteins (eg, Bax). Additionally, it effectively inhibits tumor metastasis through upregulating E-cadherin expression, suppressing matrix metalloproteinases (MMPs), and blocking critical metastasis-associated signaling pathways, including ERK/MAPK, NF-κB, and AP-1.[108] In the context of glucose metabolism, BBR improves insulin sensitivity and ameliorates lipid metabolism, evidenced by a reduction in glycated hemoglobin A1C (HbA1c) and triglyceride levels. It also modulates adipokine secretion through upregulating adiponectin mRNA expression while simultaneously decreasing leptin and resistin production, thereby mitigating hyperglycemia and reducing risks associated with metabolic syndrome.[107]

However, all these natural products universally suffer from extremely low oral bioavailability due to poor solubility, gastrointestinal instability, rapid metabolism, and difficulty in achieving clinically effective concentrations, as well as challenges in standardized quality control, leaving most in the preclinical stage.

## Nanotechnology-Based Formulations for Diabetes: Harnessing Their Antitumor Efficacy in Diabetes-Associated Cancer

Current research on antidiabetic drugs and their delivery systems remains underdeveloped, with critical challenges persisting in multiple areas. At first, the occurrence and development of DM patients with cancer are often accompanied by more complicated pathophysiological processes, presenting more challenges for diagnosis and treatment. Furthermore, some agents (such as biological drugs and natural products) exhibit limitations under physiological conditions, including low-targeting efficiency, poor bioavailability, and suboptimal patient compliance, all of which require urgent resolution. To figure out these challenges, novel therapeutic drugs based on drug delivery systems (DDS) have been developed. This section provides a comprehensive overview of the use of DDS in regulating the DM-cancer axis and fighting DM-associated cancer. We will specifically focus on nanoconstruction approaches and the therapeutic mechanisms employed.

### Nanotechnology-Based Strategies for Diagnosis and Treatment

Accurate, early diagnosis paired with targeted treatment is essential for managing diseases, especially the complex comorbidity of DM and cancer, where delayed intervention severely exacerbates pathological progression and complications. However, traditional diagnostic approaches, including fasting blood glucose tests, HbA1c assays, and oral glucose tolerance tests, often fail to capture subtle biomarker changes or require invasive sampling. Additionally, the diagnosis of DM patients with cancer is confronted with unique challenge, arising from the pathophysiological interplay between the two diseases, microenvironmental alterations that interfere with standard imaging techniques, and the general inability of conventional technologies to adapt to this "dual pathological state". Nanotechnology, characterized by tunable physicochemical properties such as high specificity, sensitivity, and multi-modal functionality, has emerged as a transformative platform to revolutionize diagnosis, offering tailored solutions for single diseases and complex comorbidities alike. For example, Chen et al[111] developed chitosan-modified copper nanoclusters (AP-CuCC) via encapsulating copper (Cu) nanoparticles within chitosan, followed by electrostatically driven immobilization of glucose oxidase (GOx) and $Ce^{3+}$. These nanoclusters exhibit exceptional peroxidase (POD)-mimetic activity and $Ce^{3+}$-mediated aggregation-induced emission (AIE) properties (Figure 2Ai). As shown in Figure 2Aii–iii, the fluorescence emission of AP-CuCC is

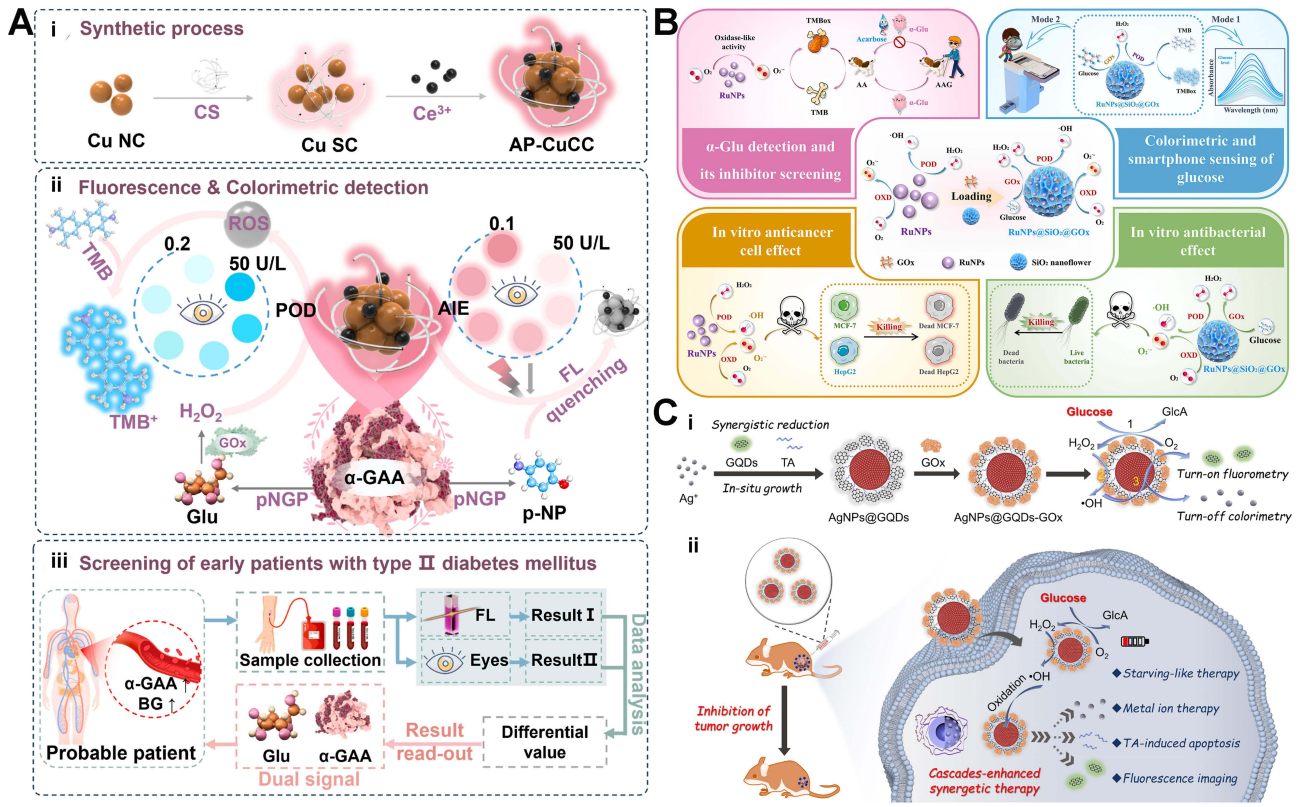


**Figure 2** Nanotechnology-based strategies for diagnosis and treatment. (**A**i–iii) the self-assembled colorimetric-fluorescence dual-mode biosensor for the codelivery of α-glucosidase and peroxidase for early diabetic screening. Reprinted with permission from Chen Z, Zhang Y, Teng R, et al. AIE multifunctional probe empowering colorimetric-fluorescence dual-mode biosensor for early diabetic screening, Biosens Bioelectron 269 (2025) 116941 Copyright © 2025[111] with permission from Elsevier. (**B**) The synthesis route and mechanism of RuNPs@SiO2@GOx-based multifunctional nanoreactor with oxidase (OXD)-mimetic and peroxidase (POD)-like activity for diabetes diagnosis and anti-cancer therapy. Reprinted with permission from Wang L, Zheng S, Lin X, et al. A RuNPs-based multifunctional nanoplatform with excellent dual enzyme-mimic activities for diabetes diagnosis, cancer cell elimination, and in vitro antibacterial, Talanta 283 (2025) 127121. Copyright © 2025[113] with permission from Elsevier. (**C**i–ii) The dual-mode glucose nanosensor for cancer cell recognition and enhanced synergistic therapy of lymph cancer via glucose-triggered cascaded catalytic reaction. Reprinted with permission from Hai X, Zhu Z, Yu K, et al. Dual-mode glucose nanosensor as an activatable theranostic platform for cancer cell recognition and cascades-enhanced synergetic therapy, Biosens Bioelectron 192 (2021) 113544. Copyright (2021)[114] with permission from Elsevier. All arrows represent direction indicators.

selectively quenched upon interaction with p-nitrophenol (p-NP), a hydrolytic product of α-glucosidase (α-GAA)-catalyzed reactions. Simultaneously, the nanoclusters' POD-like activity enables colorimetric changes via catalytic responses to hydrogen peroxide ($H_2O_2$) generated by GOx-mediated glucose oxidation. The dual-modal detection platform, by integrating both fluorescence and colorimetry, demonstrated enhanced diagnostic precision for early DM, evidenced by a 50% reduction in the false positive rate and a 25% reduction in the false negative rate compared to relying solely on colorimetry. To further enhance cancer-specific detection in DM patients, researchers have utilized disease-specific biological features to design targeted nanosensors. Li et al[112] focused on nitric oxide (NO), a molecule that is overproduced under hyperglycemic conditions, to develop an NO-responsive nanoprobe for cancer cell recognition. The team initially synthesized a nanoscaffold, ICR-Qu, by replacing the electron-donating moiety in ICG with Si-xanthene. They further incorporated diverse NO-reactive sites into this scaffold to create the DNO nanoprobe, which possesses both near-infrared II (NIR-II) fluorescence and photoacoustic (PA) imaging capabilities. To improve biocompatibility and functionality, DNO was encapsulated within water-soluble DSPE-polyethylene glycol 2000 (DSPE-PEG2000) via nanoprecipitation to fabricate DNPS with fluorescence/photoacoustic (FL/PA) imaging functionality. DNPS exhibited several advantages, including low intrinsic background, high sensitivity, and deep tissue penetration. This allows for the detection of DM by quantification of excessive NO levels and the simultaneous imaging of BC. Furthermore, DNPS distinguish the NO expression patterns between diabetic BC and nondiabetic BC models, thereby addressing the critical need to differentiate disease-specific pathological changes in comorbid conditions. Notably, DNPS exhibits favorable tumor-targeting capability by accumulating in BC tissues via the EPR effect following tail vein injection, showing

significantly stronger fluorescence signals in DMBC than in BC over 48 hours, which suggests that DM-associated hyperglycemia enhances its tumor accumulation. Besides, DNPS exhibited no toxicity toward other normal tissues.

However, the diagnosis and treatment of DM patients with cancer are also hindered by the complexity of their "dual pathological state" and the inability of traditional therapeutic strategies to simultaneously address two diseases. To overcome this, researchers have increasingly explored the potential of nanomedicines, utilizing their modular structural designs and functional advantages (eg, enzyme-mimetic activities, glucose responsiveness) to develop integrated multi-functional platforms capable of integrating DM diagnosis, cancer detection, and anti-cancer therapy. For example, Li's team[113] developed a multi-functional ruthenium nanoparticle (RuNPs) to integrate DM diagnosis with anti-cancer therapy (Figure 2B). Through a simple one-pot solvothermal reaction, they synthesized RuNPs with excellent oxidase (OXD)- and POD-activities, making them suitable for one-step detection of blood glucose under near-neutral condition. Building on this, they constructed the RuNPs@$SiO_2$@GOx nanoreactor by encapsulating RuNPs and GOx within $SiO_2$. This system not only enables colorimetric detection of hyperglycemia but also converts high glucose levels in the diabetic TME into $H_2O_2$, which further generates cytotoxic ROS via the nanozyme activity of RuNPs, thereby achieving synergistic glucose-consuming metabolic therapy and chemodynamic therapy for cancer. For DM diagnosis, RuNPs@$SiO_2$@GOx utilizes GOx to catalyze the oxidation of high-concentration glucose in the comorbid microenvironment to generate $H_2O_2$, which is then utilized by the RuNPs' POD activity to oxidize colorless TMB into blue TMBox, enabling the quantitative detection of glucose. In detail, RuNPs@$SiO_2$@GOx nanoparticles perform excellently in DM-related detection: α-Glu activity assay (linear range 1–150 U $L^{-1}$, LOD 0.19 U $L^{-1}$, $R^2$= 0.993; serum recoveries 94.7%–107.3%, RSD < 6%); α-Glu inhibitor screening (acarbose as model, linear range 0.5–50 μM, $IC_{50}$= 4.64 μM); glucose detection (RuNPs@$SiO_2$@GOx/TMB: linear range 0.8–80 μM, LOD 0.19 μM, $R^2$= 0.990; smartphone-assisted method: linear range 1–100 μM, LOD 0.31 μM), both consistent with clinical results (relative error < ±9%). For anti-cancer therapy, this nanosystem can induce $H_2O_2$ (derived from glucose) and dissolved $O_2$ to generate ROS, including $O_2\cdot^-$ and ·OH, which exert significant anti-cancer effects. In detail, RuNPs treatment increased the apoptosis rate of MCF-7 and HepG2 cells to ~68% and ~72%, respectively, which further elevated the dead cell ratio to ~91% and ~94% after RuNPs+$H_2O_2$ treatment in vitro. This approach highlights how high-level glucose, a defining characteristic of DM and a primary nutrient for cancer metabolism, can be repurposed as a therapeutic fuel for integrated comprehensive diagnosis and therapeutic strategies.

Hai et al[114] focused on the shared hallmark of both diseases to engineer a glucose-responsive nanosensor tailored. Specifically, their approach involved the in-situ synthesis of silver nanoparticles (AgNPs) via the synergistic reductive action of tannic acid (TA) and graphene quantum dots (GQDs), followed by surface functionalization with GOx to obtain AgNPs@GQDs-GOx (Figure 2Ci). This nanosensor realizes glucose-responsive imaging for both DM diagnosis and cancer localization, and simultaneously triggers a cascade therapeutic process: glucose triggers GOx-catalyzed reaction to produce $H_2O_2$, and $H_2O_2$ further induces the degradation of AgNPs to release $Ag^+$ and TA for combined metal ion therapy and pro-apoptotic therapy, thus achieving integrated diagnosis and synergistic treatment of the comorbidity. As shown in Figure 2Cii, GOx catalyzes the oxidation of glucose into gluconic acid (GlcA) and $H_2O_2$. Subsequently, GQDs (with POD-mimetic activity) convert $H_2O_2$ into hydroxyl radicals ·OH, which further oxidize metallic silver ($Ag^0$) to silver ions ($Ag^+$). This reaction reduces the UV-visible absorbance of AgNPs@GQDs-GOx and recovers GQDs fluorescence to enable the precise imaging of both the hyperglycemic state (for DM) and excessive-glucose TME (for cancer). More importantly, this diagnostic process is inherently linked to cascaded anti-cancer therapy, addressing the therapeutic needs of comorbid patients. The produced $H_2O_2$ accelerates the degradation of AgNPs@GQDs-GOx, releasing anti-cancer agents: $Ag^+$ (for enhanced metal ions therapy) and TA (for inducing apoptosis). In addition, AgNPs@GQDs-GOx exhibits excellent tumor-targeting ability by specifically recognizing cancer cells and producing strong fluorescence signals in a glucose-dependent manner, while showing no obvious signal in normal cells, and GOx decoration is essential for such selective recognition. These mechanisms achieve a cascades-enhanced synergetic therapy of lymph cancer. As a result, AgNPs@GQDs-Gox effectively induced 55.3% cancer cells to undergo apoptosis in vitro, with in vivo studies showing a cancer suppression rate of up to 50.9%. AgNPs@GQDs-GOx also exhibits low toxicity side effects and high biosafety in vivo, as H&E staining of major organs shows no obvious histopathological abnormalities compared with the PBS group.


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## Nanotechnology-Based Strategies for Oral-Delivery

Oral delivery is universally recognized as the most patient-compliant administration route, yet it remains a persistent challenge for two critical classes of therapeutic agents (biologics and natural products) due to the harsh gastrointestinal (GI) microenvironment and multiple biological barriers. Biological drugs (eg, insulin and GLP-1 analogs), mostly proteins or peptides, are prone to degradation by enzymes (such as GI enzymes and proteases) and inactivation under extreme pH fluctuations (such as gastric acid environment), forcing them to rely heavily on invasive injectable routes. Nanotechnology, characterized by its adjustable structural and functional properties, has emerged as a transformative solution to overcome these limitations. By serving as a protective shell through physical encapsulation or chemical conjugation, it effectively isolates them from external degradation factors and facilitates their translocation across GI barriers to enable oral delivery. For example, Ding et al[115] focused on the oral delivery of liraglutide (a GLP-1 analog) and prepared bovine serum albumin (BSA)-modified cationic liposomes (Figure 3A). In detail, they prepared cationic liposomes as the core carrier for liraglutide via double emulsion method, further coating the liposome surface with BSA

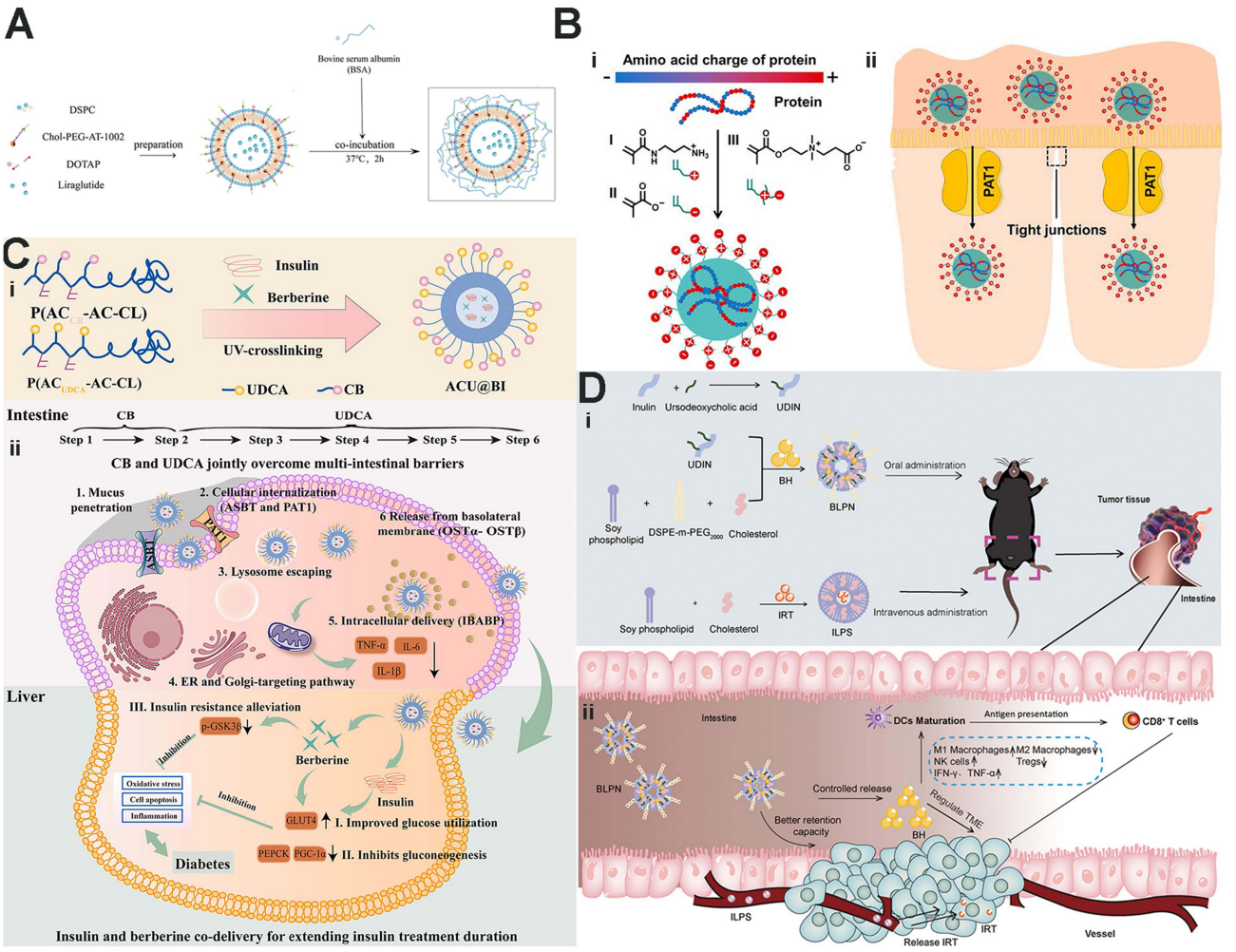


**Figure 3** Nanotechnology-based strategies for oral-delivery. (**A**) The BSA-modified Corona cationic liposomes delivery system of liraglutide for facilitating oral administration.[115] (**B**i-ii) The polyzwitterion-based protein encapsulation strategy allows for effective oral delivery of different proteins to enhance efficiency of hypoglycemic and anti-cancer treatment. Reprinted with permission from Fang HP, Chen LF, Deng Z, et al. In Situ Polymerization of Zwitterions on Therapeutic Proteins to Enable Their Effective Oral Delivery Abstract, ACS Nano (2023). Copyright © 2023[116] American Chemical Society. With permission from Elsevier (**C**i-ii) The liver-targeted zwitterionic nanoparticles (ACU@BI) for the codelivery of insulin and berberine for extending insulin treatment duration. Reprinted with permission from Ma Y, Li C, Han F, et al. Oral delivery of berberine by liver-targeted zwitterionic nanoparticles to overcome multi-intestinal barriers and extend insulin treatment duration, Chemical Engineering Journal 485 (2024). Copyright (2024).[117] With permission from Elsevier. (**D**i-ii) The oral berberine-delivery system enhances the orthotopic colorectal cancer chemotherapy via berberine-mediated immunoregulatory effect. Reprinted with permission from Xia A, Yuan W, Xu S, et al. A prebiotic inulin derivative-containing liposome for oral berberine delivery improves the orthotopic colorectal cancer chemotherapy, Nanoscale 17(25) (2025) 15448–15463. Copyright (2025)[118] Royal Society of Chemistry. All arrows represent direction indicators.

through electrostatic interactions to form PcCLs/Pc-AT-CLs liposomes. The BSA-modified liposomes design enhances its permeability through the mucus barrier while simultaneously improving encapsulation efficiency, drug stability, and controlled-release properties, demonstrating promising potential for efficient liraglutide delivery. Both PcCLs and Pc-AT-CLs nanoparticles show excellent in vivo biosafety with no obvious pathological changes or inflammatory reactions in major organs after oral administration for one week. Furthermore, Liu and Chen et al[116] developed a representative zwitterion-based strategy to enhance the oral bioavailability of biologics. They involve in-situ encapsulating proteins, including BSA, antibodies and insulin, with zwitterions to form polyzwitterion/protein nanocomplexes, which were then loaded into enteric-coated capsules (Figure 3Bi). As shown in Figure 3Bii, the enteric-coated capsules remain stable in GI environment and degrade upon entering the neutral intestinal lumen to release the nanocomplexes. With the help of polyzwitterion modification, nanocomplexes reduce nonspecific adsorption to GI mucus (reducing clearance) and enable active transport by the proton-assisted amino acid transporter 1 (PAT1) pathway, thereby improving the bioavailability of oral insulin (16.9%) and immunoglobulin G (IgG) (12.5%). Research shows that M8 nanoparticles/insulin (20 IU/kg oral) achieve 16.2% bioavailability, lower blood glucose to 36.7% (mice)/46.6% (rats)/50.6% (pigs) of initial values, and maintain hypoglycemia for 8 h, significantly superior to those of free insulin (2% bioavailability and 62.2% of initial value). In tumor therapy, free oral αPD-1 (5 mg/kg) barely inhibits tumor growth, and M8 nanoparticle/αPD−1 capsules (5 mg/kg) achieve 67.7% (B16F10) and 65.7% tumor growth inhibition rates. The enteric-coated capsules exhibit outstanding biocompatibility: negligible in vitro cytotoxicity, no significant elevation in serum endotoxin or pro-inflammatory cytokine levels, intact intestinal villus architecture, and no overt intestinal inflammation following long-term repeated oral administration.

Beyond biologics, nanotechnology also addresses the oral delivery bottlenecks of natural products. Although these compounds offer unique therapeutic advantages (such as multi-target efficacy and low toxicity) due to their complex chemical structures, approximately 70% exhibit poor solubility and bioavailability, circumscribing their therapeutic potential. This poor pharmacokinetics makes up to 90% of natural products with pharmacological activity to be excluded during new drug screening processes.[119] Nanocarriers overcome these limitations by acting as solubility enhancers for hydrophobic natural products and barrier protectors against gastrointestinal (GI) enzyme degradation. Qian et al[117] exemplified this with a liver-targeted oral-delivery nanoparticle (ACU@BI) for co-delivery of BBR and insulin (Figure 3Ci). Fabricated via solvent exchange and UV-crosslinking techniques, the nanoparticles used poly(acryloyl carbonate-co-caprolactone) (P(AC-CL)) as the biodegradable core, ursodeoxycholic acid (UDCA) as the liver-targeting ligand, and carboxy betaine (CB) as the mucus-penetrating modifier. As shown in Figure 3Cii, UDCA enabled specific recognition of bile acid transporters on intestinal epithelial cells and hepatocytes, boosting both intestinal absorption and liver accumulation of the nanoparticles, while CB reduced mucus adhesion to further improve GI transit. In DM models, this oral co-delivery achieved synergistic effects: BBR not only reverses insulin resistance primarily by facilitating the AMPK/AKT/IRS-1 signaling pathway but also prolongs the duration of insulin therapy by inhibiting GSK3-β activity, highlighting nanotechnology's role in optimizing natural product-biologic combinations (Figure 3iii). Compared with control small-molecule drugs (free insulin, free BBR), the ACU@BI exhibit superior therapeutic effects in DM treatment: oral low dose (insulin 25 U/kg + BBR 30 mg/kg) achieves approximately 10 h sustained hypoglycemia (vs insulin and BBR's 2 h), with fasting blood glucose decreasing by 2.42-fold vs the diabetic model group and significantly reduced HbA1c after 4-weeks administration. Compared with control small-molecule drugs via BBR-insulin synergy, insulin dosage is reduced by 50% while maintaining efficacy, and its crosslinked structure protects drugs from (GI) enzyme degradation without damaging intestinal tight junctions, improving biosafety. In addition, ACU@BI also exerts beneficial regulatory effects on serum lipids, oxidative stress, renal function, and inflammatory responses while improving glycogen storage and causing no obvious toxic damage to major organs as verified by H&E staining. Yin et al[118] further expanded nanotechnology's application for natural products with a colon-targeted oral nanoparticle (BLPN) for co-delivery of BBR and regorafenib (Figure 3Di). As shown in Figure 3Dii, this system was constructed by loading BBR into hybrid liposome containing a prebiotic inulin derivative (inulin-UDCA) and encapsulating regorafenib within the liposome core. Following oral administration, BLPN is specifically hydrolyzed by inulinase in the colon and releases drugs, which prolongs the retention time of BBR in the intestines and enhances the therapeutic efficacy of regorafenib. Besides, BLPN significantly enhances intestinal retention, improves drug accumulation in CRC, while causing no

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obvious pathological damage to major organs, intestinal mucosal injury, or systemic toxicity, thus exhibiting superior tumor-targeting ability and excellent biosafety.

## Nanotechnology-Based Strategies for Targeted Delivery

Traditional clinical drugs, including synthetic or natural drugs, exhibit non-specific distribution. This challenge is amplified in DM patients with cancer, where pathological alterations create multiple barriers within target tissues, critically contributing to suboptimal therapeutic outcomes. Nanotechnology allows for the modification of targeting ligands on the surface, which can specifically recognize lesion tissues (eg, pancreatic β cells, liver, and cancer), thereby enhancing the drug enrichment efficiency at lesion sites. Thus, nanotechnology provides an effective strategy to address these challenges, paving novel avenues for treating DM patients with cancers through constructing target-delivery systems.

First, nanocarrier engineering for prolonged circulation and passive targeting lays the foundation for effective delivery. For example, Qin team[120] engineered CUR-encapsulated liposomes via ethanol injection, and further incorporated poly(ethylene glycol) 2000 (PEG2000) into the bilayer of liposomal vesicles to develop long-circulating CUR-loaded liposomes (CUR-LPs). This design significantly improved CUR's bioavailability and enhanced therapeutic efficacy compared to oral administration of free CUR. Moreover, CUR-LPs exhibited metabolic benefits, alleviating insulin resistance by downregulating the expression of hepatic inflammatory factors (TNF-α and IL-6) and upregulating the levels of SOD and GSH. Notably, similar liposomal nanomedicines co-encapsulating curcumin and docetaxel (DTX) have demonstrated the ability to reverse multidrug-resistance BC, while simultaneously ameliorating DTX-induced cytotoxicity and apoptosis. In addition, this nanoparticle causes no pathological damage to major organs and reduces drug exposure in non-targeted tissues to diminish overall toxicity while enhancing antitumor effect.[121]

Second, surface functionalization with target-specific ligands enables active targeting to disease-specific cells or tissues. For example, Chen's team[122] constructed nanoparticles with dual enzymatic activities by incorporating GOx and manganese ions ($Mn^{2+}$). They further modified the particle surface with hyaluronic acid (HA), a ligand that specifically binds to CD44 receptors overexpressed on cancer cells, to get cancer-targeting nanoparticle GOx-Mn/HA. In detail, compared with GOx and GOx-Mn, GOx-Mn/HA significantly enhanced the cellular uptake in 4T1 cells via specific CD44-HA recognition in vitro and markedly increased accumulation at the tumor site 24 hours after intravenous administration. This nanomedicine not only accelerates glucose consumption through the catalytic effects of manganese nanozymes and GOx to inhibit tumor growth but also induces proptosis and increases PD-L1 expression in cancer cells, thereby triggering a strong anti-cancer immune response. Meanwhile, GOx-Mn/HA displays no obvious long-term toxicity, with liver and kidney function indexes comparable to the PBS group, demonstrating high biocompatibility.

Third, biomimetic modification enhances homologous targeting and biocompatibility to further refine delivery precision. For example, Wang & Song et al[123] engineered ultra-small platinum nanoparticles (GP) within GOx and further used biomimetic strategy to encapsulate them in cancer cell membranes that enhance GP's targeting ability and biocompatibility, ultimately obtaining GP biomimetic nanomedicines (GPNP@M). These nanomedicines exhibit exceptional BC bone tumor-targeting efficiency, with a pronounced accumulation detected at the metastatic bone lesions within just 2 hours post-administration, and this high-level retention persisted for up to 24 hours, highlighting its superior capability to localize precisely at bone tumor sites. In addition, it also exerts potent anti-tumor effects by consuming glucose through self-amplifying enzymatic activity, which induces cancer cell pyroptosis and exerts targeted chemotherapy in the high-oxidation-potential TME, thereby effectively inhibiting the progression of BC bone metastases.

Finally, synergistic targeting strategies are employed to combine multiple mechanisms for enhanced therapeutic precision. Zhu et al[124] constructed a synergistic targeted delivery system by conjugating superparamagnetic iron oxide nanoparticles (SPIONs), a magnetic nanoplatforms by applying a magnetic force (MF), to the surface of Qu-loaded human mesenchymal stem cell (huMSC)-derived exosomes. Specifically, transferrin-modified SPIONs nanoparticles (Tf-SPIONs) were synthesized through the chemical conjugation of Tf with SPIONs and then self-assembled them with Qu-loaded huMSC-derived exosomes to form Qu-exosome-SPIONs. This nanomedicine exhibited excellent targeting ability to pancreatic tissues under the influence of MF and significantly elevated Qu's concentration in islets. In detail, the external MF significantly promotes the accumulation of Qu-exosome-SPIONs on the surface of MIN-6 cells and greatly

enhances the cellular uptake of quercetin. In vivo, Qu-exosome-SPIONs/MF achieved approximately 11.5-fold higher fluorescence intensity in pancreatic islets at 10 min and 37.5-fold higher at 30 min compared with the free quercetin group, while no obvious targeting enhancement was observed in the absence of MF. After treatment, Qu-exosome-SPIONs effectively inhibited or attenuated β-cell apoptosis and promoted insulin secretion by reducing iNOS expression, NO level, and counteracting NF-κb activation, thereby facilitating the restoration of islet function. SPIONs-based Qu nanomedicine, guided by an external magnetic field, can effectively accumulate in BC tissue, significantly induce cells morphological changes, reduce the number of viable cells by approximately 70%, and increase the apoptotic cell population by 34%.[125]

## Clinical Applications of New Developed Nanotechnology

The newly developed nanotechnologies and materials introduced in the aforementioned sections exhibit significant potential for clinical applications, supported by their favorable biocompatibility, high safety, proven preclinical efficacy, and the integration of clinically relevant components. This section systematically summarizes the clinical applications of these nanomaterials, directly addressing the key concern regarding their clinical applicability.

To begin with, chitosan, as the core component of AP-CuCC nanoclusters, has shown promising potential in multiple clinical trials. For instance, both free miconazole and miconazole-loaded chitosan nanoparticles have demonstrated comparable efficacy in alleviating symptoms of oral candidiasis and reducing candida colonization.[126] In addition, AgNPs, characterized by their outstanding biocompatibility, have been extensively investigated in preclinical studies and early-phase clinical trials for various therapeutic applications, including local antibacterial therapy, wound healing, dentistry, and the prevention of implant-related infections.[127,128] Notably, AgNPs/chitosan-starch nanobiocomposites have exhibited significant inhibitory effects against human malignant melanoma, highlighting the versatility of chitosan/AgNPs-based formulations.[129]

Furthermore, as a core material of PEGylated liposomal drugs approved by the FDA and EMA, DSPE-PEG2000 has become a key component of several clinically approved formulations, such as doxorubicin liposomes (Caelyx®) and irinotecan liposomes (ONIVYDE®).[130,131] Its widespread use underscores its established role in clinical nanomedicine. In terms of DDS, cationic liposomes, due to their positively charged surface, can effectively form electrostatic interactions with negatively charged drugs (including nucleic acids and proteins), enabling efficient drug delivery. Clinically, cationic lipid-based nanoparticles have achieved remarkable success in vaccine development (eg, plasmid DNA and mRNA vaccines) and the delivery of chemotherapeutic agents (eg, paclitaxel), demonstrating their broad clinical utility.[132,133]

Finally, HA has been widely researched and applied in clinical practice due to its excellent biocompatibility, biodegradability, and specific targeting ability to CD44 receptors. Clinical trial data have confirmed that HA-modified drugs exhibit significant advantages in improving tumor-targeted delivery, reducing systemic toxicity, and enhancing therapeutic efficacy.[134] Furthermore, HA nanoparticles have been approved for clinical use in tissue engineering, wound healing, osteoarthritis, and ophthalmic applications, showcasing their diverse clinical applications beyond oncology. Moreover, owing to its excellent biocompatibility and stability, $SiO_2$ is commonly used clinically as a material for implantable medical devices, such as certain biosensors and stents, further validating the clinical relevance of these nanomaterials.[135]

## Discussion

Increasing evidence suggests that traditional therapeutic regimens encounter substantial challenges when treating patients coexisting DM and cancer. At first, conventional pharmaceuticals already face issues such as limited efficacy and significant side effects when used in the treatment of single diseases. These limitations are compounded in the comorbid state, as traditional agents lack the precision to simultaneously target the critical pathological cascades underlying both conditions. Furthermore, the reliance on combination drug regimens often introduces a high risk of drug-drug interactions, severely compromising overall therapeutic safety and efficacy. Nanomedicines offer novel therapeutic prospects for this comorbidity by enabling dual intervention in DM-related pathological processes (such as hyperglycemia and insulin resistance) and key cancer progression events, including cancer cells proliferation, invasion, and metastasis.

However, for nanomedicine technologies to achieve widespread clinical adoption, several critical issues remain to be addressed. First, most nanomedicines remain at the preclinical research stage, and their long-term biosafety, metabolic fate, and potential organ accumulation need further systematic evaluation. Second, the pharmacokinetics and targeting efficiency of nanomedicines are easily affected by individual differences and TME heterogeneity, leading to unstable therapeutic effects in vivo. Third, the preparation process of some nanoplatforms is complicated, which limits large-scale production and standardized quality control. In addition, potential issues such as protein corona formation, immune recognition, and accelerated blood clearance effect may reduce the delivery efficiency and therapeutic performance. Consequently, large-scale, multi-center clinical studies are urgently needed to rigorously validate the efficacy and safety profiles of these nanosystems, establishing a robust scientific foundation for their clinical implementation.

Notwithstanding the current challenges, future advances in nanomedicines for the treatment of DM patients with cancer are expected to focus on several pivotal directions to address these unresolved issues: i. designing biodegradable, stimuli-responsive, and highly specific nanosystems to further improve safety and targeting accuracy; ii. constructing multimodal theranostic platforms that can dynamically monitor disease status and achieve on-demand drug release; iii. optimizing preparation processes to realize scalable, reproducible, and clinically compliant production; iv. carrying out rigorous preclinical evaluation and clinical trials to promote the clinical translation of nanomedicines for diabetes, cancer, and their comorbidities.

## Conclusion

The effective management and treatment of DM patients with cancer remain a crucial and unmet clinical need. Although significant progress has been made in elucidating the underlying molecular mechanisms linking these two pathologies, extensive further investigation is still required to bridge the gap between basic research and clinical practice.

This review systematically summarizes the therapeutic challenges of traditional regimens in DM-cancer comorbidities and the innovative potential of nanomedicines, as well as the key barriers hindering their clinical translation. We sincerely hope this review inspires the design and fabrication of tailored drugs and nanosystems for the treatment of DM with cancer disease, propelling this amalgamated treatment approach into tangible clinical applications, thereby enhancing the treatment efficacy for DM patients with cancer.

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## Disclosure

The authors declare no conflicts of interest in this work.

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