J Iraqi Soc Pharm Sci. 2026;1(1):28-39. Publication of The Iraqi Society of Pharmaceutical Sciences

Review Article

Critical Review of Sitagliptin Efficacy as Anticancer Agent: Hope or Hype?

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Received: 5 July 2026; Revised: 5 August 2026; Accepted: 11 August 2026

Abstract

Sitagliptin, a widely prescribed DPP-4 inhibitor for type 2 diabetes, has been implicated in both protective and harmful cancer associations, yet the totality of evidence remains unresolved. This narrative review synthesized evidence from 35 original articles (2010-2026) across in silico, in vitro, in vivo, and clinical investigations. In silico docking predicts high-affinity binding to DPP4, CTNNB1, MET, CD24, and SOX4. In vitro studies demonstrate antiproliferative, pro-apoptotic, and anti-migratory effects across multiple cancer cell lines; however, most used suprapharmacological concentrations (25-100 times therapeutic levels), raising clinical relevance concerns. In vivo studies show tumor suppression in hepatocellular carcinoma, prolonged survival in ovarian cancer, and protective effects in colon cancer models, though one study reported promotion of breast cancer metastasis. Clinical evidence is contradictory: meta-analyses show no overall increased cancer risk (OR 0.91-0.93), while Taiwanese cohort studies report protective effects for breast (HR 0.718), prostate (HR 0.613), and oral cancers (HR 0.345), but increased risks for pancreatic (HR 1.40-1.50) and thyroid (HR 1.52) cancers. Large Japanese and TECOS trials found no increased risk. Proposed mechanisms include immune modulation via CXCL10/CXCR3-mediated CD8+ T-cell trafficking, AMPK activation, HIF-1α suppression, NF-κB inhibition, epigenetic modulation, and apoptosis induction. Despite promising preclinical evidence, concentration disconnect and inconsistent clinical outcomes preclude clinical recommendation of sitagliptin as an anticancer agent. Metformin remains preferred in cancer patients; however, no strong evidence supports discontinuing sitagliptin, except possibly in those with a pancreatic cancer history. Prospective biomarker-driven trials are urgently needed.

Keywords: Cancer; Dipeptidyl peptidase-4 inhibitor; DPP-4; Drug repurposing; Sitagliptin.

مراجعة نقدية لفعالية سيتاجليبتين كعامل مضاد للسرطان: أمل أم مجرد ضجة؟

الخلاصة

إن عقار سيتاغليبتين، المثبط واسع الاستخدام لأنزيم DPP-4 في علاج السكري من النوع الثاني، ارتبط بتأثيرات متضاربة مع السرطان، إذ تشير بعض الدراسات إلى تأثيرات وقائية وأخرى إلى تأثيرات ضارة، ولا يزال الدليل الإجمالي غير حاسم. استعرض هذا المقال السردي الأدلة من 35 دراسة أصلية (2010-2026) شملت تحليلات حاسوبية، ودراسات مخبرية وحيوانية وسريرية. أظهرت الدراسات الحاسوبية ارتباطاً عالياً لسيتاغليبتين بالبروتينات الورمية DPP4 و CTNNB1 و MET و CD24 و SOX4. وأثبتت الدراسات المخبرية تأثيرات مضادة للتكاثر الخلوي ومحفزة للموت المبرمج، لكن معظمها استخدم تراكيز تفوق المستويات العلاجية بـ 25-100 مرة، مما يثير تساؤلات حول الأهمية السريرية. وأظهرت الدراسات الحيوانية تثبيطاً للأورام في سرطان الكبد، وإطالة البقيا في سرطان المبيض، وتأثيرات وقائية في سرطان القولون، غير أن إحدى الدراسات أشارت إلى تعزيز انتشار سرطان الثدي. وتتناقض الأدلة السريرية: إذ أظهرت التحليلات التلوية عدم وجود زيادة عامة في خطر السرطان (نسبة الأرجحية 0.91-0.93)، بينما أشارت الدراسات التايوانية إلى تأثيرات وقائية لسرطان الثدي (0.718)، والبروستات (0.613)، والفم (0.345)، ولكنها أشارت أيضاً إلى زيادة مخاطر سرطان البنكرياس (1.40-1.50) والغدة الدرقية (1.52). في المقابل، لم تجد التجارب اليابانية أي زيادة في خطر السرطان. وتشمل الآليات المقترحة: التعديل المناعي عبر تنشيط الخلايا التائية+CD8 ، وتفعيلAMPK ، وتثبيط HIF-1α وNF-κB ، والتعديل الجيني، وتحفيز الموت المبرمج. وعلى الرغم من الأدلة قبل السريرية الواعدة، إلا أن الفجوة بين التراكيز والنتائج السريرية المتضاربة تمنع التوصية باستخدام سيتاغليبتين كعامل مضاد للسرطان. ويبقى الميتفورمين الخيار المفضل في مرضى السكري المصابين بالسرطان، ولا توجد أدلة قوية تدعم إيقاف سيتاغليبتين، باستثناء وجود تاريخ لسرطان البنكرياس. تبقى هناك حاجة ماسة لتجارب سريرية مستقبلية موجهة بالعلامات الحيوية.

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Article citation: Mohammed HM, Hussein AM, Abdullah RK, Mahmood MK, Abdalrazaq NA, Hashim RM. Critical Review of Sitagliptin Efficacy as Anticancer Agent: Hope or Hype? *J Iraqi Soc Med Sci*. 2026;0(0):28-39.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) affects approximately 465 million adults worldwide, with projections reaching 700 million by 2045 [1]. A recent global analysis of the Global Burden of Disease Study 2021 data estimated that cancer mortality attributable to high fasting plasma glucose reached 328,309 deaths in 2021, representing a 195% increase from 1990 levels [2]. Epidemiological studies have consistently demonstrated that individuals with T2DM face a significantly higher risk of developing several malignancies, including hepatocellular carcinoma, pancreatic cancer, colorectal cancer, breast cancer, and endometrial cancer [3]. Fu *et al.* reported that type 2 diabetic patients using DPP-4 inhibitors had a higher incidence of colorectal cancer compared to patients using other antidiabetic drugs, with subgroup analyses showing increased risk in males (OR 2.07) and patients younger than 65 years (OR 2.81) [4]. The biological links between diabetes and cancer include chronic hyperglycemia, hyperinsulinemia, insulin resistance, and chronic inflammation [5]. A meta-analysis by Hajishah *et al.* demonstrated that SGLT2 inhibitors were associated with a significantly

lower overall cancer risk compared to DPP-4 inhibitors (RR 0.77), with particular benefits for liver, lung, and prostate cancers [6]. Similarly, Hidayat *et al.* found that observational studies showing increased pancreatic cancer risk with incretin-based therapies reflected methodological biases rather than true causal associations [7]. A growing body of evidence suggests that antidiabetic medications may differentially affect cancer risk, with metformin showing protective effects and insulin potentially increasing risk [8, 9]. The relationship between diabetes and cancer has been extensively reviewed [10,11]. An *et al.* conducted a network meta-analysis of 87 high-quality randomized controlled trials and found that most antidiabetic drugs significantly reduced cancer risk, with biguanides ranking highest for pancreatic cancer reduction and GLP-1 receptor agonists showing protective effects against prostate, uterine, and hepatocellular cancers [12]. Dipeptidyl peptidase-4 (DPP-4), also known as CD26, is a transmembrane glycoprotein that cleaves N-terminal dipeptides from a wide range of substrates. These include incretin hormones (glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)), chemokines (CXCL9, CXCL10, CXCL11, and CXCL12), neuropeptides, and growth factors [13]. Beyond its enzymatic function, DPP-4 plays critical roles in immune regulation through its expression on T lymphocytes as a costimulatory molecule, cell adhesion, and signal transduction [14-16]. DPP-4 also regulates cytokine and chemokine activity, modulates immune responses, and influences tumor biology through its effects on cellular invasiveness [17]. Given these broad functions, DPP-4 inhibition could theoretically modulate cancer development and progression. The role of DPP-4 in cancer biology has been the subject of several reviews [18-22]. Sitagliptin (Januvia®), the first-in-class DPP-4 inhibitor, received FDA approval on October 16, 2006, and was subsequently introduced into clinical practice for the management of T2DM. Since then, additional DPP-4 inhibitors, including vildagliptin, linagliptin, saxagliptin, anagliptin, and alogliptin, have been developed and widely prescribed due to their favorable safety profile and low risk of hypoglycemia [23]. The clinical pharmacology and safety of DPP-4 inhibitors have been extensively reviewed, with particular attention to cardiovascular outcomes from large randomized controlled trials such as TECOS (sitagliptin), SAVOR-TIMI 53 (saxagliptin), and EXAMINE (alogliptin), which collectively demonstrated cardiovascular safety of this drug class [24-28]. Away from cardiovascular outcomes, real-world evidence has suggested potential class-specific effects on cancer risk. A systematic review by Kenawy *et al.* found that SGLT-2 inhibitor users had lower overall cancer risk compared to sulfonylureas (OR 0.54), GLP-1 agonists (OR 0.70), and DPP-4 inhibitors (OR 0.72) [29]. However, Overbeek *et al.* found no consistent association between DPP-4 inhibitors and site-specific cancer risk, though observational studies suggested a possible reduction in breast cancer risk (HR 0.76) [30]. Similarly, Bea *et al.* reported no increased thyroid cancer risk with DPP-4 inhibitors (HR 0.95) compared to SGLT2 inhibitors in a Korean population-based cohort [31]. Despite these reassuring safety data, the relationship between DPP-4 inhibitors and cancer remains highly controversial. Some preclinical studies report antiproliferative and pro-apoptotic effects [32,33], while others report no effect or promotion of metastasis [34,35]. Laeeq *et al.* reviewed the immunomodulatory roles of antidiabetic drugs and found that DPP-4 inhibitors and GLP-1 receptor agonists had mixed data regarding pancreatic cancer risk, while metformin consistently showed protective effects [36]. Rouette *et al.* conducted a population-based cohort study and found no association between DPP-4 inhibitors or GLP-1 receptor agonists and lung cancer risk (HR 1.07 and 1.02, respectively) [37]. Clinical studies show reduced cancer risk in some populations but increased risk for pancreatic and thyroid cancers in others [38-40]. The controversy has been fueled by differing study designs, populations, and analytical approaches [41-44]. This narrative review synthesizes all available evidence from original studies examining associations between the DPP-4 inhibitor sitagliptin and cancer, organized by evidence type: in silico, *in vitro*, *in vivo*, and clinical studies. By presenting all studies without selective exclusion, this review provides a comprehensive resource for researchers and clinicians. Understanding the relationship between sitagliptin and cancer is clinically relevant, given that diabetes affects nearly more than 500 million people worldwide, with projections exceeding 1.31 billion by 2050, and sitagliptin is a widely prescribed antidiabetic agent [45, 46]. This narrative review addresses the following key questions: 1) What is the association between sitagliptin use and cancer risk across different study types? 2) What mechanisms (DPP-4-dependent and independent) mediate sitagliptin's effects on cancer? 3) Does the evidence differ by cancer type, study design, or geographic region? 4) What are the critical knowledge gaps that preclude clinical recommendations for sitagliptin in cancer?

METHODS

Literature search

A literature search was conducted using PubMed and Google Scholar for articles published between January 2010 and May 2026. Although sitagliptin received FDA approval in October 2006, a preliminary scoping review confirmed that no original research examining associations between sitagliptin, and cancer outcomes was published before 2010. The earliest studies relevant to this review appeared between 2010 and 2011, with the majority of publications emerging after 2015.

Therefore, a 2010 start date was selected to capture the complete body of evidence without including empty search years. The search strategy combined the following terms: (sitagliptin OR "dipeptidyl peptidase 4 inhibitor" OR "DPP-4 inhibitor" OR "DPP4i") AND (neoplasm OR cancer OR tumor OR malignancy OR carcinoma). The search was performed using Publish or Perish version 8.19.5300.9483 software, and references were managed using Zotero version 9.0.6 software.

Inclusion criteria

All original research articles examining associations between DPP-4 inhibitors and any cancer-related outcome were included. Studies were included regardless of whether sitagliptin was investigated alone or as part of a class of DPP-4 inhibitors. In cases where studies reported on multiple DPP-4 inhibitors, data specific to sitagliptin were extracted where available. Only articles published in English in peer-reviewed journals were included. Preprints, conference abstracts, editorials, and dissertations were excluded. All studies were included regardless of study design, sample size, journal, or outcome direction. Positive, negative, and null findings were all retained. The final search was conducted on 23 May 2026.

Study selection and categorization

The initial search identified 45 records (30 from PubMed, 15 from Google Scholar). After removing six duplicates, 39 records were screened by title and abstract. All records were included at this stage. Full texts of all 39 records were sought and retrieved. After full-text assessment, 4 records were excluded: 3 because they investigated DPP-4 inhibitors other than sitagliptin, and 1 because no abstract was available. A total of 35 original studies met the inclusion criteria and were included in this narrative review (Figure 1), created using the PRISMA2020 Shiny app [47]. The 35 included studies were categorized into four evidence types: in silico (molecular docking, bioinformatics), *in vitro* (cell line studies), *in vivo* (animal models), and clinical/human studies (cohort studies, randomized controlled trials, meta-analyses, and case reports).

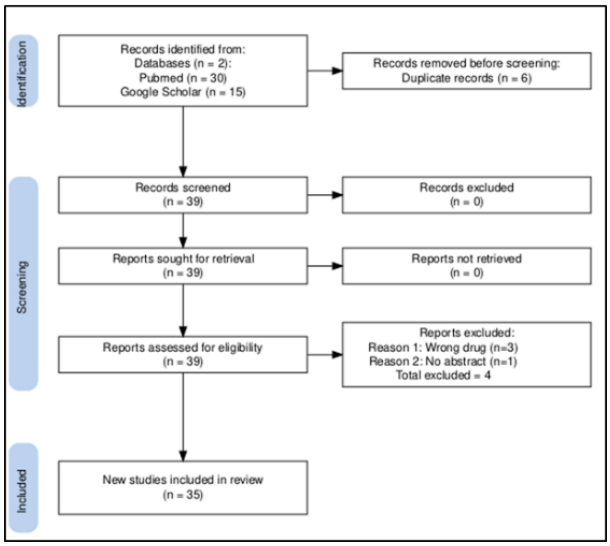

Figure 1: PRISMA 2020 flow diagram of the study selection process.

Data Extraction

Key variables extracted included, for in silico studies, target proteins and binding energies; for *in vitro* studies, cell lines, concentrations, and key findings; for *in vivo* studies, animal models, doses, and outcomes; and for clinical studies, population, sample size, hazard ratios or odds ratios, and follow-up duration.

RESULTS

In silico evidence

Three in silico studies evaluated sitagliptin's binding to cancer-relevant targets across different malignancies (Table 1). **Bladder and prostate cancer**. Naveed *et al.* (2025) identified TOP2A, UBE2C, and CKS2 as overexpressed genes in bladder and prostate cancer, with sitagliptin showing stronger binding (-178.98, -125, and -112 kcal/mol) than standard inhibitors [48]. **Colorectal cancer**. Shih *et al.* (2024) extended these findings to colorectal cancer, where sitagliptin exhibited higher binding energies with CD24 (-9.6 kcal/mol) and SOX4 (-9.1 kcal/mol) than with DPP4 (-7.4 kcal/mol) or CTNNB1 (-7.4 kcal/mol); *in vitro* validation confirmed suppression of cancer cell viability, migration, colony, and sphere formation [49].

Table 1: Summary of in silico docking studies investigating binding affinities of sitagliptin to cancer-relevant protein targets

Study	Tissue	Target Protein(s)	Binding Energy (kcal/mol)
Cheng *et al.*, 2022	Thyroid cancer	DPP4	-8.6
		CTNNB1 (β-catenin)	-7.3
		Mesenchymal-epithelial transition factor (MET)	-7.6
Shih *et al.*, 2024	Colorectal cancer	DPP4	-7.4
		CD24	-9.6
		CTNNB1 (β-catenin)	-7.4
		SRY-box transcription factor 4 (SOX4)	-9.1
Naveed *et al.*, 2025	Bladder/Prostate cancer	TOP2A	-178.98
		UBE2C	-125
		CKS2	-112

Thyroid cancer. Cheng *et al.* (2022) reported binding energies of -8.6 kcal/mol (DPP4), -7.3 kcal/mol (CTNNB1), and -7.6 kcal/mol (MET) in thyroid cancer, with sitagliptin showing comparable or better affinities than standard inhibitors [50]. Across thyroid, colorectal, bladder, and prostate cancers, sitagliptin consistently showed favorable binding to multiple targets. However,

computational predictions require functional validation, partially provided by Shih *et al.*

In vitro evidence

Ten *in vitro* studies evaluated DPP-4 inhibitors, including sitagliptin, in cancer cell lines across multiple cancer types (Table 2). **Bladder Cancer**. Mohtadi and colleagues (2025) found an IC50 of 543 µg/mL for sitagliptin alone in HTB-9 bladder cancer cells. Meanwhile, combination with cisplatin enhanced cytotoxicity, downregulated phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) signaling, increased Bcl-2-associated X protein (Bax) and caspases-3, -7, and -8, and decreased B-cell lymphoma 2 (Bcl-2) expression [51]. **Breast Cancer**. Ruteaga-Navarro and colleagues (2021) treated MCF-7 breast cancer cells with sitagliptin at clinically relevant concentrations of 0.5-2.0 µM [44]. Sitagliptin downregulated messenger RNA expression of lysine acetyltransferase 7 (KAT7) (a histone acetyltransferase) and sirtuin 1 (SIRT1) (a histone deacetylase), suggesting epigenetic modulation. No effects on cell morphology or protein profiles were observed at these concentrations [52]. **Colorectal Cancer.** Three in vitro studies examined colorectal cancer models. Amritha and colleagues (2015) compared sitagliptin and vildagliptin in HT-29 cells and found that sitagliptin exhibited more potent antiproliferative effects [53]. Varela-Calviño and colleagues (2021) studied CD26/DPP4 in a panel of human colorectal cancer cell lines (HT-29, HCT-116, SW-480, SW-620, RKO, T-84, Caco-2). Sitagliptin reduced cell-to-cell homotypic aggregation, motility, and invasion in collagen matrix-dependent assays, with effects opposite to TGF-β1 on epithelial-to-mesenchymal transition and cell cycle [54]. Shih and colleagues (2024) reported an IC50 of 140 µM for DLD-1 cells and 270 µM for HCT116 cells. In this context, sitagliptin at 11.25 µM suppressed migration, colony formation, and sphere formation, and combination with 5-fluorouracil (5-FU) showed synergistic effects [49]. **Endometrial Cancer**. Yang and colleagues (2017) demonstrated that DPP4 inhibition in endometrial cancer cells reduced proliferation and invasion [55]. **Gastric Cancer**. Wang and colleagues (2020) showed that sitagliptin at 1-2 mM inhibited proliferation and colony formation in AGS, HGC-27, and MKN45 gastric cancer cells in a dose-dependent manner. The suggested mechanism was that sitagliptin activated adenosine monophosphate-activated protein kinase (AMPK), leading to Yes-associated protein (YAP) phosphorylation at Ser127 and cytoplasmic retention, thereby reducing YAP nuclear translocation and downregulating melanoma-associated antigen-A3 (MAGE-A3) expression [33]. **Hepatocellular Carcinoma**. Rogalska and colleagues (2016) examined sitagliptin in HepG2 cells, where sitagliptin alone at concentrations up to 4.5 mM did not reduce cell viability but increased p53 levels and nuclear factor kappa-B (NF-κB) expression; however, unlike metformin, which significantly enhanced cell death, sitagliptin did not enhance the cytotoxic effect of epothilone A (a natural anti-mitotic anticancer agent) [32]. **Ovarian Cancer**. Kosowska and colleagues (2020) investigated sitagliptin at 50 µM with or without paclitaxel (10 nM) in SKOV-3 and OVCAR-3 ovarian cancer cells. Sitagliptin alone had minimal effects, but combination therapy increased caspase 3/7 activity and reduced migration and invasion in SKOV-3 cells, which have high DPP4 expression. OVCAR-3 cells, which have low DPP4 expression, showed less response [56]. **Thyroid Cancer**. Lee and colleagues (2017) examined sitagliptin in K1 and BCPAP papillary thyroid cancer cells. DPP4 silencing or sitagliptin treatment (1000 nM) suppressed colony formation, migration, and invasion via downregulation of TGFBR1 and SMAD2 phosphorylation. *In vivo*, sitagliptin (20 mg/kg) reduced tumor growth in a murine xenograft model. High DPP4 expression was associated with extrathyroidal extension, BRAF V600E mutation, and advanced tumor stage [57]. A critical limitation across all these studies is the use of sitagliptin concentrations (typically 50-200 µM and up to 4.5 mM in some studies) that are 25 to 100 times higher than therapeutic plasma levels achieved with standard clinical dosing (~2 µM) [58]. Only one study used clinically relevant concentrations. The *in vitro* findings, including the concentration disconnect, are summarized in Table 2.

Table 2: Summary of *in vitro* studies evaluating the effects of sitagliptin on cancer cell lines: concentrations, key mechanistic findings, and outcomes

Cancer Type	Cell Line(s)	Sitagliptin Concentration	Key Mechanistic Findings	Outcome
Bladder	HTB-9	100-1000 µg/mL	↓PI3K/AKT/mTOR; ↑Bax, ↑caspase-3, -7, -8; ↓Bcl-2	Enhanced cisplatin sensitivity
Breast	MCF-7	0.5-2.0 µM	↓KAT7, ↓SIRT1 messenger RNA	Epigenetic modulation
Colorectal	DLD-1, HCT116	11.25-500 µM	↓DPP4, ↓CD24, ↓CTNNB1, ↓SOX4; synergy with 5-FU	↓Viability, ↓migration, ↓colony formation
Colorectal	HT-29	50-200 µM	Antiproliferative (sitagliptin > vildagliptin)	↓Proliferation
Endometrial	Ishikawa, HEC-1A	10-100 µM	↓Proliferation, ↓invasion via DPP4 downregulation	Antiproliferative
Gastric	AGS, HGC-27, MKN45	1-2 mM	AMPK activation, ↑YAP phosphorylation, ↓MAGE-A3	↓Proliferation, ↓colony formation
Hepatocellular	HepG2	0.5-4.5 mM	↑p53, ↑BAX/BCL2 ratio, ↑NF-κB	Moderate cytotoxicity
Ovarian	SKOV-3, OVCAR-3	50 µM	↓Migration, invasion (SKOV-3 only); ↑caspase 3/7 with paclitaxel; ↓MMP-1, -2, -7, -10	↓Metastatic potential
Thyroid	BCPAP, TPC-1	10-100 µM	↓Proliferation, ↓migration	Antiproliferative

Note: Therapeutic plasma concentration of sitagliptin is approximately 2 µM. Most studies used concentrations 25-100 times higher.

In vivo evidence

Nine *in vivo* studies evaluated DPP-4 inhibitors in animal models of cancer across six cancer types: hepatocellular carcinoma, ovarian cancer, breast cancer, colorectal cancer, lung cancer, and colon carcinogenesis (Table 3).

Table 3: Summary of *in vivo* studies evaluating the effects of sitagliptin in animal models of cancer: doses, routes, treatment durations, and main findings

Cancer Type	Model	Sitagliptin Dose	Duration	Main Findings
Breast	4T1 allograft	Not specified	Variable	Promoted metastasis via CXCL12/CXCR4/mTOR axis
Hepatocellular carcinoma	DEN-treated mice	20-80 mg/kg	60 days	↑Survival; ↓HIF-1α via AKT-AMPK-mTOR; ↓VEGF, ↓MMP-2
Hepatocellular carcinoma	DEN-treated rats	10-20 mg/kg	20 weeks	↓Liver enzymes; ↓IL-6, TNF-α, IL-1β; ↓NF-κB
Hepatocellular carcinoma	STAM mice (NASH-HCC)	30 mg/kg	10 weeks	↓Tumor number (1.8 vs. 4.5); ↓tumor volume (11.2 vs. 37.5 mm^3); ↓p62/Keap1/Nrf2 pathway
Colon	DMH-treated rats	10 mg/kg	32 weeks	Reduced MDF; ↓ROS
Colon	ob/ob mice	3 mg/kg	20 weeks	↓Tumor number (6.7 vs. 10.6); ↓Aberrant crypt foci (3.1 vs. 12.4); ↓IL-6 mRNA
Colorectal	MC38/CT26 syngeneic	Not specified	Variable	Enhanced anti-PD-L1 efficacy; ↓M2 macrophages; ↑CD8+ T cells
Colorectal	HT-29, HCT-116, SW-480, SW-620, RKO, T-84, Caco-2 (*in vitro*)	Not specified	Variable	↓Cell-to-cell aggregation; ↓motility; ↓invasion (collagen matrix-dependent); opposite effects to TGF-β1 on EMT and cell cycle
Ovarian	ID8 syngeneic mice	50 mg/kg	Until endpoint	↑Median survival (138 vs. 108 days); ↑CD8+ T cells; ↓Tregs; ↓CCL22, IL-10

All studies used sitagliptin in doses ranging from 3 mg/kg to 80 mg/kg, administered orally either by gavage or mixed with food, with treatment durations spanning 10 weeks to 60 days. **Breast Cancer**. Yang and colleagues (2019) reported contradictory findings [34]. DPP-4 inhibition promoted breast cancer metastasis in a 4T1 allograft model via activation of the C-X-C motif chemokine ligand 12 (CXCL12)/C-X-C motif chemokine receptor 4 (CXCR4)/mTOR axis and the reactive oxygen species-nuclear factor erythroid 2-related factor 2-heme oxygenase-1 (ROS-NRF2-HO-1) pathway. **Colorectal Cancer.** Four studies examined colorectal cancer models. Femia and colleagues (2013) showed that long-term sitagliptin administration reduced colon carcinogenesis and reactive oxygen species in DMH-induced rats [59]. Yorifuji and colleagues (2016) used ob/ob mice with 1,2-dimethylhydrazine/dextran sulfate sodium (DMH/DSS)-induced colon tumors [60]. Sitagliptin at 3 mg/kg orally significantly reduced tumor number (6.7 versus 10.6) and aberrant crypt foci (3.1 versus 12.4) and improved survival. Fujiwara and colleagues (2017) evaluated the impact of sitagliptin on intestinal tumorigenesis in ApcMin/+ mice fed a high-fat diet. The daily treatment of these mice with sitagliptin did not increase the number of intestinal tumors; however, sitagliptin significantly suppressed the plasma levels of CXCL5 and SDF-1, which were elevated in these mice [61]. Zuo and colleagues (2023) used MC38 and CT26 syngeneic models [62]. Sitagliptin enhanced anti-programmed death-ligand 1 (anti-PD-L1)-mediated tumor suppression by inhibiting M2 macrophage polarization via suppression of the NADPH oxidase 1/NADPH oxidase 2-reactive oxygen species-extracellular signal-regulated kinase (NOX1/NOX2-ROS-ERK) pathway. **Hepatocellular Carcinoma.** Three studies examined DPP-4 inhibitors in hepatocellular carcinoma models. Jiang and colleagues (2018) treated diethylnitrosamine (DEN)-induced hepatocellular carcinoma rats with sitagliptin at 10 or 20 mg/kg orally for 20 weeks [63]. Sitagliptin dose-dependently decreased serum liver enzymes, reduced inflammatory cytokines (interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β)), and prevented NF-κB activation. Kawaguchi and colleagues (2018) used STAM mice, a model of nonalcoholic steatohepatitis-related hepatocellular carcinoma, treated with sitagliptin at 30 mg/kg for 10 weeks [64]. Tumor number (1.8 versus 4.5) and tumor volume (11.2 versus 37.5 mm^3) significantly decreased. Metabolomic analysis revealed that sitagliptin altered the pentose phosphate pathway. Abd El-Fattah and colleagues (2022) used DEN-induced hepatocellular carcinoma mice receiving sitagliptin at 20, 40, or 80 mg/kg for 60 days [65]. Sitagliptin at 80 mg/kg significantly increased survival and inhibited hypoxia-inducible factor 1-alpha (HIF-1α) activation via the AKT-AMPK-mTOR axis. **Ovarian Cancer**. Wilson and colleagues (2021) used an ID8 syngeneic mouse model of ovarian cancer [66]. Sitagliptin at 50 mg/kg/day in food prolonged median survival from 108 to 138 days and reduced visible metastatic deposits. Flow cytometry showed increased CD8+ T-cell infiltration, decreased regulatory T cells (Tregs), and reduced immunosuppressive cytokines, including C-C motif chemokine ligand 22 (CCL22) and interleukin-10 (IL-10).

Clinical and Epidemiological Evidence

Thirteen clinical studies evaluated sitagliptin and cancer risk in human populations. Of these, several were meta-analyses or cohort studies that included sitagliptin as part of a class of DPP-4 inhibitors, while others focused specifically on sitagliptin (Table 4). **Case Reports**. Kurihara and colleagues (2024) reported a case of incidental renal cell carcinoma and DPP-4 inhibitor-

related kidney disease [67]. **Japanese Cohort Study**. In 2015, Green *et al.* evaluated the cardiovascular outcomes and conducted a large double-blind study of 14,671 patients (sitagliptin vs placebo). They found no increased cancer risk during a median follow-up of 3 years [68]. Sugiyama and colleagues (2024) analyzed 349,000 patients and found no increased cancer risk with sitagliptin compared to other DPP-4 inhibitors (HR 1.01) [69]. **Korean Cohort Studies**. Lee and colleagues (2019) studied 33,208 newly diagnosed T2DM patients and found increased pancreatitis (HR 1.27) and pancreatic cancer risk (HR 1.50) [70]. Choi and colleagues (2019) propensity-matched 1,538 patients and found no significant difference in overall cancer risk compared to metformin (HR 1.00) [71]. Kim and colleagues (2023) propensity-matched 102,964 patients (51,482 per group) and found no significant association between DPP-4 inhibitor use and pancreatic cancer risk (HR 0.99, 95% CI 0.88-1.12) over a median follow-up of 7.95 years. No cumulative effect was observed with higher medication adherence [72]. **Meta-Analyses**. Dicembrini and colleagues (2020) meta-analyzed 157 RCTs and found no increased overall cancer risk (OR 0.93, 95% CI 0.85-1.02), with possible colorectal cancer reduction [73]. Li and colleagues (2022) meta-analyzed 115 randomized controlled trials (RCTs) comprising 121,961 patients and found that DPP-4 inhibitors were associated with a reduced incidence of overall neoplasm (odds ratio (OR) 0.91, 95% confidence interval (CI) 0.84-0.97), particularly rectal and skin cancers [74]. However, previous meta-analyses have confirmed these favorable side effect profiles when DPP-4 inhibitors were compared with competitors, with Monami and colleagues (2014) reporting no increased risk of pancreatitis with DPP-4 inhibitors (MH-OR 0.93, 95% CI 0.51-1.69) [75], and Karagiannis and colleagues (2012) finding no significant difference in side effect profile [76]. **Taiwanese Cohort Studies**. In 2016, Tseng conducted two studies on 71,137 users of sitagliptin and reported an increased risk of pancreatic cancer among sitagliptin users (HR 1.40) [39] and also examined 58,238 other users and reported an increased risk of thyroid cancer, particularly within the first year of use (HR 1.516) [40]. In 2017, the same author conducted three separate studies: a study of 32,457 female sitagliptin users found a reduced risk of breast cancer (HR 0.718) [38]; a study of 37,924 male users found a reduced risk of prostate cancer (HR 0.613) [77]; and a third study of 39,195 (21,282 males) patients reported that sitagliptin may reduce oral cancer risk when the cumulative duration exceeds 15.63 months (HR 0.345; 95% CI 0.164-0.725) or cumulative dose exceeds 42,200 mg (HR 0.347; 95% CI 0.165-0.731) [78]. In contrast, Hsu and colleagues conducted a population-based cohort study and found no association between incretin-based therapy and acute pancreatitis (adjusted HR 1.06; 95% CI 0.72-1.55) or pancreatic cancer (6 vs. 10 cases, p= 0.32) [79].

Table 4: Summary of clinical and epidemiological studies evaluating DPP-4 inhibitors and cancer risk in human populations: meta-analyses, retrospective cohort studies, and case reports

Study/Region	Total samples	Main Findings
Japan	363,671	No ↑ cancer risk in general populations
Korea	137,710	Conflicting: one study reported ↑ pancreatic cancer; two studies found no association
Meta-Analyses	121,961+	No ↑ overall cancer; ↓ Overall, rectal, skin; No ↑pancreatic/pancreatitis
Taiwan	488,199	Mixed: ↓ Breast, prostate, oral; ↑Pancreatic, thyroid; Neutral for pancreatitis

Summary of Proposed Mechanisms

Based on the synthesized evidence, DPP-4 inhibitors may exert anticancer effects through several mechanisms, which are summarized in Table 5 and illustrated in Figures 2 and 3. DPP-4-dependent immune modulation appears to be a major pathway. Preservation of full-length CXCL10 enhances CXCR3-mediated CD8+ T-cell trafficking into tumors, as demonstrated in ovarian cancer and lung cancer models [62, 66]. This is accompanied by reduced regulatory T cells (Tregs) and M2-polarized tumor-associated macrophages [35,62], and decreased immunosuppressive cytokines, including CCL22 and IL-10 [66]. Additional mechanisms include AMPK activation leading to YAP phosphorylation in gastric cancer [33], HIF-1α suppression via AKT-AMPK-mTOR in hepatocellular carcinoma [65], NF-κB inhibition [63], epigenetic modulation through KAT7 and SIRT1 downregulation in breast cancer [52], and apoptosis induction via Bcl-2/Bax ratio modulation and caspase activation in bladder and ovarian cancers [51,57]. However, pro-metastatic effects in breast cancer involve NRF2 activation and the CXCL12/CXCR4/mTOR axis, suggesting that DPP-4 inhibition may have context-dependent, cancer-type-specific effects [34]. Despite these proposed anticancer mechanisms, safety concerns regarding pancreatic events have been raised. Muhammed and colleagues (2023) analyzed data from the FDA Adverse Event Reporting System (FAERS) and VigiBase and found strong signals for pancreatic events with sitagliptin, showing the highest risk for pancreatitis and pancreatic carcinoma. Their meta-analysis of RCTs revealed that gliptins had a higher risk of acute pancreatitis compared to placebo/active comparator (OR 1.44; 95% CI 1.03, 2.01; p= 0.03) [80]. The immunoregulatory functions of DPP-4, particularly through CD26 expression on T cells, have been well-characterized in previous reviews [81,82].

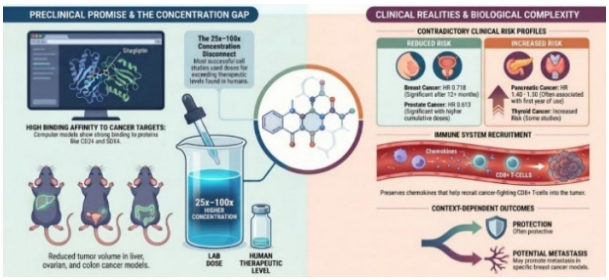

Figure 2: Preclinical promise and clinical complexity of sitagliptin repurposing in oncology. This figure illustrates the dichotomy between robust preclinical evidence (in silico, *in vitro*, *in vivo*) showing anticancer effects and the contradictory clinical evidence showing both protective and harmful associations depending on cancer type and geographic region. Refer to Tables 1-4 for detailed data and Table 5 for mechanisms.

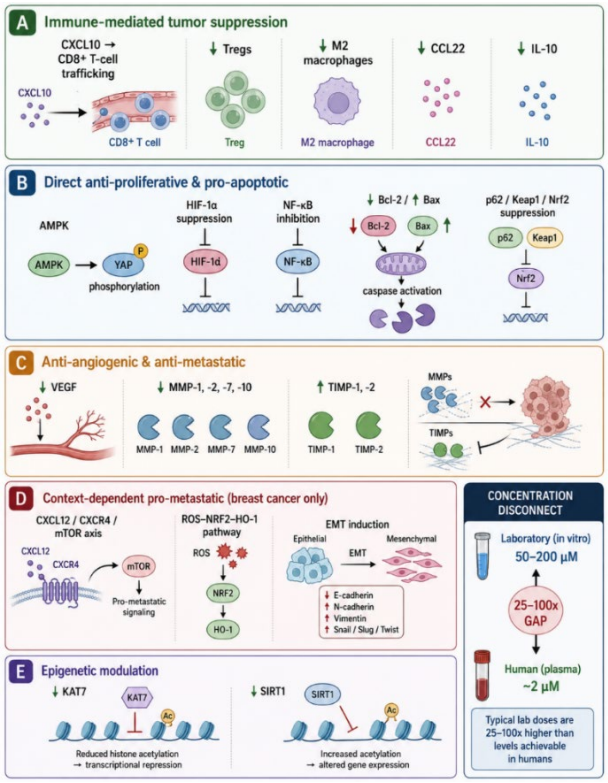

Figure 3: Comprehensive mechanistic pathways of DPP-4 inhibitors in cancer. This figure integrates the proposed mechanisms identified in this review, including immune modulation (DPP-4-dependent), direct anti-tumor effects (AMPK activation, HIF-1α suppression, NF-κB inhibition, apoptosis induction), angiogenesis inhibition, context-dependent metastasis promotion (breast cancer only), epigenetic regulation, and the concentration disconnect. Refer to Table 5 for a structured summary of mechanisms with evidence sources and cancer types.

DISCUSSION

This narrative review synthesized thirty-five studies examining associations between sitagliptin, a DPP-4 inhibitor, and cancer across in silico, *in vitro*, *in vivo*, and clinical evidence types. In silico docking studies predict favorable binding of sitagliptin to DPP4, CTNNB1, MET, CD24, and SOX4 (Table 1). *In vitro* studies demonstrate antiproliferative, pro-apoptotic, and anti-migratory effects across multiple cancer cell lines (Table 2), but the most significant limitation is the use of sitagliptin concentrations that are 25 to 100 times higher than therapeutic plasma levels. *In vivo* studies show consistent tumor suppression in hepatocellular carcinoma, prolonged survival in ovarian cancer, and protective effects in colon cancer models (Table 3). However, one study reported that DPP-4 inhibition promoted breast cancer metastasis. Clinical evidence is contradictory: meta-analyses show no overall increased cancer risk, while individual cohort studies show both protective and harmful effects depending on cancer type and geographic location (Table 4). Proposed mechanisms include immune modulation, AMPK activation, HIF-1α suppression, NF-κB inhibition, epigenetic modulation, and apoptosis induction (Table 5). The most significant limitation across *in vitro* studies is the use of sitagliptin at concentrations of 50 to 200 μM and up to 4.5 mM in some studies. Therapeutic plasma concentrations of sitagliptin at the standard 100-mg dose are approximately 0.08-0.90 μM [58]. This 25- to 100-fold difference raises serious concerns about the clinical relevance of *in vitro* antiproliferative effects. This concentration disconnect represents a fundamental challenge to the translation of preclinical findings to clinical practice. Only one study, conducted by Ruteaga-Navarro and colleagues (2021), used clinically relevant concentrations of 0.5 to 2 μM, finding epigenetic modulation without direct cytotoxicity and suggesting that at therapeutic doses, sitagliptin may not directly kill cancer cells but could modulate gene expression through histone acetylation and deacetylation pathways [52]. The concentration disconnects identified in this review highlights a broader challenge in drug repurposing, where the therapeutic potential of existing drugs must be carefully evaluated at clinically achievable concentrations to ensure meaningful translation to patient care [83-86]. Our findings align with meta-analyses showing no overall increased cancer risk with DPP-4 inhibitors [73, 74]. These results are consistent with the broader body of evidence on incretin-based therapies. Suryadevara *et al.* [87] concluded that extensive data from the past two decades indicate incretin-based therapies do not increase pancreatic cancer risk, with preclinical data showing beneficial effects on cancer cell lines requiring further evaluation. The TECOS study by Buse *et al.* found numerically more pancreatitis cases with sitagliptin (23 vs 12) but fewer pancreatic cancer cases (9 vs 14), with meta-analysis showing a small absolute increased risk for pancreatitis [88]. Sondergaard *et al.* reviewed that DPP-4 inhibitors and GLP-1 agonists do not significantly modify cancer risk, while insulin use is associated with a nearly 50% increase in total cancer risk [89]. However, the geographic variation in clinical outcomes warrants discussion. Taiwanese cohort studies by Tseng and colleagues consistently reported protective effects for breast, prostate, and oral cancers [38,77,78] but harmful effects for pancreatic and thyroid

cancers [39, 40]. The same author also found a positive diabetes-prostate cancer link (RR 5.83), most pronounced in those aged 40-64 years (RR 2.09), with nephropathy, ischemic heart disease, and dyslipidemia as significant risk factors, while antidiabetic medications showed no association [90].

Table 5: Summary of proposed mechanisms of action for dpp-4 inhibitors in cancer: dpp-4-dependent immune modulation, DPP-4-independent direct anti-tumor effects, and context-dependent pro-metastatic pathways

Mechanism Type	Pathway	Evidence Source	Cancer Type(s)
DPP-4-dependent immune modulation	Preserved CXCL10 → CXCR3+ CD8+ T-cell trafficking	Wilson *et al.*, 2021; Zuo *et al.*, 2023	Ovarian, lung
	↓Tregs, ↓M2 macrophages	Saito *et al.*, 2021; Zuo *et al.*, 2023	Colorectal, lung
	↓Immunosuppressive cytokines (CCL22, IL-10)	Wilson *et al.*, 2021	Ovarian
DPP-4-independent	AMPK activation → YAP phosphorylation → ↓proliferation	Wang *et al.*, 2020	Gastric
	HIF-1α suppression via AKT-AMPK-mTOR	Abd El-Fattah *et al.*, 2022	Hepatocellular carcinoma
	NF-κB inhibition → ↓inflammation	Jiang *et al.*, 2018	Hepatocellular carcinoma
	Epigenetic modulation (↓KAT7, ↓SIRT1)	Ruteaga-Navarro *et al.*, 2021	Breast
	Apoptosis (↓Bcl-2/Bax, ↑caspases)	Mohtadi *et al.*, 2025; Kosowska *et al.*, 2020	Bladder, ovarian
Pro-metastatic (breast cancer only)	NRF2 activation; CXCL12/CXCR4/mTOR axis	Yang *et al.*, 2019	Breast

In contrast, the large Japanese cohort study by Sugiyama and colleagues (2024) found no increased cancer risk [69]. These discrepancies may reflect differences in study design, patient populations, genetic backgrounds, dietary patterns, or prescribing practices. The Korean studies also showed conflicting results, with Lee and colleagues (2019) reporting increased pancreatic cancer risk [70], while Kim and colleagues (2023) found no association [72]. A meta-analysis by Yonatan *et al.* found no significant association between incretin-based therapies and cholangiocarcinoma risk, with pooled HRs of 1.07 for GLP-1 receptor agonists and 1.05 for DPP-4 inhibitors, providing reassurance regarding biliary tract safety [91]. The pancreatic cancer signal has been particularly contentious. Early pharmacovigilance studies by Elashoff and colleagues (2011) raised concerns [41], but subsequent meta-analyses have largely refuted an association [75,76]. The TECOS trial, a large randomized controlled trial of sitagliptin, found no increased pancreatic cancer risk [68]. However, the increased risk of acute pancreatitis observed in some studies [78] remains a concern, as chronic pancreatitis is a known risk factor for pancreatic cancer. Several long-term safety studies have provided reassurance regarding sitagliptin's overall safety profile. Nishimura *et al.* demonstrated in a randomized 24-week trial that sitagliptin combined with repaglinide significantly improved glycemic control without weight gain or severe hypoglycemia [92]. Tada *et al.* and Katzeff *et al.* showed sustained HbA1c reductions with sitagliptin over 24 months in elderly and general T2DM populations, respectively [93,94]. Ferrannini *et al.* reported comparable safety profiles between empagliflozin, sitagliptin, and metformin over 90 weeks, with hypoglycemic events rare across all groups [95]. Yoshikawa *et al.* confirmed long-term sitagliptin safety in a Japanese post-marketing surveillance study of 3,326 patients, with adverse drug reactions occurring in only 6.3% of patients [96]. Mpratsiakou *et al.* found DPP-4 inhibitors safe and effective for new-onset diabetes after kidney transplantation, with significant HbA1c reduction (from 6.6% to 6.1%) and stable renal function over 12 months [97]. Wang *et al.* reported that sitagliptin use was associated with a higher risk of hospitalization for heart failure (HR 1.21), though no excessive mortality was observed, suggesting clinicians should consider cardiovascular monitoring [98]. Dhas *et al.* comprehensively reviewed antidiabetic drug repurposing for cancer, concluding that metformin shows consistent anti-cancer properties while other antidiabetic drugs demonstrate heterogeneous responses requiring further mechanistic studies [99]. The proposed mechanisms of DPP-4 inhibitors in cancer are multifaceted and context-dependent (Table 5). DPP-4-dependent immune modulation appears to be a major pathway. Preservation of full-length CXCL10 enhances CXCR3-mediated CD8+ T-cell trafficking into tumors, as demonstrated in ovarian cancer and lung cancer models [62, 66]. This is accompanied by reduced regulatory T cells (Tregs) and M2-polarized tumor-associated macrophages [35,62] and decreased immunosuppressive cytokines, including CCL22 and IL-10 [66]. The immunomodulatory role of CD26/DPP-4 has been extensively documented, particularly in T-cell function [81, 82]. DPP-4-independent mechanisms have also been identified. AMPK activation leads to YAP phosphorylation and reduced nuclear translocation, decreasing proliferation in gastric cancer [33]. HIF-1α suppression via the AKT-AMPK-mTOR axis reduces angiogenesis in hepatocellular carcinoma [65]. NF-κB inhibition reduces inflammation [63]. Epigenetic modulation through downregulation of KAT7 and SIRT1 was demonstrated in breast cancer [52]. Apoptosis induction via Bcl-2 to Bax ratio modulation and caspase activation was shown in bladder and ovarian cancers [51,57]. However, pro-metastatic effects in breast cancer involve NRF2 activation and the CXCL12/CXCR4/mTOR axis, suggesting that DPP-4 inhibition may have context-dependent, cancer-type-specific effects [34]. This duality highlights the complexity of targeting DPP-4 in cancer and the need for careful patient selection.

Strengths and Limitations

This review comprehensively includes all available evidence across study types without outcome-based exclusion, reducing selective reporting bias. The geographic diversity spans multiple countries. However, as a narrative review without meta-analysis, no pooled effect estimates are provided. Publication bias remains possible, and heterogeneity across studies precludes direct comparison. Unmeasured confounders in clinical studies cannot be excluded.

Quality of Included Studies

No formal risk of bias assessment was performed, consistent with the narrative review methodology. However, key limitations across studies included (1) supratherapeutic concentrations *in vitro*, (2) lack of blinding in some animal studies, and (3) potential detection bias in clinical cohort studies. Future studies should address these limitations through standardized methodologies.

Clinical Implications

For diabetic patients with cancer, current evidence does not support sitagliptin as anticancer monotherapy. There is no strong evidence to discontinue DPP-4 inhibitors in patients already taking them, except possibly those with a pancreatic cancer history. Metformin remains the preferred antidiabetic agent in cancer patients [100,101]. Clinicians should be aware of potential pancreatic and thyroid cancer signals reported in some studies, particularly during the first year of use, though the large Japanese cohort study provides reassurance of overall safety. The clinical implications of DPP-4 inhibitor use in cancer patients have been reviewed by many authors in this review.

Knowledge Gap and Future Studies

Preclinical validation: Direct enzymatic assays, clinically relevant *in vitro* concentrations (≤10 μM), and long-term animal studies (≥6 months) are needed to validate docking predictions and assess tumor growth and metastasis. Biomarker-driven trials: Prospective clinical trials in biomarker-selected patients (DPP4/CD26 expression, CXCL10/CXCR3 axis, tumor-infiltrating lymphocytes) are needed to identify responders and guide patient selection. Comparative and mechanistic studies: Head-to-head comparisons of different DPP-4 inhibitors and mechanistic studies on cancer stem cells and the tumor microenvironment are warranted. Formulation approaches: Nanoparticle formulations may achieve higher tumor concentrations while avoiding systemic toxicity. Enhanced clinical evidence: Prospective cohort studies with long-term follow-up and individual patient data meta-analyses are needed to address limitations of retrospective studies.

Conclusion

This narrative review of thirty-five studies demonstrates that DPP-4 inhibitors exhibit anticancer potential in preclinical models of hepatocellular carcinoma, ovarian cancer, gastric cancer, colorectal cancer, and bladder cancer through immune modulation, AMPK activation, YAP phosphorylation, HIF-1α suppression, NF-κB inhibition, epigenetic modulation, and apoptosis induction. However, the concentration disconnects, cancer-type-specific contradictions, and inconsistent clinical outcomes preclude current clinical recommendations. The large Japanese cohort study provides reassurance of overall safety, and meta-analyses show no increased overall cancer risk. However, signals for pancreatic and thyroid cancer warrant continued pharmacovigilance. Future research must prioritize direct enzymatic validation, clinically relevant *in vitro* studies, long-term animal studies, and prospective biomarker-driven clinical trials. The potential for drug repurposing of DPP-4 inhibitors in oncology remains an area of active investigation that requires rigorous, well-designed studies to determine whether the preclinical promise can be translated to clinical benefit.

Conflict of interests

The authors declared no conflict of interest.

Funding source

The authors did not receive any source of funds.

Data sharing statement

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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