Biomedicine & Pharmacotherapy 191 (2025) 118507

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

From basics to clinics: New opportunities for metformin in tumor metabolic intervention and treatment

Huiying Lv [a,b,d], Haofei Gong [a,b,d], Ran Zhao [c,a,b,d], Xuan Gao [e,a,b,d], Wenyue Liu [a,b,d], Lijun Zhao [a,b,d,1], Ruili Sun [a,b,c,d,1,*]

[a] Henan Key Laboratory of Immunology and Targeted Drugs, School of Medical Technology, Henan Medical University, Xinxiang, China
[b] Henan Collaborative Innovation Center of Molecular Diagnosis and Laboratory Medicine, School of Medical Technology, Henan Medical University, Xinxiang, China
[c] Department of Pathology, The Third Affiliated Hospital of Henan Medical University, Xinxiang, China
[d] Xinxiang Key Laboratory of Tumor Microenvironment and Immunotherapy, Henan Medical University, Xinxiang, China
[e] School of Basic Medical Sciences, Henan Medical University, Xinxiang, China

ARTICLE INFO

Keywords:
Metformin
Tumor metabolism
Immunometabolism
Therapeutic strategies
Translational medicine

ABSTRACT

Metformin, a cornerstone therapy for type 2 diabetes, has recently garnered attention for its multifaceted antitumor potential in cancer prevention and treatment. Emerging preclinical studies reveal that metformin suppresses tumor growth and metastasis through integrated mechanisms beyond singular metabolic pathways, while enhancing sensitivity to immunotherapy. Clinical evidence preliminarily supports its survival benefits and risk reduction in breast, colorectal, and hepatocellular carcinomas, particularly when combined with conventional or novel anticancer agents, demonstrating synergistic efficacy. Epidemiological and real-world data further highlight its preventive value in high-risk populations. Despite heterogeneity in therapeutic responses across cancer types and individuals, as well as unresolved challenges in long-term safety and acquired resistance, innovative drug delivery systems and precision oncology approaches are expanding its therapeutic boundaries. Bridging mechanistic insights with clinical translation, metformin is poised to emerge as a pivotal agent in metabolic-immunological synergy, offering novel paradigms for personalized cancer interception and therapy. This review systematically deciphers metformin's pleiotropic mechanisms in cancer metabolism and anti-tumor immunity while critically evaluating its translational prospects, thereby illuminating new avenues for combinatorial metabolic-immunotherapeutic strategies.

1. Introduction

Malignant tumors have become a paramount challenge to global public health. According to the GLOBOCAN 2022 database released by the International Agency for Research on Cancer (IARC), the global incidence of new cancer cases and the number of cancer deaths are projected to continue escalating, posing a severe threat to human health [1]. Although conventional therapies—including surgery, radiotherapy, and chemotherapy—have undergone continuous refinement, tumor heterogeneity-driven drug resistance and recurrence persistently undermine clinical outcomes [2]. In recent years, novel therapeutic strategies targeting tumor metabolic dysregulation have emerged as a major research focus. These strategies aim to disrupt tumor cells'dependence on metabolic reprogramming, thereby paving the way for overcoming drug resistance [3].

In this context, metformin, a first-line oral medication for type 2 diabetes mellitus that has been on the market for decades, is gaining significant attention due to its potential for 'drug repurposing' in oncology [4]. As a biguanide derivative characterized by its simple structure (comprising two guanidine groups connected by a methylene bridge) and strong hydrophilicity, metformin (chemical formula: $C_4H_{11}N_5$) enters cells via organic cation transporters (OCTs) to exert its biological effects [5]. Its unique appeal lies in the fact that metformin is a non-cytotoxic compound with high safety profile, low cost, and ready availability [6]. Furthermore, it demonstrates good combinability and synergistic potential with existing anti-tumor therapies, such as chemotherapy, targeted therapy, and immune checkpoint inhibitors [7]. More importantly, extensive research has uncovered its

* Corresponding author at: Henan Key Laboratory of Immunology and Targeted Drugs, School of Medical Technology, Henan Medical University, Xinxiang, China.
E-mail addresses: Lijun_Zhao123@163.com (L. Zhao), sunruili2016@126.com (R. Sun).
[1] These authors jointly supervised this work and are co-corresponding authors.

https://doi.org/10.1016/j.biopha.2025.118507
Received 1 July 2025; Received in revised form 14 August 2025; Accepted 25 August 2025
Available online 1 September 2025

multi-dimensional anti-tumor mechanisms that extend far beyond its glucose-lowering effects. These mechanisms encompass not only the classical AMP-activated protein kinase (AMPK)-dependent regulation of energy stress but also extend to direct intervention in glucose/lipid/amino acid metabolic networks, tumor immune microenvironment (TIME) remodeling, suppression of cancer stem cells (CSCs) properties; and modulation of epigenetic regulation, among others [8–10].

A large body of epidemiological evidence shows that diabetic patients who have been treated with metformin for a long time have a significantly lower risk of developing various types of cancer (including liver cancer, colorectal cancer (CRC), breast cancer, etc.), and enjoy better cancer-related prognosis [11]. Preclinical basic research has also confirmed that metformin can inhibit multiple tumor lineages by regulating epigenetic mechanisms, targeting CSCs, and inhibiting tumor growth [12]. Clinical translational research has further confirmed that its combination with chemotherapy, immune checkpoint inhibitors (ICIs), and other therapies can produce synergistic effects [13]. However, translating these encouraging findings into universal clinical benefits remains a significant challenge. The antitumor effects of metformin exhibit significant heterogeneity and uncertainty in clinical trials, with its efficacy profoundly influenced by tumor type, molecular subtype, dosage, and the patient's individual genetic background. For example, the mutation status of the upstream kinase LKB1 directly determines the activation efficiency of the AMPK pathway, while the OCT1 transporter genetic polymorphisms affect drug uptake and bioavailability in cells [14]. These factors together constitute key biomarkers for predicting therapeutic efficacy.In addition, its low oral bioavailability and short half-life pharmacokinetic characteristics also limit its ability to reach effective therapeutic concentrations in tumor tissues [15].

To address these challenges and maximize their clinical potential, cutting-edge translational strategies have emerged. Among them, precision delivery systems based on nanotechnology are becoming the most promising approach to overcoming pharmacokinetic bottlenecks.The strategy of loading metformin onto smart nanocarriers not only significantly improves its bioavailability and tumor targeting enrichment, but also facilitates synergistic co-delivery with other therapies (such as chemotherapy and phototherapy), resulting in a '1 + 1 > 2' effect [16–20]. Additionally, the deep integration of bioinformatics and artificial intelligence technologies are being used to mine public databases in depth to identify and validate predictive biomarkers and provide data support for the construction of individualized dosing models [21]. The integration of these emerging technologies is driving metformin's oncology research from 'universal' application to a new era of 'precision' intervention. In light of this, this review systematically synthesizes recent progress in metformin research – spanning basic mechanisms to clinical applications, critically examines its complexities and controversies as a metabolic modulator, and highlights its potential in advanced strategies such as synergy with conventional/novel therapies and nanotechnology-enabled precision delivery. Our goal is to offer a theoretical foundation and practical guidance for advancing the precise utilization of this 'century-old drug' in contemporary cancer treatment.

2. Metformin and tumor metabolism

The anti-tumor effects of metformin primarily stem from its dual modulation of energy metabolism and signaling pathways. Its canonical mechanism involves AMPK activation and subsequent mTOR inhibition, suppressing tumor cell proliferation and metabolic reprogramming [22]. As an energy sensor, AMPK activation blocks mTORC1 signaling, downregulates Cyclin D1 to induce G1-phase arrest, and reduces ATP production through mitochondrial complex I (MCI) inhibition, ultimately triggering apoptosis [23]. Recent advances reveal that metformin's anti-cancer activity extends beyond the AMPK/mTOR axis to orchestrate a synergistic regulatory network encompassing glucose,

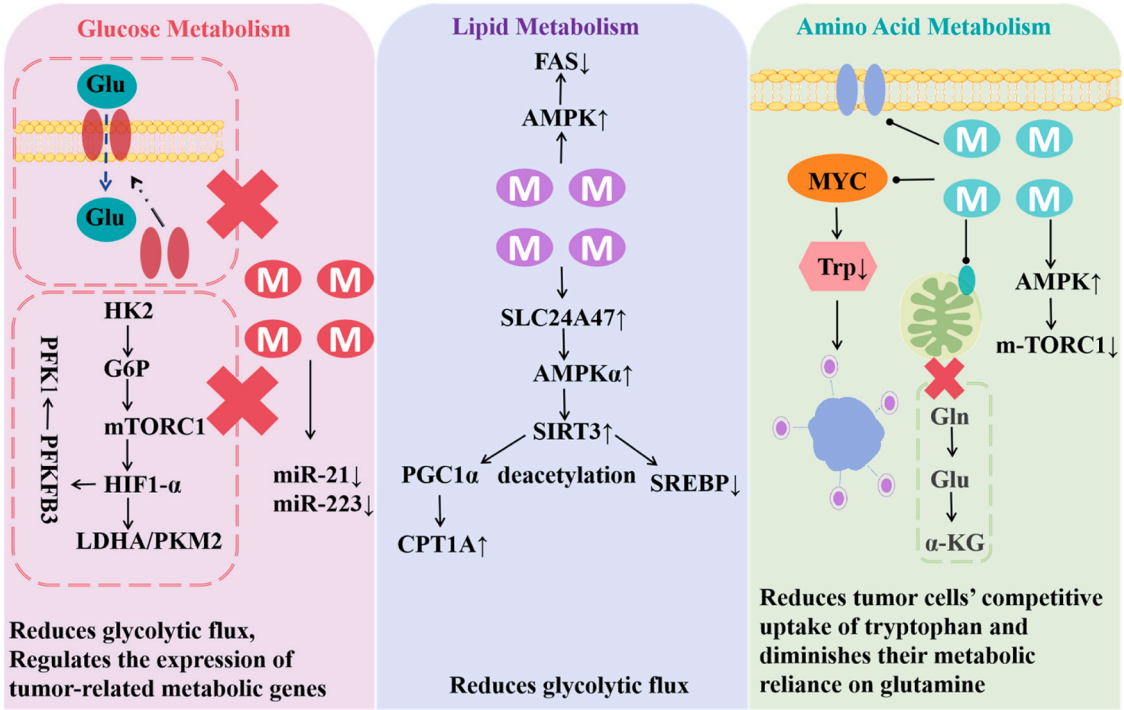

Fig. 1. Metformin exerts multiple mechanisms of anti-tumor effect by regulating tumor cell metabolism. In glucose metabolism: targeting key molecules such as Glut4, HK2, LDHA/PKM2 to reduce glucose uptake and glycolysis, and regulating metabolic genes through miRNA or DNA methylation. In lipid metabolism: activating AMPK to inhibit FAS, blocking fatty acid synthesis, targeting the SLC25A47-AMPKα-SIRT3 axis to maintain lipid homeostasis and inhibit the conversion of NAFLD to HCC. In amino acid metabolism: downregulating MYC to reduce tryptophan uptake, enhancing CD8 + T cell function, interfering with glutamine metabolism, and weakening tumor metabolic dependency. Schematic elements: red double ellipse (Glut4), red crosses (inhibitory effect), purple small cells (CD8 + T cells), blue double ellipses represent (SLC7A5 transporters), cyan ellipses represent (MCI), dashed boxes (pathways or mechanisms).

lipid, and amino acid metabolism (Fig. 1). By targeting these dysregulated pathways, metformin disrupts tumor energy supply and biosynthesis, effectively impeding cancer progression.

2.1. Glucose metabolic reprogramming

Metformin disrupts glucose metabolism in cancer cells through multimodal mechanisms. Herman et al. demonstrated its suppression of GLUT4 activity and expression via AMPK-dependent/independent pathways, limiting glucose uptake [24]. Mostafavi et al. identified metformin-mediated inhibition of hexokinase II (HK2), lactate, and succinate accumulation, reducing energy availability and glycolysis [25]. Welponer et al. in cutaneous squamous cell carcinoma models showed simultaneous suppression of oxidative phosphorylation and glycolysis, curtailing tumor growth [26]. Ouyang et al. reported in thyroid cancer that metformin downregulates Warburg effect drivers (LDHA, PKM2) while upregulating IDH1, shifting metabolic balance [27]. In hepatocellular carcinoma (HCC), Hu et al. revealed HIF-1α/PFKFB3/PFK1 axis inhibition by metformin, reducing glycolytic flux, with HK2 knockout enhancing drug sensitivity [28]. Epigenetic regulation via miRNA modulation (e.g., miR-21, miR-223 suppression) and DNA methylation further illustrate metformin's multi-layered control of glycolytic genes [24].

2.2. Lipid metabolism regulation

Metformin disrupts lipid metabolism in cancer cells through AMPK-mediated suppression of fatty acid synthase (FASN), thereby limiting tumor lipid supply [29]. This inhibitory effect on lipogenesis has been validated in prostate and breast cancer models, where metformin significantly attenuates de novo lipogenesis [30,31]. Furthermore, Smith et al. revealed that metformin treatment reduces intracellular phosphocholine synthesis and inhibits fatty acid release from adipose tissue, effectively blocking tumor lipid acquisition [32]. Emerging evidence further delineates metformin's indirect regulation of AMPKα via targeting the hepatocyte-specific mitochondrial NAD+ transporter SLC25A47. This mechanism suppresses SREBP accumulation and reactivates SIRT3, forming a regulatory axis critical for maintaining lipid homeostasis and preventing NAFLD-driven HCC progression [33].

2.3. Amino acid metabolic modulation

Metformin selectively targets tumor-associated amino acid metabolism, which not only fuels cancer proliferation but also modulates immune cell functionality within the tumor microenvironment (TME) [34]. In CRC, Huang et al. demonstrated that metformin downregulates MYC and inhibits the tryptophan transporter SLC7A5, alleviating tumor competition for tryptophan and restoring CD8 + T cell cytotoxic activity [35]. Espinos et al. highlighted metformin's intervention in L-arginine metabolism, suggesting amino acid-specific modulation as a novel avenue for precision therapy [36]. In breast cancer MCF-7 cells, metformin exhibits dual control over glutamine metabolism: (1) MCI inhibition depletes NAD^+, blocking glutamate-to-α-ketoglutarate conversion; (2) AMPK/mTORC1 axis activation reduces glutamine dependency [37]. Collectively, these findings underscore metformin's capacity to disrupt oncogenic amino acid flux across tumor types, enabling environment-dependent metabolic remodeling and therapeutic synergy.

3. Beyond metabolic regulation: multidimensional anti-tumor mechanisms of metformin

The antitumor effects of metformin do not originate from a single target but are achieved through a complex regulatory network that encompasses the entire body system, tumor cells themselves, and the TME. Its mechanism of action can be clearly divided into three interrelated levels: indirect systemic regulation, direct intrinsic effects on tumor cells, and multiple remodeling effects on the TME (Fig. 2).

3.1. Indirect systemic regulatory effects

The most classic indirect mechanism of action of metformin stems from its core function as a hypoglycemic agent. By inhibiting gluconeogenesis in the liver, metformin can lower circulating blood glucose levels and, in turn, reduce the levels of insulin and insulin-like growth factor-1 (IGF-1) secreted by the body to compensate for hyperglycemia. Insulin and IGF-1 are key growth and survival signals for various tumor cells, driving tumor proliferation by activating pro-cancer signaling pathways such as PI3K/AKT/mTOR and RAS/RAF/MAPK. Therefore, metformin indirectly 'cuts off' the key growth signals for tumor cells by reducing serum insulin/IGF-1 levels, thereby exerting a broad-spectrum anti-tumor effect. Furthermore, emerging research suggests that metformin can also reshape the composition and metabolism of the gut microbiota, such as regulating bile acid metabolism to activate the farnesoid X receptor (FXR), thereby disrupting tumor-stromal interactions and inhibiting the progression of liver cancer [38].

3.2. Direct intrinsic effects on tumor cells

Independent of its systemic hypoglycemic effects, metformin can be efficiently taken up into tumor cells by organic cation transporter 1 (OCT1) and exert direct antitumor effects.

The primary direct target of metformin is MCI. By inhibiting MCI, metformin blocks oxidative phosphorylation, leading to a sharp decrease in intracellular ATP production and a significant increase in the AMP/ATP ratio. This energy stress state activates the cell's key energy sensor-AMPK. Activated AMPK inhibits mTORC1, a key regulatory node promoting anabolic processes, through phosphorylation, thereby comprehensively suppressing protein, lipid, and nucleic acid synthesis and arresting the cell cycle at the G1 phase, ultimately leading to the cessation of tumor cell proliferation and apoptosis [39,40].

In addition to the AMPK/mTOR axis, metformin also interferes with multiple key carcinogenic signaling pathways. For instance, metformin can effectively target and eliminate CSCs. Its mechanism includes inhibiting key stem cell maintenance pathways such as Wnt/β-catenin, thereby weakening the self-renewal ability and tumorigenic potential of CSCs, which is of crucial significance for preventing tumor recurrence and overcoming treatment resistance [41]. In addition, metformin can reverse drug resistance in some tumors by inhibiting the IKBK/NF-κB signaling axis [42]. At the same time, it can also disrupt the chromosomal stability of liver cancer cells by interfering with the mitotic checkpoint protein BUB1, thereby inducing cell death [43].

Moreover, metformin can also inhibit tumor metastasis by regulating epigenetic mechanisms, such as upregulating tumor-suppressive miRNAs (e.g., miR-26a) and downregulating oncogenic miRNAs (e.g., miR-21) [44]. Furthermore, research has found that metformin can directly bind to the substrate binding site of histone methyltransferase CARM1, inhibiting the expression of CCNE1 and thereby effectively inhibiting the cell cycle of ovarian cancer cells [45].

3.3. Multiple effects on the TME

Tumor growth relies on the support of its complex microenvironment. Metformin has demonstrated a powerful ability to reshape the TME, particularly by transforming immunosuppressive 'cold' tumors into immune-activated 'hot' tumors, laying the foundation for its synergistic application with immunotherapy. Metformin is a powerful immunomodulator that enhances anti-tumor immunity at multiple levels (Fig. 3).

Metformin can enhance antitumor immune responses by regulating immune cells in the TME. For example, metformin can reduce the production of reactive oxygen species (ROS), there 'rescuing' tumor-infiltrating CD8 + T cells from hypoxia-induced apoptosis and

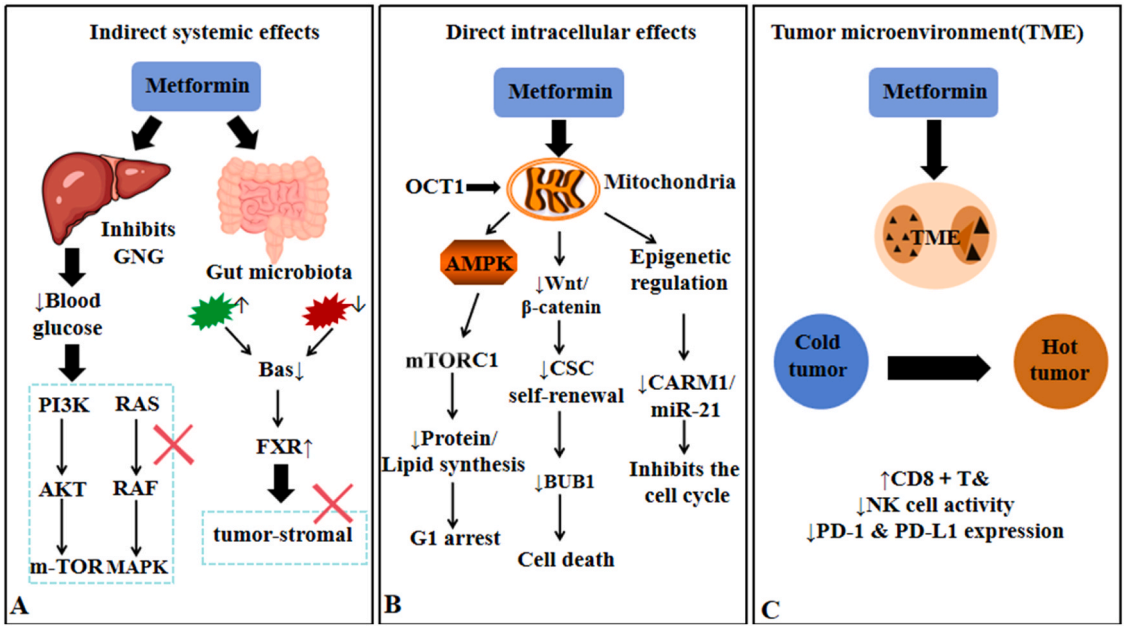

Fig. 2. The multi-dimensional anti-tumor mechanisms of metformin. (A) Indirect systemic effects: Metformin lowers serum insulin/IGF-1 levels by inhibiting hepatic gluconeogenesis, thereby suppressing pro-tumorigenic pathways such as PI3K/AKT/mTOR. It also remodels the gut microbiota to disrupt tumor-stroma interactions. (B) Direct intracellular effects: After entering tumor cells via OCT1, metformin activates AMPK by inhibiting mitochondrial complex I (MCI). Activated AMPK in turn inhibits mTORC1-driven anabolism and cell cycle. Moreover, metformin suppresses cancer stem cell (CSC) pathways (e.g., Wnt/β-catenin). Besides, it can regulates epigenetic mechanisms. (C) Remodeling of the tumor microenvironment (TME): Metformin transforms immunosuppressive 'cold tumors' into immune-active 'hot' tumors. Its mechanisms include enhancing CD8 + T cell function, reducing regulatory T cells (Tregs) and tumor-associated macrophages (TAMs), and down-regulating PD-L1 expression on cancer cells, thereby boosting anti-tumor immunity.Schematic elements: green burst shapes (beneficial microbiota), red burst shapes (harmful microbiota), red 'X' symbols (inhibitory actions), dashed boxes (signaling pathways/mechanism).

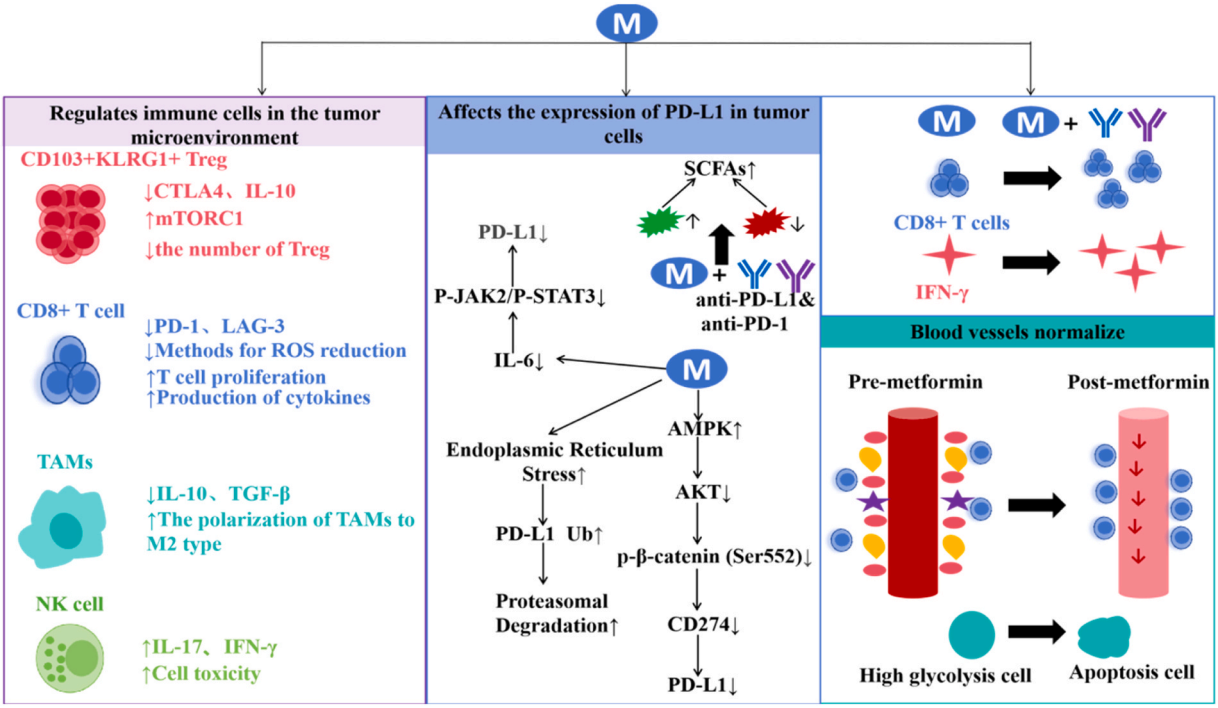

Fig. 3. Metformin enhances anti-tumor immunity through three primary mechanisms: (1) It modulates immune cells by reversing CD8 + T cell exhaustion (↓PD-1/LAG-3), inhibiting Treg function (↓CTLA-4/IL-10), boosting NK cell activity, and suppressing immunosuppressive cells. (2) It remodels the tumor microenvironment by inhibiting angiogenesis and inflammation, thereby restricting tumor growth. (3) It downregulates PD-L1 expression via blockade of β-catenin phosphorylation, ERAD modulation, and IL-6/JAK2/STAT3 pathway inhibition; when combined with immunotherapy, metformin further enhances PD-1/PD-L1 inhibitor efficacy through gut microbiota-mediated increases in CD8 + T cell infiltration and IFN-γ production. Schematic elements: dark red cylinders (leaky vessels), light red cylinders (normal vessels), red dots (RBCs), yellow circles (plasma proteins), purple stars (inflammatory factors), red arrows (blood flow), green burst shapes (beneficial microbiota), red burst shapes (harmful microbiota).

exhaustion, while also inhibiting the expression of inhibitory receptors such as PD-1 and LAG-3 on their surfaces [46]. By inhibiting mTORC1 signaling, the number of tumor-infiltrating regulatory T cells (Tregs) is effectively reduced, particularly the terminally differentiated CD103 +KLRG1 + subpopulation, and the expression of their effector molecules such as CTLA4 and IL-10 is decreased [47]. At the same time, metformin can enhance the activity of CD8 + T cells and NK cells through AMPK-dependent T cell metabolic reprogramming, while inhibiting the function of immune-suppressive cells such as Tregs and TAMs, thereby enhancing the anti-tumor immune response [48].

Metformin can also influence the TME by altering the survival conditions of tumor cells. For example, studies have shown that metformin can inhibit tumor-associated angiogenesis and inflammatory responses, promote tumor cell apoptosis, and alter cellular metabolism, thereby inhibiting tumor growth and metastasis [11]. Metformin can also enhance anti-tumor immunity by improving tumor vascular maturity and perfusion, thereby increasing CD8 + T lymphocyte tumor infiltration. This mechanism is known as vascular normalization, which promotes immune cell infiltration into tumor areas and enhances immune responses [49].

Furthermore, metformin influences PD-L1 expression in tumor cells via several mechanisms, thereby augmenting the efficacy of immunotherapy. Specifically, metformin can decrease AKT-mediated Ser552 phosphorylation of β-catenin, leading to reduced transcription of CD274 (the gene encoding PD-L1) [50]. By affecting the endoplasmic reticulum-associated degradation (ERAD) pathway, metformin reduces PD-L1 stability and membrane localization, thereby enhancing cytotoxic T lymphocyte (CTL) activity [51]. Metformin can also downregulate PD-L1 expression in esophageal squamous cell carcinoma by inhibiting the IL-6/JAK2/STAT3 signaling pathway, thus enhancing anti-tumor immune responses [52]. Moreover, when combined with anti-PD-1/PD-L1 therapy, metformin can enhance treatment efficacy by modulating the gut microbiota. For example, metformin, by altering the composition of the gut microbiota, improved the efficacy of anti-PD-L1 antibodies and promoted anti-tumor immunity by increasing CD8 + T cell infiltration and IFN-γ expression [53].

In summary, extensive preclinical studies (Table 1) have provided a solid biological basis for the antitumor activity of metformin. Its multidimensional mechanism of action, ranging from systemic metabolism and tumor cell intrinsic mechanisms to microenvironmental remodeling (Fig. 2), suggests its enormous potential for application in cancer therapy and points the way forward for subsequent clinical translation studies.

4. Clinical application and translational exploration of metformin

Metformin has emerged as a prime example of ‘repurposing old drugs’ due to its multifaceted antitumor potential (Fig. 2). However, the translation of metformin from basic research to clinical application is fraught with complexity and challenges. This chapter aims to systematically review the clinical translation landscape of metformin in cancer therapy, through in-depth analysis of its controversial clinical trial results, synergistic mechanisms with conventional and emerging therapies, dose optimization and personalized dosing strategies, as well as cutting-edge nanodelivery systems, to provide direction for the future application of metformin in the context of precision oncology.

4.1. Clinical trials across tumor types

Although basic research and some observational studies have provided strong evidence for the antitumor potential of metformin, its performance in clinical trials has shown significant heterogeneity, and even neutral or negative conclusions have been drawn in several large randomized controlled trials (RCTs) (Table 2), sparking widespread discussion and reflection [58].

In 2005, an observational study has reported a reduction in cancer incidence among metformin users, sparking exploration into the potential use of metformin (an antidiabetic drug) as a cancer prevention and treatment drug, leading to widespread experimental, observational, and clinical research [59]. Subsequently, several non-randomized observational studies reported that metformin use was associated with a reduced overall cancer risk [60], In particular, it shows a preventive effect in gastrointestinal cancers [7]. However, these studies were found to be affected by time-related bias in 2012 [61]. For example, newly diagnosed diabetic patients may begin using metformin only after their condition has stabilized for a period of time, and the favorable survival outcomes during this period may be erroneously attributed to the drug itself. Additionally, the study identified significant publication bias, suggesting the need for further research on the efficacy of metformin in non-diabetic populations [7]. Furthermore, new users are often healthier than older users or patients using other drugs (such as sulfonylureas or insulin), introducing the confounding factor of the ‘healthy user effect’ When subsequent studies corrected for these biases through more rigorous designs (such as new user/active comparator designs), the association between metformin and cancer risk was significantly weakened or even eliminated [58]. These findings may prompt clinicians to re-evaluate the clinical application of metformin. Future studies will determine the optimal dosage and treatment duration, as well as the patient groups most likely to benefit.

In contrast to the optimistic results of observational studies, subsequent large, prospective, placebo-controlled RCTs in non-diabetic cancer patients failed to confirm the survival benefit of metformin. For example, the NCIC CTG MA.32 study (n = 3649) was a landmark trial that showed metformin failed to improve invasive disease-free survival (IDFS) in patients with early-stage breast cancer when added to standard therapy (HR=1.01, 95 % CI: 0.84–1.21) [58]. Multiple RCTs targeting castration-resistant prostate cancer (CRPC) (such as COU-AA-302 and COU-AA-301) also failed to demonstrate that metformin combined with standard therapy could significantly improve PFS or OS, possibly because its clinical dose was much lower than the anticancer concentration used in preclinical experiments [62]. Given the close association

Table 1
Preclinical (in vitro and in vivo) research evidence of metformin’s anti-tumor effects.

Cancer types	Study models	Key findings & mechanisms	Quantitative data/effects	Ref.
Triple-negative breast cancer	MDA-MB−231 and HS578T cell lines; mouse xenograft models	Disrupts downstream signaling pathways including FGFR4/JAK1/STAT3, FGFR4/AKT, and FGFR4/ERK	Synergizes with SAHA to effectively suppress cancer cells proliferation and promote apoptosis	[54]
Prostate cancer	ENZ-resistant cell line; mouse xenograft model	Inhibits mitochondrial function, reduces basal oxygen consumption rate, spare respiratory capacity and ATP production	Delays the onset of CRPC in mouse models	[55]
Pancreatic adenocarcinoma	BxPC−3 cell line	Exerts inhibitory effects via miR−378a−3p/VEGFA/RGC−32 axis	Suppresses tumor volume by 30 %	[56]
Lung cancer	A549 cell line; mouse xenograft model	Downregulates ERBB2 and PI3K signaling	Suppresses tumor growth by 60 % in synergy with doxorubicin	[57]
Colorectal cancer	HCT116 cell line	Inhibits Wnt signaling and reduces CSCs self-renewal capacity	Reduces tumorsphere formation by 50 %	[41]

Table 2
Representative clinical trials and results analysis of metformin in different tumor types.

Cancer Types	Trial ID	Phase/Type	Patient Population	Dosage & Regimen	Key Findings/Primary Endpoint	Interpretation	Ref.
Esophageal carcinoma	NCT03238686	Phase II clinical trial	Non-diabetic esophageal adenocarcinoma	Metformin(250 mg/day)+ neoadjuvant therapy	Immune modulation:increases CD8 + T cell infiltration and remodels the immune microenvironment	Positive. Low doses can exert immunomodulatory effects, provides a basis for combination immunotherapy	[64]
Ovarian cancer	NCT01576186	Phase II clinical trial, (single arm)	Recurrent ovarian cancer (n = 38)	Metformin(850 mg BID) + chemotherapy	Targetes CSCs: reduces the proportion of ALDH+ /CD133 + CSCs; median PFS reaches 18 months	Positive. Shows potential for targeting CSCs and preventing recurrence	[65]
Breast cancer(early period	NCICCTG MA.32	Phase III clinical trial, randomized controlled study, adjuvant therapy	Non-diabetic, high-risk HR or HR- (n = 3649)	Metformin(850 mg BID) vs. Placebo	No significant benefit. IDFS is not improved(HR=0.96, p = 0.52)	Neutral/Negative. The adjuvant therapeutic effect is unclear in unscreened non-diabetic populations	[66]
Prostate cancer	Not specified	Phase III randomized controlled trial	Non-metastatic castration-resistant prostate cancer	500 mg/day	Significantly improvesprogression-free survival	Neutral/Negative. In non-diabetic late-stage patients, combination therapy doesn't show a survival advantage	[67]
Pancreatic adenocarcinoma (later period)	NCT01210911	Phase II clinical trial, randomized controlled trial	Advanced adenocarcinoma (n = 121)	Metformin(1000 mg/day) + FOLFIRINOX vs. FOLFIRINOX	No significant benefitno improvement in PFS or OS	Neutral/Negative. No benefit is observed when used in combination with potent chemotherapy in aggressive pancreatic cancer	[63]
Non-small cell lung cancer	Not specified	Retrospective/Preclinical studies	LKB1 mutant NSCLC	Not applicable	Potential biomarker: Tumor cells with LKB1 mutations are more sensitive to metformin	Suggests that it is a biomarker. LKB1 mutations are potential biomarkers for predicting the efficacy of metformin therapy	[14]

between pancreatic cancer and metabolic disorders, metformin was once held in high regard, but clinical trial results were equally disappointing. A multicentre, randomized, double-blind, placebo-controlled study from the Netherlands (clinical trial registration number: NCT01210911) showed that adding standard-dose metformin to gemcitabine and erlotinib treatment in patients with advanced pancreatic cancer did not improve survival outcomes [63].

4.2. The complexity of the antitumor effects of metformin

These neutral results highlight the complexity of metformin's antitumor effects, whose efficacy is not universal but highly dependent on specific contexts.

4.2.1. Patient selection and metabolic background

The core pharmacological action of metformin is to improve insulin resistance. Therefore, its antitumor effects (especially indirect effects) may vary significantly among patients with different metabolic states. Most of the positive data from early observational studies come from cancer patients with type 2 diabetes mellitus (T2DM). In these populations, the indirect anticancer effects of metformin, which act by lowering insulin and IGF-1 levels, may predominate [68]. In trials targeting non-diabetic or normoglycemic patients, although metformin treatment also significantly reduced the number of abnormal crypts, the role of this key pathway was greatly weakened [69]. Additionally, studies have found that even in non-diabetic patients, subgroups with insulin resistance and hyperinsulinemia may benefit more from metformin treatment [70,71]. In addition, studies have shown that newly diagnosed patients with baseline HbA1c levels close to 9 % can achieve target levels in nearly 70 % of cases when treated with 2000 mg of metformin monotherapy [72].

4.2.2. Tumor heterogeneity and molecular subtypes

'Cancer' is not a single disease, different tumors, and even different subtypes of the same tumor, have vastly different molecular backgrounds and metabolic dependencies. The efficacy of metformin may also be highly dependent on the specific molecular characteristics of tumor cells. For example, when metformin is used to treat tumor cells with LKB1 defects, the cells cannot adapt to or regulate the energy stress caused by metformin through activation of the LKB1-AMPK pathway, thereby increasing their sensitivity to metformin and making them more prone to cell death [73]. Patients with PTEN deficiency may be more sensitive to metformin [74]. A study showed that in prostate cancer patients receiving androgen deprivation therapy, metformin significantly improved biochemical recurrence rates only in the PTEN-deficient subgroup [75]. Hormone receptor (HR)-positive breast cancer patients may benefit more from metformin than triple-negative breast cancer (TNBC) patients, which may be related to the dependence of HR+ tumors on energy metabolism [76,77].

4.2.3. Dosage, timing, and combination therapy strategies

The concentration of metformin that can induce cell apoptosis or significantly inhibit tumor growth in preclinical studies (typically 5–20 mM) is much higher than the blood concentration that can be achieved in humans with the standard clinical dose (850–1000 mg BID), which is approximately 10–40 μM [78]. This means that in clinical practice, metformin may be used more as a metabolic regulator or sensitizer for chemotherapy/radiotherapy/immunotherapy, rather than as a direct cytotoxic drug [79]. The aforementioned esophageal cancer study, in which a low dose of 250 mg/day was able to reshape the immune microenvironment, is a case in point [64]. Therefore, exploring the optimal treatment window and dosage is an important direction for current research.

In addition, the timing of metformin administration is critical. Short-term preoperative administration of metformin aims to modulate the TME. For example, a phase II esophageal cancer trial showed that low-

dose metformin can reshape the immune microenvironment and increase T-cell infiltration [64]. During the neoadjuvant phase, it may improve metabolic status and target CSCs to create favorable conditions for subsequent surgery or chemoradiotherapy. During the adjuvant phase, the goal is to prevent recurrence, and it may be effective for patients with specific metabolic risks or molecular characteristics [65]. However, in advanced or metastatic disease, its monotherapy efficacy is limited, and it is more often required to be combined with other therapies to enhance efficacy. For example, when combined with PD-1/PD-L1 inhibitors, it can leverage their potential to improve the TME and overcome immune suppression; when combined with drugs targeting the PI3K/mTOR pathway, it can produce synergistic effects.

4.3. Combination use of metformin with traditional and emerging therapies

The antitumor efficacy of metformin as a monotherapy remains unclear in most clinical settings. Its greatest clinical application potential lies in its use as an effective sensitizer or enhancer in combination with existing anticancer therapies to achieve synergistic effects greater than the sum of their individual effects. This synergistic effect is not a simple summation of individual effects, but rather stems from metformin's profound intervention in tumor cell metabolism, signaling pathways, resistance mechanisms, and theTME. This section will delve into the complex mechanisms underlying the synergistic effects of metformin with traditional and emerging therapies (Table 3).

4.3.1. Synergistic effects with traditional chemotherapy and radiotherapy

Metformin can enhance the cytotoxic effects of traditional cytotoxic drugs and radiotherapy through multiple mechanisms, particularly demonstrating significant value in overcoming treatment resistance.

Platinum-based drugs are the cornerstone of many chemotherapy regimens for solid tumors, and the combination of metformin and cisplatin is one of the most extensively studied areas of research. A systematic review and meta-analysis encompassing 44 studies confirmed that metformin combination therapy significantly reduces tumor volume and inhibits cancer cell survival compared with cisplatin monotherapy. Although the analysis indicated significant heterogeneity in the existing evidence, the synergistic potential revealed cannot be ignored, and large-scale prospective RCTs are called for to confirm the survival benefit [80]. The mechanism of this synergistic effect is multidimensional. For example, in gallbladder cancer, metformin synergizes with cisplatin by upregulating P21 and P27 and downregulating Cyclin D1, thereby arresting cells in the G0/G1 phase. Simultaneously, it effectively induces apoptosis by inhibiting key survival pathways such as PI3K/AKT/ERK[81]. In drug-resistant lung cancer, metformin successfully reverses cisplatin resistance caused by mechanisms such as drug efflux or enhanced DNA damage repair by regulating the AMPK-mTOR axis and activating ROS-mediated stress pathways [82]. In ovarian cancer, synergistic effects manifest as downregulation of multidrug resistance protein 1 (MDR1) and DNA repair key protein (ERCC1) expression, fundamentally dismantling the cancer cells' resistance defences [83].

A pooled analysis of two Phase II clinical trials showed that metformin combined with platinum-based chemotherapy resulted in significant survival improvement (PFS HR=0.31; OS HR=0.42) in patients with squamous cell lung cancer with high FDG-PET uptake, confirming its clinical translational potential as a metabolic sensitizer [84,85]. Besides, the study clearly indicated that the combination of metformin and cisplatin can significantly inhibit the Hedgehog pathway, a key signaling pathway that regulates the stemness and drug resistance of CSCs. At the same time, this combination therapy can also downregulate the expression of pluripotency transcription factors such as Oct-4, Sox2, and Nanog, thereby precisely eliminating CSCs subpopulations with high tumorigenicity and drug resistance, and preventing tumor recurrence at its source [83].

The synergistic effects of metformin are also widely observed in combination with other chemotherapy drugs. A systematic review of doxorubicin (Dox) indicated that metformin can enhance the cytotoxicity of Dox against various tumors, such as breast cancer and liver cancer, by activating AMPK and inhibiting mTORC1, while also reducing its cardiotoxic side effects [80]. In osteosarcoma, metformin enhances cell sensitivity to Dox by downregulating IGF1R and FEN1 expression and upregulating miR-610 [86]. In addition, the study found that in CRC, metformin directly compensates for the metabolic defects caused by 5-fluorouracil (5-FU) treatment by increasing the intracellular folate pool, thereby significantly enhancing its cytotoxicity. This is a sophisticated metabolic complementary strategy [87]. In glioblastoma multiforme (GBM), it can effectively enhance the efficacy of temozolomide (TMZ) [88].

4.3.2. Synergistic effects of endocrine and epigenetic therapies

In hormone-dependent cancers, metformin can enhance the effects of endocrine therapy. In prostate cancer, adding metformin to androgen

Table 3
Synergistic mechanism and application of metformin and multiple antitumor therapies.

Combination class	Partner drug/ therapy	Cancer types	Key synergistic mechanism	Key therapeutic effect	Ref.
Chemotherapy	Cisplatin	Ovarian cancer	Targets CSCs (Hedgehog pathway↓); reversals of drug resistance (MDR1/ERCC1↓); induces DNA damage/S-phase block	Overcomes platinum resistance; eradicates CSCs	[83]
	Cisplatin	Drug-resistant lung cancer	Regulates the AMPK-mTOR axis; induces ROS-mediated stress	Reverses cisplatin resistance	[82]
	Cisplatin	Gallbladder cancer	Induces G0/G1 phase block (P21/P27↑, Cyclin D1↓); inhibition of the PI3K/AKT /MAPK pathway	Synergistically induces apoptosis	[81]
	Doxorubicin	Osteosarcoma	Regulates IGF−1R/FEN1/miR−610 axes	Enhances chemotherapy sensitivity of doxorubicin	[86]
	5-Fluorouracil	Colorectal cancer	Increases the intracellular folate pool to compensate for the defect of 5-FU metabolism	Enhances 5-FU cytotoxicity and reverses drug resistance	[87]
Radiotherapy	Radiotherapy/ Temozolomide	Glioblastoma	Inhibits mitochondrial respiration, produces superoxides, and induces cell cycle arrest	Enhances sensitivity to chemoradiotherapy	[88]
Endocrine therapy	Androgen deprivation	Prostate cancer	Inhibits androgen receptor signaling; compensates for metabolic disorders caused by ADT	Improves outcomes for advanced/ metastatic patients	[89]
Targeted therapy	Gefitinib	Bladder cancer	Synergizes anti-proliferation and pro-apoptosis	Overcomes EGFR inhibitor resistance	[93]
	Bevacizumab	Ovarian cancer	Decreases the proportion of CD44/CD117 CSCs; improves tumor hypoxia	Synergistically inhibits tumor growth and promotes stemness of tumor cells	[94]
Immunotherapy	Immune checkpoint inhibitors	Various solid tumors	Remodels TME (cold → hot tumor); increases CD8 +T cell infiltration	Creates favorable conditions for the efficacy of immune checkpoint inhibitors	[64]
	Oncology vaccines	Various solid tumors	Reduces PD-L1 expression in tumor cells	Enhances the anti-tumor immune response	[46]

deprivation therapy (ADT) has been shown to improve patient prognosis, possibly by inhibiting androgen receptor signaling or compensating for the adverse metabolic consequences of ADT [89]. Moreover, its collaboration with epigenetic drugs such as thioesterase A (TSA) in osteosarcoma revealed a new, AMPK-independent synergistic mechanism involving G1/G2 cell cycle arrest and apoptosis induction [90].

4.3.3. Synergistic effects with emerging targeted therapies and immunotherapies

In the era of precision medicine, the role of metformin has expanded from a sensitizer to an immunomodulator and a drug resistance reverser.

In the field of immunotherapy, metformin has demonstrated a powerful ability to reshape the tumor immune microenvironment. It can transform immunosuppressive 'cold' tumors into immunologically active 'hot' tumors. Its mechanisms include: (1) Downregulates PD-L1 expression: Metformin can directly reduce PD-L1 levels on the surface of tumor cells, thereby relieving inhibition of T cells [91]. (2) Improves T cell function: Protecting and enhancing the migratory capacity of CD8 + T cells by alleviating metabolic exhaustion of T cells within tumors [92]. (3) Modulates immune cell components: low-dose metformin can induce pro-tumor M2 macrophages to convert to anti-tumor M1 macrophages and increase the infiltration of CD8 + T cells and B cells, paving the way for the efficacy of ICIs [64].

In the field of targeted therapy, metformin primarily overcomes adaptive resistance by intervening in the metabolic reprogramming of tumors. For example, when EGFR inhibitors (such as gefitinib) are used to treat bladder cancer, tumor cells may escape by activating other pathways. The intervention of metformin can target the metabolic level, forming a 'dual blockade' with gefitinib, thereby exerting powerful antiproliferative and pro-apoptotic effects and effectively overcoming resistance [93].

In summary, the synergistic mechanism of action between metformin and various anticancer therapies is complex and profound. It works through multiple pathways, including targeting tumor metabolism, reversing drug resistance, regulating DNA damage repair, and reshaping the immune microenvironment, offering highly promising clinical translational value for enhancing the efficacy of existing cancer treatment strategies and overcoming their limitations.

4.4. Dose optimization and precision approaches

The dose-response relationship of metformin in cancer treatment exhibits significant cancer-type dependency (Table 4). In a Phase I clinical trial for acute lymphoblastic leukemia (ALL), 1000 mg/m^2/day was established as the recommended Phase II dose (RP2D), demonstrating both favorable safety and antitumor effects via AMPK activation and suppression of the unfolded protein response (UPR) [95]. Importantly, dose-dependent mechanistic differences are evident. For instance, Park et al. revealed that low-dose metformin activates Src signaling through the AMPK-FAO pathway, while high-dose metformin inhibits tumor progression, with synergistic effects observed when combined with Src inhibitors such as dasatinib [96]. Lee et al. further demonstrated that high-dose metformin synergizes with temozolomide in glioma treatment, significantly enhancing apoptosis and prolonging survival in murine models [97], highlighting the need for tumor type-specific dose optimization.

Now, molecular subtype-guided personalized therapy is emerging as a cornerstone of metformin's clinical application. In gastrointestinal cancers, metformin exerts dual mechanisms: for diabetic patients, it inhibits insulin-IGF-1 axis-driven PI3K/AKT pathway activation, whereas in non-diabetic patients, it enhances chemosensitivity by downregulating the COX-2/PGE2 inflammatory circuit and inducing p21-dependent cell cycle arrest [98]. In LKB1-mutated non-small cell lung cancer (NSCLC), metformin combined with caloric restriction effectively remodels theTME to improve therapeutic responses [14].

4.5. Precision delivery strategies based on nanotechnology

Although metformin has demonstrated strong antitumor potential in basic research, its clinical translation has been limited by inherent pharmacokinetic (PK) defects: low oral bioavailability (approximately 50–60 %), short plasma half-life (approximately 6.2 h), and poor tumor tissue targeting efficiency due to its hydrophilicity. These factors make it difficult to achieve the effective anticancer concentrations observed in vitro experiments (typically at the mM level) at tumor sites, thereby significantly impairing its clinical efficacy [11]. To overcome this bottleneck, nanotechnology-based drug delivery systems (NDDS) have

Table 4
Effect-dose relationship of metformin in different cancer types.

Cancer Types	Recommended dosage/ scheme	Key effect mechanisms	Benefit	Ref.
Acute lymphoblastic leukemia	1000 mg/m^2/day (RP2D)	Activates AMPK and inhibits unfolded protein response	Good safety and anti-tumor activity	[95]
Breast cancer (mouse model)	High dose metformin (200 mg/kg) +dasatinib (20 mg/kg)	Inhibits Src signaling	Shows a synergistic inhibitory effect	[96]
Glioma (mouse model)	Metformin (10 mg/25 g/day)+ temozolomide (15 mg/kg/day)	Enhances AMPK phosphorylation, inhibits m-TOR phosphorylation target, AKT phosphorylation target and p53 expression, and inhibits FASN expression	Significantly prolongs mouse survival	[97]
Gastrointestinal tumors	Individualized dosage (diabetic/non-diabetic stratification)	Diabetics: inhibition of insulin-IGF−1/PI3K/AKT; Non-diabetic patients: down-regulating COX−2/PGE2, and induces p21 block	Enhances chemotherapy sensitivity	[98]
LKB1 mutant non-small cell lung cancer (mouse model)	Metformin (300 mg/kg)+ calorie restriction	Reshapes the TME	Improves chemotherapy/immunotherapy response rates	[14]
Pancreatic ductal adenocarcinoma (mouse model)	Low dose metformin(1 mg/ml) and simvastatin(50 mg/kg)	Reduces the transcriptional activity of Hippo effectors, YAP, and TAZ	Inhibits the development of PDAC	[99]
Rectal cancer (with diabetes)	Higher dose (> 1000 mg/day) + neoadjuvant chemoradiotherapy	Is significantly associated with improved levels	Improves tumor regression grade	[100]
Bladder cancer (mouse model)	Injectes metformin 26 or 104 mg/kg into the bladder twice a week	Activates AMPK and reduces phosphorylation of AKTand ERK	Quickly eliminates tumors	[101]
Colorectal cancer (with diabetes)	High dose	A 10 % reduction in CRC risk for each 1 kg increase in cumulative dose	Reduces the risk of colorectal adenoma and cancer in diabetic patients and improves the prognosis of colorectal cancer patients	[102]

emerged, providing innovative and promising solutions for the precise and efficient delivery of metformin(Table 5) [103]. Extensive research has confirmed that encapsulating metformin in carefully designed nanocarriers can significantly enhance its biological activity, achieving a '1 + 1 > 2' therapeutic effect and promoting its evolution into a modern precision anti-cancer drug [104].

4.5.1. Nano-carriers that enhance bioavailability and tumor targeting

Nano-carriers can significantly improve the delivery efficiency of metformin by enhancing drug solubility, protecting the drug from premature degradation, exploiting the unique pathophysiological characteristics of the tumor microenvironment. Additionally, nanoparticles can passively accumulate in tumor tissues through the enhanced penetration and retention effect (EPR effect) [104]. To further enhance targeting specificity, researchers often modify the surface of nanocarriers with specific ligands to achieve active targeting. For example, the Basu team developed a hyaluronic acid-graphene oxide-metformin (HA-GO-Met) composite nanomaterial system, which leverages the specific binding between HA and the CD44 receptor highly expressed on the surface of tumor cells to precisely target triple-negative breast cancer (TNBC). This system requires only a low dose of metformin to effectively regulate the miR-10b/PTEN signaling axis and inhibit the activity of the NF-κB/p65 pathway, thereby efficiently inducing apoptosis, inhibiting tumor migration, and suppressing cancer stem cell characteristics in both in vitro and in vivo models, while demonstrating excellent biosafety [105]. Similarly, Ghorbanzadeh et al. designed polyethylene glycol-coated nanoparticles [106], the lecithin-chitosan nanoparticles developed by the Abd-Rabou team [107] and the pectin nanoparticles developed by the Gouhar team [108], have both confirmed that the nanotechnology strategy can generally enhance the antitumor activity of metformin. The specific mechanisms of action are shown in Table 5.

4.5.2. A co-delivery system that achieves synergistic efficiency gains

Co-encapsulating metformin with traditional chemotherapy drugs in the same nanocarrier is an effective way to overcome drug resistance and achieve synergistic effects. This co-delivery system ensures that two (or more) drugs arrive at the tumor site at the same time and in the same place in precise synergistic proportions.For example, the MPLO@HA nanomedicine developed by Li et al. is created by conjugating metformin, oxaliplatin (OxPt), and lauric acid (LA) to oligomeric ethyleneimine (OEI), which is then combined with hyaluronic acid (HA). The MPLO@HA nanodrug exhibits multi-responsiveness, responding to pH, glutathione, and hyaluronidase in the TME, enabling precise targeting and controlled release at the tumor site [109]. Meng et al. designed and synthesised pH/GSH-responsive degradable copper-metformin nanocatalytic polymers loaded with Dox (Dox@Cu-MetNPs). In the TME, Dox@Cu-MetNPs undergo self-degradation, releasing Dox, Cu^2, and Met. Met damages mitochondrial respiratory chain complex I, increasing O^2 levels at the tumor site and alleviating tumor hypoxia; Dox not only serves as a chemotherapeutic agent but also promotes the conversion of O_2 into H_2O_2 through a cascade catalytic reaction, thereby increasing H_2O_2 levels in the tumor site; Cu^+/Cu^{2+} reacts with H_2O_2 in a Fenton-like reaction, accelerating the accumulation of highly toxic ROS in the tumor site. Additionally, the accumulation of O_2 facilitates the entry of Dox into tumor cells, thereby enhancing the efficacy of chemotherapy [110].

4.5.3. Nanoformulations as highly effective sensitizers

Metformin, as a potential sensitizer for radiotherapy and chemotherapy, works through mechanisms such as regulating the AMPK/mTOR pathway, reshaping the tumor immune microenvironment, and improving tumor hypoxia [111]. In particular, metformin can improve the sensitivity of radiotherapy by inhibiting hypoxia-inducible factor-1α (HIF-1α) and improving the hypoxic state of tumor tissue [112]. However, conventional oral administration struggles to achieve effective sensitizing concentrations at tumor sites. This challenge is perfectly addressed by nanocarrier systems. By encapsulating metformin into targeted carriers-particularly those modified with biomolecules like folic acid or RGD peptides-we can significantly boost drug concentration in tumor tissues prior to radiotherapy [113]. This can not only maximize its radiopositive effect, but also effectively reduce the toxic and side effects on surrounding normal tissues, which opens up a new way to realize low dose and high efficiency of combined treatment mode.

In summary, nanotechnology provides a powerful tool for overcoming the inherent limitations of metformin. Through innovative nanomedicine formulation design, metformin is transitioning from a non-specific adjuvant drug to a modern anticancer agent capable of achieving spatiotemporal precision control via advanced delivery technologies. These cutting-edge explorations not only revitalize the clinical application of metformin but also pave the way for future development of precision tumor treatment strategies based on metabolic regulation.

5. Epidemiological and real-world evidence

5.1. Complex association between metformin and cancer risk

Epidemiological studies reveal that metformin's cancer-preventive effects exhibit significant cancer-type specificity. Meta-analyses demonstrate its potential to reduce overall cancer risk (RR=0.80), CRC (RR=0.82), and pancreatic cancer (RR= 0.71) incidence, though with inter-study heterogeneity and publication bias [118]. Korean cohort studies confirmed a 34 % reduction in CRC risk in males

Table 5
Metformin delivery system based on nanotechnology and its application strategy in tumor treatment.

Nanocarrier system	Strategy/co-therapy	Targeting/MechanismTargeting/mechanism of action	Cancer model	Key findings	Ref.
HA NPs	Single drug, oral delivery	Biological adhesion; improves intestinal absorption	Diabetes combined with cancer	The dosage is 22.84 %, which significantly enhances the oral bioavailability	[114]
HA-GO	Single drug, active targeting	HA-CD44 receptor targeting; regulation of miR−10b/PTEN axis	Triple-negative breast cancer	Efficient induction of apoptosis, inhibition of migration and CSCs characteristics at low doses	[105]
Chitosan NPs	Co-delivery: with doxorubicin	PH responsivity release; synergistic chemotherapy; TAMs reprogramming (M2→M1)	Lung cancer (A549)	Significant synergistic tumor inhibition; achieves the dual effect of chemotherapy and immunomodulation	[115]
Lecithin-chitosan NPs	Single drug	Efficient delivery; regulation of lncRNA H19/miR−29b−3p axis	Colorectal cancer	Significantly inhibits CRC cell proliferation, migration and invasion	[107]
Chitosan NPs	Radioembolism: with silver NPs/ radiotherapy	Enhances the enrichment in the tumor site; radiosensitization	Mammary cancer	Significantly enhances the sensitivity of cancer cells to radiation therapy	[19]
PEG-M Liposomes	Co-delivery: with artemisinin (ART)	Magnetic targeting; drug synergy	Lung cancer (A549)	Achieves targeted co-delivery and enhances the synergistic anti-tumor effect	[116]
ZnO-Met-FA NPs	Co-delivery: with folic acid	Zinc oxide nanoparticles trigger oxidative stress and lead to cell death; increases the expression of folate receptors	Bladder cancer (T24), melanoma (A375)	Improves targeting efficiency and enhances radiotherapy sensitivity	[117]

(HR= 0.66) and 41 % in females (HR= 0.59) [119], and Swedish research indicated a 32 % lower risk of esophageal squamous cell carcinoma (HR=0.68) [120]. Notably, metformin shows dose-dependent protective effects against non-melanoma skin cancer (SCC/BCC OR=0.64) [121] and lung cancer (HR=0.73 for cumulative use ≥5 years) [122], mediated through metabolic reprogramming and inflammatory microenvironment modulation.

However, conflicting evidence exists. A nationwide cohort analysis found no significant association between metformin and overall cancer risk (HR=0.96), with neither low-dose (≤1 g/day) nor high-dose (>1 g/day) regimens showing significant effects [123]. Israeli [124] and Swedish [125] studies similarly reported no risk reduction for specific cancers like gastric adenocarcinoma. This heterogeneity may stem from variations in study design, population characteristics, and diabetes duration. Large-scale prospective studies are needed to clarify metformin's potential role in cancer prevention.

5.2. Impact of metformin on cancer patient survival

Numerous studies indicate metformin use is associated with significantly improved survival in various cancers, though benefits are cancer-type specific. For instance, head and neck cancer patients showed higher 5-year survival rates (75.3 % vs. 69.8 %) [126]. In CRC, metformin reduced cancer-specific mortality (HR=0.80) and improved overall survival [127]. Meta-analyses confirmed prolonged survival and reduced recurrence in HCC patients with T2DM [128]. Consistent benefits were also observed in digestive system cancers, particularly gastric cancer patients post-gastrectomy [129] and diabetic pancreatic cancer patients [130,131].

Survival advantages are most pronounced in specific subgroups and combination therapies. In bladder cancer, metformin enhanced outcomes in BCG-treated non-muscle-invasive patients, reducing cancer-specific mortality [132]. Similarly, it correlated with prolonged disease-free survival in cervical cancer [133] and progression-free survival in glioblastoma (10.13 vs. 4.67/6.7 months) [134]. However, inconsistent results in endometrial and prostate cancers suggest efficacy may depend on tumor biology, patient heterogeneity, and treatment protocols.

5.3. Metformin's preventive potential in high-risk populations

Preclinical studies demonstrate metformin's chemopreventive potential in high-risk populations. In genetic mouse models of pancreatic cancer, metformin suppressed acinar-ductal metaplasia (ADM) and pancreatic intraepithelial neoplasia (PanIN) formation, inhibiting tumor growth and extending survival in KPC mice [135]. Similarly, in ErbB2-overexpressing breast cancer models, metformin selectively targeted CD61 (high)/CD49f (high) tumor-initiating cell subpopulations by downregulating ErbB2/EGFR expression and related signaling pathways [136]. Preliminary human studies also suggest potential risk reduction for colorectal and lung cancers in high-risk groups [137,138], highlighting its promise for precision prevention strategies.

6. Controversies and challenges of metformin in cancer therapy

6.1. Safety

The safety of metformin in oncology settings has been rigorously evaluated in clinical trials. In a phase II study involving locally advanced cervical cancer patients, metformin (850 mg twice daily) administered one week prior to and during chemoradiation demonstrated comparable rates of grade ≥ 3 adverse events (AEs) to the control group, with gastrointestinal toxicity being the most common reversible complication [139]. Similarly, a multicenter I-II trial in NSCLC established a maximum tolerated dose of 1500 mg/day when combined with erlotinib (150 mg), showing manageable AEs (diarrhea, anorexia, and dermatitis) responsive to supportive care [15]. While these findings support short-term safety in specific contexts, comprehensive validation across diverse cancer types and therapeutic combinations is essential to ensure broad clinical applicability.

6.2. Individual heterogeneity and predictive biomarkers

The clinical antitumor effects of metformin are significantly constrained by interindividual and intertumor heterogeneity, which has become a key obstacle to the precise application of this drug. This heterogeneity is rooted in multiple levels, including the patient's systemic metabolic state, host genetic background, and intrinsic molecular characteristics of the tumor.

At the clinical phenotype level, the patient's metabolic status is a key determinant of treatment efficacy. For example, a preoperative randomized trial targeting breast cancer clearly indicated that insulin resistance (marked by a HOMA index > 2.8) is a prerequisite for metformin to exert its antiproliferative effect (reduction in Ki-67), and that serum metformin concentrations are positively correlated with treatment response only in this metabolically dysregulated subgroup [140]. This finding highlights the potential limitations of metformin efficacy when used in individuals with normal metabolism.

At the host pharmacogenomics level, key gene polymorphisms responsible for drug transport directly affect the bioavailability and intracellular concentration of metformin. Organic cation transporter 1, encoded by the SLC22A1 gene, is the main gateway for metformin to enter the liver and various tumor cells [16,141]. Numerous studies have confirmed that alleles in the SLC22A1 gene that cause functional impairment (such as the rs628031 and rs34059554 variants) significantly reduce the intracellular uptake of metformin, thereby weakening its hypoglycemic and potential antitumor effects [142]. Given the significant differences in OCT1 genotype frequencies across different ethnic groups [143], integrating OCT1 genotyping into clinical practice is crucial for predicting treatment efficacy and guiding personalized medication.

From the perspective of intrinsic molecular biology of tumors, specific gene mutations are the most powerful biomarkers for predicting metformin sensitivity. Among them, the functional status of the tumor suppressor gene LKB1 (STK11) is a prime example. LKB1 is the primary upstream kinase that activates AMPK, and its loss-of-function mutations are commonly found in various tumors, including NSCLC [144]. These LKB1-deficient tumor cells are unable to initiate the classic AMPK-mediated adaptive response to energy stress, and therefore exhibit a high sensitivity to the energy crisis induced by metformin, known as 'synthetic lethality' [145], this makes the LKB1 mutation status a highly promising predictive biomarker for identifying patient populations most likely to benefit from metformin therapy.

In conclusion, to overcome the heterogeneity of metformin's efficacy, future clinical research must abandon the 'one size fits all' model and turn to a multidimensional and individualized treatment framework integrating clinical metabolic typing, host pharmacogenomic testing and tumor molecular characterization analysis.

6.3. Long-term efficacy and drug resistance

Emerging evidence highlights dual facets of metformin's long-term effects. In ovarian cancer, chronic low-dose metformin administration impedes chemoresistance development by reducing cancer stem cell populations and pluripotency marker expression [146]. Conversely, breast cancer models demonstrate cross-resistance to tamoxifen and irreversible ER suppression via AKT/Snail1 pathway hyperactivation following prolonged metformin exposure [147]. Notably, lung cancer studies reveal that metformin-resistant cells (A549-R) exhibit enhanced invasiveness through mitochondrial fragmentation and pro-inflammatory gene upregulation [148]. These paradoxical outcomes underscore the need for resistance-countering strategies, such as

intermittent dosing or combination therapies targeting compensatory pathways.

7. Future perspectives

Metformin has evolved from a conventional glucose-lowering agent to a pivotal tool for investigating tumor metabolism-immune crosstalk and a promising adjunctive antitumor therapy. Despite robust preclinical evidence, its clinical translation faces three critical barriers: significant interpatient response heterogeneity, suboptimal oral bioavailability, and the absence of validated predictive biomarkers. These limitationscollectively constrain its broad clinical implementation and precision application.

Future advancements crucially require: (1) Development of predictive biomarkers integrating tumor mutational profiles, metabolic signatures, and immune microenvironment features to stratify optimal responders; (2) Mechanistic exploration of synergistic combinations with chemotherapy (reversing drug resistance), immune checkpoint inhibitors (enhancing T cell activation), and radiotherapy through chronomodulated dosing strategies; (3) Engineering nanotechnology-based delivery platforms (e.g., tumor-targeted nanoparticles) to improve intralesional drug accumulation while minimizing systemic toxicity; (4) Validation of its chemopreventive efficacy in high-risk populations (e.g., BRCA mutation carriers) and post-treatment metabolic health management to reduce recurrence risks. Such multidimensional optimization aims to amplify therapeutic benefits while mitigating current pharmacokinetic and pharmacodynamic limitations.

Furthermore, large-scale bioinformatics analysis of integrated public cancer genomics and transcriptomics datasets is crucial for bridging the gap between preclinical mechanisms and clinical practice. Publicly available databases, such as the Cancer Genome Atlas (TCGA) and the Gene Expression Omnibus (GEO), provide valuable resources for validating the hypothesized targets and mechanism pathways of metformin in large, heterogeneous human tumor cohorts. For example, the expression levels of metformin transporters such as SLC22A1 (OCT1) or key pathway components such as PRKAA1 (AMPKα) and STK11 (LKB1) can be associated with clinical outcomes, including patient survival and treatment response, across multiple cancer types. This in silico (computer simulation) approach enables rapid and cost-effective assessment of whether genes associated with metformin action in cell lines have prognostic or predictive significance in real patients. Additionally, gene expression profiles derived from metformin-treated cells (data often available in GEO) can be used to query TCGA data to identify patient subgroups whose tumors exhibit a ‘metformin-sensitive’ transcriptional profile. Such analyses help prioritize hypotheses for prospective clinical validation and aid in the discovery of new predictive biomarkers, thereby accelerating the transformation of metformin from an ‘old drug with new uses’ to a precision oncology tool. By integrating multidisciplinary strategies, metformin could transition from a‘ broad-spectrum-agent’ to a precision tool in personalized oncology, ultimately fulfilling its potential as an indispensable component of modern cancer therapeutics.

Abbreviations

International Agency for Research on Cancer: IARC; Organic cation transporters: OCTs; AMP-activated protein kinase: AMPK; Colorectal cancer: CRC; Hepatocellular carcinoma: HCC; Hexokinase II: HK2; Mitochondrial complex I: MCI; Tumor microenvironment: TME; Fatty acid synthase: FASN; Insulin-like growth factor-1: IGF-1; Epithelial-mesenchymal transition: EMT; Farnesoid X receptor: FXR; Reactive oxygen species: ROS; Regulatory T cells: Tregs; Randomized controlled trials: RCTs; Castration-resistant prostate cancer: CRPC; Type 2 diabetes mellitus: T2DM; Hormone receptor: HR; Ttriple-negative breast cancer: TNBC; 5-fluorouracil: 5-FU; Glioblastoma multiforme: GBM; Temozolomide: TMZ; Androgen deprivation therapy: ADT; Thioesterase A: TSA; Immune checkpoint inhibitors: ICIs; Organic cation transporter 1: OCT1; Acute lymphoblastic leukemia: ALL; Unfolded protein response: UPR; Non-small cell lung cancer: NSCLC; Pharmacokinetic: PK; Nanotechnology-based drug delivery systems: NDDS; Retention effect: EPR effect; Oligomeric ethyleneimine: OEI; Hyaluronic acid: HA; Hypoxia-inducible factor-1α: HIF-1α; Endoplasmic reticulum-associated degradation: ERAD; Cytotoxic T lymphocyte: CTL; Tumor immune microenvironment: TIME; Recommended Phase II dose: RP2D; Acinar-ductal metaplasia: ADM; Pancreatic intraepithelial neoplasia: PanIN; Adverse events: AEs; Insulin-like growth factor-1: IGF-1; Hormone receptor: HR; Trichostatin A: TSA; Doxorubicin: Dox; Oxaliplatin: OxPt; Lauric acid: LA.

CRediT authorship contribution statement

Ruili Sun: Conceptualization. **Lijun Zhao**: Writing – review & editing. **Huiying Lv**: Writing – original draft. **Haofei Gong**: Visualization. **Ran Zhao**: Visualization. **Xuan Gao**: Visualization. **Wenyue Liu**: Visualization.

Declaration of Competing Interest

All authors disclosed no relevant relationships.

Acknowledgments

This work was supported by Key Scientific Research Projects of Higher Education Institutions in Henan Province (grant numbers. 25A320018 and 25A180011), Key Scientific and Technological Projects of Henan Province (grant numbers.252102311135) , The Zhongyuan Academician Fund from Henan Province (grant numbers. C24185) and 111 Project (grant numbers. D20036).

Data availability

The data that has been used is confidential.

References

[1] A.M. Filho, M. Laversanne, J. Ferlay, M. Colombet, M. Piñeros, A. Znaor, et al., The GLOBOCAN 2022 cancer estimates: data sources, methods, and a snapshot of the cancer burden worldwide, Int. J. Cancer 156 (7) (2025) 1336–1346.
[2] A. Zafar, S. Khatoon, M.J. Khan, J. Abu, A. Naeem, Advancements and limitations in traditional anti-cancer therapies: a comprehensive review of surgery, chemotherapy, radiation therapy, and hormonal therapy, Discov. Oncol. 16 (1) (2025) 607.
[3] Y. Xiao, T.J. Yu, Y. Xu, R. Ding, Y.P. Wang, Y.Z. Jiang, et al., Emerging therapies in cancer metabolism, Cell Metab. 35 (8) (2023) 1283–1303.
[4] C.R. Sirtori, S. Castiglione, C. Pavanello, Metformin: from diabetes to cancer to prolongation of life, Pharmacol. Res. 208 (2024) 107367.
[5] Y. Shu, S.A. Sheardown, C. Brown, R.P. Owen, S. Zhang, R.A. Castro, et al., Effect of genetic variation in the organic cation transporter 1 (OCT1) on metformin action, J. Clin. Investig. 117 (5) (2007) 1422–1431.
[6] R.J. Smith Jr., R. Zollo, S. Kalvapudi, Y. Vedire, A.G. Pachimatla, C. Petrucci, et al., Obesity-specific improvement of lung cancer outcomes and immunotherapy efficacy with metformin, J. Natl. Cancer Inst. 117 (4) (2025) 673–684.
[7] L. O'Connor, M. Bailey-Whyte, M. Bhattacharya, G. Butera, K.N.L. Hardell, A. B. Seidenberg, et al., Association of metformin use and cancer incidence: a systematic review and meta-analysis, J. Natl. Cancer Inst. 116 (4) (2024) 518–529.
[8] M.Y. Zamanian, M. Golmohammadi, A. Yumashev, A. Hjazi, M.A. Toama, M. A. AbdRabou, et al., Effects of metformin on cancers in experimental and clinical studies: focusing on autophagy and AMPK/mTOR signaling pathways, Cell Biochem. Funct. 42 (4) (2024) e4071.
[9] Y. Wang, X. Jia, B. Cong, Advances in the mechanism of metformin with wide-ranging effects on regulation of the intestinal microbiota, Front. Microbiol. 15 (2024) 1396031.
[10] J. Liu, X. Li, Y. Li, Q. Gong, K. Luo, Metformin-based nanomedicines for reprogramming tumor immune microenvironment, Theranostics 15 (3) (2025) 993–1016.
[11] R.S. Pal, T. Jawaid, M.A. Rahman, R. Verma, P.K. Patra, S.V. Vijaypal, et al., Metformin's anticancer odyssey: revealing multifaceted mechanisms across diverse neoplastic terrains- a critical review, Biochimie 233 (2025) 109–121.

[12] S. Dutta, R.B. Shah, S. Singhal, S.B. Dutta, S. Bansal, S. Sinha, et al., Metformin: a review of potential mechanism and therapeutic utility beyond diabetes, Drug Des. Dev. Ther. 17 (2023) 1907–1932.
[13] L. Zhu, K. Yang, Z. Ren, D. Yin, Y. Zhou, Metformin as anticancer agent and adjuvant in cancer combination therapy: current progress and future prospect, Transl. Oncol. 44 (2024) 101945.
[14] G. Ndembe, I. Intini, M. Moro, C. Grasselli, A. Panfili, N. Panini, et al., Caloric restriction and metformin selectively improved LKB1-mutated NSCLC tumor response to chemo- and chemo-immunotherapy, J. Exp. Clin. Cancer Res. 43 (1) (2024) 6.
[15] F. Morgillo, M. Fasano, C.M. Della Corte, F.C. Sasso, F. Papaccio, G. Viscardi, et al., Results of the safety run-in part of the METAL (METformin in Advanced Lung cancer) study: a multicentre, open-label phase I-II study of metformin with erlotinib in second-line therapy of patients with stage IV non-small-cell lung cancer, ESMO Open 2 (2) (2017) e000132.
[16] S. Zhang, A. Zhu, F. Kong, J. Chen, B. Lan, G. He, et al., Structural insights into human organic cation transporter 1 transport and inhibition, Cell Discov. 10 (1) (2024) 30.
[17] L. Sun, H.J. Yao, J.C. Li, B.Q. Zhao, Y.A. Wang, Y.G. Zhang, Activated carbon nanoparticles loaded with metformin for effective against hepatocellular cancer stem cells, Int. J. Nanomed. 18 (2023) 2891–2910.
[18] A. Wang, L.A. Madden, V.N. Paunov, Enhanced anticancer effect of lysozyme-functionalized metformin-loaded shellac nanoparticles on a 3D cell model: role of the nanoparticle and payload concentrations, Biomater. Sci. 12 (18) (2024) 4735–4746.
[19] F. Shiridokht, H. Dadashi, S. Vandghanooni, M. Eskandani, A. Farajollahi, Metformin-loaded chitosan nanoparticles augment silver nanoparticle-induced radiosensitization in breast cancer cells during radiation therapy, Colloids Surf. B Biointerfaces 245 (2025) 114220.
[20] C. Chen, L. Yang, Y. Peng, W.J. Zhang, X.X. Yang, W. Zhou, Autophagic blockage by metformin-loaded PLGA nanoparticles causes cell cycle arrest of HepG2 cells, Nanomedicine 19 (1) (2024) 43–58.
[21] J.M. Dennis, K.G. Young, P. Cardoso, L.M. Güdemann, A.P. McGovern, A. Farmer, et al., A five-drug class model using routinely available clinical features to optimise prescribing in type 2 diabetes: a prediction model development and validation study, Lancet 405 (10480) (2025) 701–714.
[22] V. Penugurti, R.K. Manne, L. Bai, R. Kant, H.K. Lin, AMPK: the energy sensor at the crossroads of aging and cancer, Semin. Cancer Biol. 106-107 (2024) 15–27.
[23] C.C. Hsu, D. Peng, Z. Cai, H.K. Lin, AMPK signaling and its targeting in cancer progression and treatment, Semin. Cancer Biol. 85 (2022) 52–68.
[24] R. Herman, N.A. Kravos, M. Jensterle, A. Janež, V. Dolžan, Metformin and insulin resistance: a review of the underlying mechanisms behind changes in GLUT4-Mediated glucose transport, Int. J. Mol. Sci. 23 (3) (2022).
[25] S. Mostafavi, H. Zalpoor, Z.M. Hassan, The promising therapeutic effects of metformin on metabolic reprogramming of cancer-associated fibroblasts in solid tumors, Cell Mol. Biol. Lett. 27 (1) (2022) 58.
[26] T. Welponer, D.D. Weber, L. Trattner, B. Tockner, S. Aminzadeh-Gohari, V. Leb-Reichl, et al., Metformin shows anti-neoplastic properties by inhibition of oxidative phosphorylation and glycolysis in epidermolysis bullosa-associated aggressive cutaneous squamous cell carcinoma, J. Eur. Acad. Dermatol. Venereol. 38 (1) (2024) 112–123.
[27] J. Ouyang, Y. Feng, Y. Zhang, Y. Liu, S. Li, J. Wang, et al., Integration of metabolomics and transcriptomics reveals metformin suppresses thyroid cancer progression via inhibiting glycolysis and restraining DNA replication, Biomed. Pharmacother. 168 (2023) 115659.
[28] L. Hu, Z. Zeng, Q. Xia, Z. Liu, X. Feng, J. Chen, et al., Metformin attenuates hepatoma cell proliferation by decreasing glycolytic flux through the HIF-1α/PFKFB3/PFK1 pathway, Life Sci. 239 (2019) 116966.
[29] M. Foretz, B. Guigas, L. Bertrand, M. Pollak, B. Viollet, Metformin: from mechanisms of action to therapies, Cell Metab. 20 (6) (2014) 953–966.
[30] S. Cai, Y. Deng, Z. Zou, W. Tian, Z. Tang, J. Li, et al., Metformin inhibits the progression of castration-resistant prostate cancer by regulating PDE6D induced purine metabolic alternation and cGMP / PKG pathway activation, Cancer Lett. 622 (2025) 217694.
[31] J. Farheen, M.Z. Iqbal, A. Mushtaq, Y. Hou, X. Kong, Hippophae rhamnoides-derived phytomedicine nano-system modulates bax/fas pathways to reduce proliferation in triple-negative breast cancer, Adv. Health Mater. (2024) e2401197.
[32] T.A. Smith, S.M. Phyu, Metformin decouples phospholipid metabolism in breast cancer cells, PLOS One 11 (3) (2016) e0151179.
[33] L. Cheng, R. Deepak, G. Wang, Z. Meng, L. Tao, M. Xie, et al., Hepatic mitochondrial NAD + transporter SLC25A47 activates AMPKalpha mediating lipid metabolism and tumorigenesis, Hepatology 78 (6) (2023) 1828–1842.
[34] J. Zhang, M. Chen, Y. Yang, Z. Liu, W. Guo, P. Xiang, et al., Amino acid metabolic reprogramming in the tumor microenvironment and its implication for cancer therapy, J. Cell Physiol. 239 (11) (2024) e31349.
[35] X. Huang, T. Sun, J. Wang, X. Hong, H. Chen, T. Yan, et al., Metformin reprograms tryptophan metabolism to stimulate CD8+ T-cell function in colorectal cancer, Cancer Res. 83 (14) (2023) 2358–2371.
[36] B.A. Espinosa-Rodriguez, D. Treviño-Almaguer, P. Carranza-Rosales, M. A. Ramirez-Cabrera, K. Ramirez-Estrada, E.U. Arredondo-Espinoza, et al., Metformin May alter the metabolic reprogramming in cancer cells by disrupting the L-Arginine metabolism: a preliminary computational study, Int. J. Mol. Sci. 24 (6) (2023).
[37] T.Y.L. Huynh, I. Oscilowska, J. Sáiz, M. Nizioł, W. Baszanowska, C. Barbas, et al., Metformin treatment or PRODH/POX-Knock out similarly induces apoptosis by reprograming of amino acid metabolism, TCA, urea cycle and pentose phosphate pathway in MCF-7 breast cancer cells, Biomolecules 11 (12) (2021).
[38] C. Ma, M. Han, B. Heinrich, Q. Fu, Q. Zhang, M. Sandhu, et al., Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells, Science 360 (6391) (2018).
[39] S.A. Hawley, F.A. Ross, C. Chevtzoff, K.A. Green, A. Evans, S. Fogarty, et al., Use of cells expressing gamma subunit variants to identify diverse mechanisms of AMPK activation, Cell Metab. 11 (6) (2010) 554–565.
[40] K. Inoki, Y. Li, T. Zhu, J. Wu, K.L. Guan, TSC2 is phosphorylated and inhibited by akt and suppresses mTOR signalling, Nat. Cell Biol. 4 (9) (2002) 648–657.
[41] C. Yan, S. Liu, Q. Song, Y. Hu, Metformin inhibits self-renewal of colorectal cancer stem cells by inhibiting mitochondrial oxidative phosphorylation, Nan Fang. Yi Ke Da Xue Xue Bao 43 (8) (2023) 1279–1286.
[42] W. Wu, J.L. Yang, Y.L. Wang, H. Wang, M. Yao, L. Wang, et al., Reversal of multidrug resistance of hepatocellular carcinoma cells by metformin through inhibiting NF-κB gene transcription, World J. Hepatol. 8 (23) (2016) 985–993.
[43] Z. Shi, Z. Xiao, L. Hu, Y. Gao, J. Zhao, Y. Liu, et al., The genetic association between type 2 diabetic and hepatocellular carcinomas, Ann. Transl. Med. 8 (6) (2020) 380.
[44] N. Alimoradi, N. Firouzabadi, R. Fatehi, How metformin affects various malignancies by means of microRNAs: a brief review, Cancer Cell Int. 21 (1) (2021) 207.
[45] S. Dhang, A. Mondal, C. Das, S. Roy, Metformin inhibits the histone methyltransferase CARM1 and attenuates H3 histone methylation during gluconeogenesis, J. Biol. Chem. 301 (3) (2025) 108271.
[46] V. Finisguerra, T. Dvorakova, M. Formenti, P. Van Meerbeeck, L. Mignion, B. Gallez, et al., Metformin improves cancer immunotherapy by directly rescuing tumor-infiltrating CD8 t lymphocytes from hypoxia-induced immunosuppression, J. Immunother. Cancer 11 (5) (2023).
[47] L. Wei, Z. Luo, J. Li, H. Li, Y. Liang, J. Li, et al., Metformin inhibits proliferation and functions of regulatory t cells in acidic environment, Nan Fang. Yi Ke Da Xue Xue Bao 39 (12) (2019) 1427–1435.
[48] A.R. Petrovic, I.P. Jovanovic, M.M. Jurisevic, M.Z. Jovanovic, M.M. Jovanovic, S. P. Pavlovic, et al., Metformin promotes antitumor activity of NK cells via overexpression of miRNA-150 and miRNA-155, Am. J. Transl. Res. 15 (4) (2023) 2727–2737.
[49] G.Y. Li, Y.Q. Feng, Y.F. Jia, K.F. Wang, Y. Li, S.J. Zhang, et al., Metformin enhances t lymphocyte anti-tumor immunity by increasing the infiltration via vessel normalization, Eur. J. Pharmacol. 944 (2023) 175592.
[50] S.H. Park, J. Lee, H.J. Yun, S.H. Kim, J.H. Lee, Metformin suppresses both PD-L1 expression in cancer cells and Cancer-Induced PD-1 expression in immune cells to promote antitumor immunity, Ann. Lab Med. 44 (5) (2024) 426–436.
[51] J.H. Cha, W.H. Yang, W. Xia, Y. Wei, L.C. Chan, S.O. Lim, et al., Metformin promotes antitumor immunity via endoplasmic-reticulum-associated degradation of PD-L1, Mol. Cell 71 (4) (2018) 606–620, e607.
[52] Y. Lu, D. Xin, L. Guan, M. Xu, Y. Yang, Y. Chen, et al., Metformin downregulates PD-L1 expression in esophageal squamous cell catrcinoma by inhibiting IL-6 signaling pathway, Front. Oncol. 11 (2021) 762523.
[53] X. Zhao, C. Liu, L. Peng, H. Wang, Metformin facilitates anti-PD-L1 efficacy through the regulation of intestinal microbiota, Genes Immun. 25 (1) (2024) 7–13.
[54] Z. Gu, F. Ye, H. Luo, X. Li, Y. Gong, S. Mao, et al., Metformin sensitizes triple-negative breast cancer to histone deacetylase inhibitors by targeting FGFR4, J. Biomed. Sci. 32 (1) (2025) 36.
[55] K. Simpson, D.B. Allison, D. He, J. Liu, C. Wang, X. Liu, Metformin in overcoming enzalutamide resistance in castration-resistant prostate cancer, J. Pharmacol. Exp. Ther. 392 (1) (2025) 100034.
[56] J. He, Y. Luo, Y. Ding, L. Zhu, Metformin inhibits the progression of pancreatic cancer through regulating miR-378a-3p/VEGFA/RGC-32 axis, Cancer Med. 13 (23) (2024) e70446.
[57] A. Nazemiyeh, H. Dadashi, M. Mashinchian, A. Karimian-Shaddel, A. Mohabbat, M. Eskandani, et al., Exploring the synergistic effects of metformin and doxorubicin loaded chitosan nanoparticles for A549 lung cancer therapy, Sci. Rep. 15 (1) (2025) 22657.
[58] O.H.Y. Yu, S. Suissa, Metformin and cancer: solutions to a real-world evidence failure, Diabetes Care 46 (5) (2023) 904–912.
[59] J.M. Evans, L.A. Donnelly, A.M. Emslie-Smith, D.R. Alessi, A.D. Morris, Metformin and reduced risk of cancer in diabetic patients, Bmj 330 (7503) (2005) 1304–1305.
[60] S. Gandini, M. Puntoni, B.M. Heckman-Stoddard, B.K. Dunn, L. Ford, A. DeCensi, et al., Metformin and cancer risk and mortality: a systematic review and meta-analysis taking into account biases and confounders, Cancer Prev. Res. 7 (9) (2014) 867–885.
[61] S. Suissa, L. Azoulay, Metformin and the risk of cancer: time-related biases in observational studies, Diabetes Care 35 (12) (2012) 2665–2673.
[62] B.E. Wilson, A.J. Armstrong, J. de Bono, C.N. Sternberg, C.J. Ryan, H.I. Scher, et al., Effects of metformin and statins on outcomes in men with castration-resistant metastatic prostate cancer: secondary analysis of COU-AA-301 and COU-AA-302, Eur. J. Cancer 170 (2022) 296–304.
[63] S. Kordes, M.N. Pollak, A.H. Zwinderman, R.A. Mathôt, M.J. Weterman, A. Beeker, et al., Metformin in patients with advanced pancreatic cancer: a double-blind, randomised, placebo-controlled phase 2 trial, Lancet Oncol. 16 (7) (2015) 839–847.
[64] S. Wang, Y. Lin, X. Xiong, L. Wang, Y. Guo, Y. Chen, et al., Low-Dose metformin reprograms the tumor immune microenvironment in human esophageal cancer: results of a phase II clinical trial, Clin. Cancer Res. 26 (18) (2020) 4921–4932.

[65] J.R. Brown, D.K. Chan, J.J. Shank, K.A. Griffith, H. Fan, R. Szulawski, et al., Phase II clinical trial of metformin as a cancer stem cell-targeting agent in ovarian cancer, JCI Insight 5 (11) (2020).
[66] S. Niraula, R.J. Dowling, M. Ennis, M.C. Chang, S.J. Done, N. Hood, et al., Metformin in early breast cancer: a prospective window of opportunity neoadjuvant study, Breast Cancer Res. Treat. 135 (3) (2012) 821–830.
[67] S. Roy, F. Saad, Y. Sun, S. Malone, D.E. Spratt, A.U. Kishan, et al., Effect of concomitant medications on treatment response and survival in non-metastatic castrate resistant prostate cancer: exploratory analysis of the SPARTAN trial, Eur. J. Cancer 211 (2024) 114197.
[68] Y. Dong, Y. Qi, H. Jiang, T. Mi, Y. Zhang, C. Peng, et al., The development and benefits of metformin in various diseases, Front. Med. 17 (3) (2023) 388–431.
[69] P. Sena, S. Mancini, M. Benincasa, F. Mariani, C. Palumbo, L. Roncucci, Metformin induces apoptosis and alters cellular responses to oxidative stress in Ht29 colon cancer cells: preliminary findings, Int. J. Mol. Sci. 19 (5) (2018).
[70] Q. Wen, M. Hu, M. Lai, J. Li, Z. Hu, K. Quan, et al., Effect of acupuncture and metformin on insulin sensitivity in women with polycystic ovary syndrome and insulin resistance: a three-armed randomized controlled trial, Hum. Reprod. 37 (3) (2022) 542–552.
[71] C.V. Calkin, K.N.R. Chengappa, K. Cairns, J. Cookey, J. Gannon, M. Alda, et al., Treating insulin resistance with metformin as a strategy to improve clinical outcomes in Treatment-Resistant bipolar depression (the TRIO-BD Study): a randomized, quadruple-masked, placebo-controlled clinical trial, J. Clin. Psychiatry 83 (2) (2022).
[72] L. Guo, L. Chen, B. Chang, L. Yang, Y. Liu, B. Feng, A randomized, open-label, multicentre, parallel-controlled study comparing the efficacy and safety of biphasic insulin aspart 30 plus metformin with biphasic insulin aspart 30 monotherapy for type 2 diabetes patients inadequately controlled with oral antidiabetic drugs: the merit study, Diabetes Obes. Metab. 20 (12) (2018) 2740–2747.
[73] M. Moro, E. Caiola, M. Ganzinelli, E. Zulato, E. Rulli, M. Marabese, et al., Metformin enhances Cisplatin-Induced apoptosis and prevents resistance to cisplatin in Co-mutated KRAS/LKB1 NSCLC, J. Thorac. Oncol. 13 (11) (2018) 1692–1704.
[74] H. Lu, X. Han, J. Ren, K. Ren, Z. Li, Q. Zhang, Metformin attenuates synergic effect of diabetes mellitus and helicobacter pylori infection on gastric cancer cells proliferation by suppressing PTEN expression, J. Cell Mol. Med. 25 (10) (2021) 4534–4542.
[75] D.E. Spratt, C. Zhang, Z.S. Zumsteg, X. Pei, Z. Zhang, M.J. Zelefsky, Metformin and prostate cancer: reduced development of castration-resistant disease and prostate cancer mortality, Eur. Urol. 63 (4) (2013) 709–716.
[76] D.L. Hershman, B.E. Chen, C. Sathe, W.R. Parulekar, J. Lemieux, J.A. Ligibel, et al., Metformin, placebo, and endocrine therapy discontinuation among participants in a randomized double-blind trial of metformin vs placebo in hormone receptor-positive early-stage breast cancer (CCTG MA32), Breast Cancer Res. Treat. 200 (1) (2023) 93–102.
[77] A. Sonnenblick, D. Agbor-Tarh, I. Bradbury, S. Di Cosimo, H.A. Azim Jr., D. Fumagalli, et al., Impact of diabetes, insulin, and metformin use on the outcome of patients with human epidermal growth factor receptor 2-positive primary breast cancer: analysis from the ALTTO phase III randomized trial, J. Clin. Oncol. 35 (13) (2017) 1421–1429.
[78] M. Foretz, B. Guigas, B. Viollet, Metformin: update on mechanisms of action and repurposing potential, Nat. Rev. Endocrinol. 19 (8) (2023) 460–476.
[79] A.J. Scheen, Clinical pharmacokinetics of metformin, Clin. Pharmacokinet. 30 (5) (1996) 359–371.
[80] F. Jalali, F. Fakhari, A. Sepehr, J. Zafari, B.O. Sarajar, P. Sarihi, et al., Synergistic anticancer effects of doxorubicin and metformin combination therapy: a systematic review, Transl. Oncol. 45 (2024) 101946.
[81] T. Bi, A. Zhu, X. Yang, H. Qiao, J. Tang, Y. Liu, et al., Metformin synergistically enhances antitumor activity of cisplatin in gallbladder cancer via the PI3K/AKT/ERK pathway, Cytotechnology 70 (1) (2018) 439–448.
[82] E. Jafarzadeh, B.O. Sarajar, A.R. Lalani, N. Rastegar-Pouyani, S. Aliebrahimi, V. Montazeri, et al., Combating drug resistance in lung cancer: exploring the synergistic potential of metformin and cisplatin in a novel combination therapy; a systematic review, Curr. Top. Med. Chem. (2025).
[83] E. Jafarzadeh, V. Montazeri, S. Aliebrahimi, A.H. Sezavar, M.H. Ghahremani, S. N. Ostad, Targeting cancer stem cells and hedgehog pathway: enhancing cisplatin efficacy in ovarian cancer with metformin, J. Cell Mol. Med. 29 (10) (2025) e70508.
[84] Y. Lee, J. Joo, Y.J. Lee, E.K. Lee, S. Park, T.S. Kim, et al., Randomized phase II study of platinum-based chemotherapy plus controlled diet with or without metformin in patients with advanced non-small cell lung cancer, Lung Cancer 151 (2021) 8–15.
[85] A.B. Parikh, K.A. Marrone, D.J. Becker, J.R. Brahmer, D.S. Ettinger, B.P. Levy, A pooled analysis of two phase II trials evaluating metformin plus platinum-based chemotherapy in advanced non-small cell lung cancer, Cancer Treat. Res. Commun. 20 (2019) 100150.
[86] S. Dong, Y. Xiao, Z. Zhu, X. Ma, Z. Peng, J. Kang, et al., Metformin sensitises osteosarcoma to chemotherapy via the IGF-1R/miR-610/FEN1 pathway, Eur. J. Histochem. 67 (2) (2023).
[87] S. Wang, Y. Lin, Q. Zhao, H. Chen, S. Du, Z. Zeng, Metformin reverses 5-FU resistance induced by radiotherapy through mediating folate metabolism in colorectal cancer, Mol. Med. 31 (1) (2025) 199.
[88] I.F. Moretti, A.M. Lerario, P.R. Sola, J. Macedo-da-Silva, M.D.S. Baptista, G. Palmisano, et al., GBM cells exhibit susceptibility to metformin treatment according to TLR4 pathway activation and metabolic and antioxidant status, Cancers 15 (3) (2023).
[89] D. Mahalingam, S. Hanni, A.V. Serritella, C. Fountzilas, J. Michalek, B. Hernandez, et al., Utilizing metformin to prevent metabolic syndrome due to androgen deprivation therapy (ADT): a randomized phase II study of metformin in non-diabetic men initiating ADT for advanced prostate cancer, Oncotarget 14 (2023) 622–636.
[90] J. Duo, Y. Ma, G. Wang, X. Han, C. Zhang, Metformin synergistically enhances antitumor activity of histone deacetylase inhibitor trichostatin a against osteosarcoma cell line, DNA Cell Biol. 32 (4) (2013) 156–164.
[91] L.E. Munoz, L. Huang, R. Bommireddy, R. Sharma, L. Monterroza, R.N. Guin, et al., Metformin reduces PD-L1 on tumor cells and enhances the anti-tumor immune response generated by vaccine immunotherapy, J. Immunother. Cancer 9 (11) (2021).
[92] S. Wabitsch, J.D. McCallen, O. Kamenyeva, B. Ruf, J.C. McVey, J. Kabat, et al., Metformin treatment rescues CD8(+) T-cell response to immune checkpoint inhibitor therapy in mice with NAFLD, J. Hepatol. 77 (3) (2022) 748–760.
[93] M. Peng, Y. Huang, T. Tao, C.Y. Peng, Q. Su, W. Xu, et al., Metformin and gefitinib cooperate to inhibit bladder cancer growth via both AMPK and EGFR pathways joining at akt and erk, Sci. Rep. 6 (2016) 28611.
[94] Y. Fan, H. Cheng, Y. Liu, S. Liu, S. Lowe, Y. Li, et al., Metformin anticancer: reverses tumor hypoxia induced by bevacizumab and reduces the expression of cancer stem cell markers CD44/CD117 in human ovarian cancer SKOV3 cells, Front. Pharmacol. 13 (2022) 955984.
[95] M. Trucco, J.C. Barredo, J. Goldberg, G.M. Leclerc, G.A. Hale, J. Gill, et al., A phase I window, dose escalating and safety trial of metformin in combination with induction chemotherapy in relapsed refractory acute lymphoblastic leukemia: metformin with induction chemotherapy of vincristine, dexamethasone, PEG-asparaginase, and doxorubicin, Pediatr. Blood Cancer 65 (9) (2018) e27224.
[96] J.H. Park, K.H. Jung, D. Jia, S. Yang, K.S. Attri, S. Ahn, et al., Biguanides antithetically regulate tumor properties by the dose-dependent mitochondrial reprogramming-driven c-Src pathway, Cell Rep. Med. 6 (2) (2025) 101941.
[97] J.E. Lee, J.H. Lim, Y.K. Hong, S.H. Yang, High-Dose metformin plus temozolomide shows increased Anti-tumor effects in glioblastoma in vitro and in vivo compared with monotherapy, Cancer Res. Treat. 50 (4) (2018) 1331–1342.
[98] A.D. Cunha Júnior, A.C. Bragagnoli, F.O. Costa, J.B.C. Carvalheira, Repurposing metformin for the treatment of gastrointestinal cancer, World J. Gastroenterol. 27 (17) (2021) 1883–1904.
[99] Y. Teper, L. Ye, R.T. Waldron, A. Lugea, X. Sun, J. Sinnett-Smith, et al., Low dosage combination treatment with metformin and simvastatin inhibits obesity-promoted pancreatic cancer development in Male KrasG12D mice, Sci. Rep. 13 (1) (2023) 16144.
[100] N.Y. Lin, K.Y. Tsai, Y.L. Huang, B.K. Jong, Z.H. Yu, C.C. Cheng, et al., Metformin's impact on tumor regression grade in diabetic patients with rectal cancer undergoing neoadjuvant chemoradiotherapy, Sci. Rep. 15 (1) (2025) 25759.
[101] M. Peng, Q. Su, Q. Zeng, L. Li, Z. Liu, L. Xue, et al., High efficacy of intravesical treatment of metformin on bladder cancer in preclinical model, Oncotarget 7 (8) (2016) 9102–9117.
[102] M. Deng, S. Lei, D. Huang, H. Wang, S. Xia, E. Xu, et al., Suppressive effects of metformin on colorectal adenoma incidence and malignant progression, Pathol. Res. Pract. 216 (2) (2020) 152775.
[103] M. Liu, R. Wang, M.P.M. Hoi, Y. Wang, S. Wang, G. Li, et al., Nano-Based drug delivery systems for managing diabetes: recent advances and future prospects, Int. J. Nanomed. 20 (2025) 6221–6252.
[104] B. Banerjee, S. Banerjee, T. Sharma, B.C. Nandy, A.K. Nayak, A. Mondal, Metformin and its nanoformulations in cancer prevention and therapy, Curr. Pharm. Des. (2025).
[105] A. Basu, P. Upadhyay, A. Ghosh, A. Bose, P. Gupta, S. Chattopadhyay, et al., Hyaluronic acid engrafted metformin loaded graphene oxide nanoparticle as CD44 targeted anti-cancer therapy for triple negative breast cancer, Biochim Biophys. Acta Gen. Subj. 1865 (3) (2021) 129841.
[106] F. Ghorbanzadeh, D. Jafari-Gharabaghlou, M.R. Dashti, M. Hashemi, N. Zarghami, Advanced nano-therapeutic delivery of metformin: potential anti-cancer effect against human colon cancer cells through inhibition of GPR75 expression, Med. Oncol. 40 (9) (2023) 255.
[107] A.A. Abd-Rabou, A.M. Abdelaziz, O.G. Shaker, G. Ayeldeen, Metformin-loaded lecithin nanoparticles induce colorectal cancer cytotoxicity via epigenetic modulation of noncoding RNAs, Mol. Biol. Rep. 48 (10) (2021) 6805–6820.
[108] S.A. Gouhar, M. Nasr, C.A. Fahmy, M.A.M. AboZeid, S.M. El-Daly, Enhancing the anticancer effect of metformin through nanoencapsulation: apoptotic induction, inflammatory reduction, and suppression of cell migration in colorectal cancer cells, Arch. Pharm. 358 (1) (2025) e2400628.
[109] X. Li, M. Wu, Y. Wu, Y. Xin, L. Gao, M. Elsabahy, et al., Multifunctional nanodrug for simultaneously combating chemoresistance and immunosuppression in fusobacterium nucleatum-associated colorectal cancer, Acta Biomater. 195 (2025) 406–420.
[110] X. Meng, X. Zhang, Y. Lei, D. Cao, Z. Wang, Biodegradable copper-metformin nanoscale coordination polymers for enhanced chemo/chemodynamic synergistic therapy by reducing oxygen consumption to promote H(2)O(2) accumulation, J. Mater. Chem. B 9 (8) (2021) 1988–2000.
[111] T. Tsakiridis, H. Skinner, G. Pond, A. Swaminath, J. Wright, Metformin for chemo-radio-sensitization of NSCLC, Radiother. Oncol. 120 (2) (2016) 363–364.
[112] V.N. Sivalingam, A. Latif, S. Kitson, R. McVey, K.G. Finegan, K. Marshall, et al., Hypoxia and hyperglycaemia determine why some endometrial tumours fail to respond to metformin, Br. J. Cancer 122 (1) (2020) 62–71.

[113] S. He, Y. Huang, J. Liu, H. Liu, Y. Chen, T. Zou, et al., A Metformin-Based multifunctional nanoplatform as a DNA damage amplifier for maximized radio-immunotherapy to overcome radiotherapy resistance, ACS Nano 19 (15) (2025) 14848–14864.
[114] S. Bhujbal, A.K. Dash, Metformin-Loaded hyaluronic acid nanostructure for oral delivery, AAPS PharmSciTech 19 (6) (2018) 2543–2553.
[115] Y. Wen, Y. Liu, C. Chen, J. Chi, L. Zhong, Y. Zhao, et al., Metformin loaded porous particles with bio-microenvironment responsiveness for promoting tumor immunotherapy, Biomater. Sci. 9 (6) (2021) 2082–2089.
[116] R. Shahbazi, Z. Mirjafary, N. Zarghami, H. Saeidian, Efficient PEGylated magnetic nanoniosomes for co-delivery of artemisinin and metformin: a new frontier in chemotherapeutic efficacy and cancer therapy, Sci. Rep. 14 (1) (2024) 27380.
[117] N. Ezzat, N. Emadeldien, M.K. Ali, S. Fahd, S. Shebl, M. Elshishiny, et al., In vitro evaluation of zinc Oxide-Metformin folic acid nanocomposite as a targeted drug delivery system for cancer therapy, Asian Pac. J. Cancer Prev. 26 (2) (2025) 443–452.
[118] D. Soranna, L. Scotti, A. Zambon, C. Bosetti, G. Grassi, A. Catapano, et al., Cancer risk associated with use of metformin and sulfonylurea in type 2 diabetes: a meta-analysis, Oncologist 17 (6) (2012) 813–822.
[119] J.W. Lee, E.A. Choi, Y.S. Kim, Y. Kim, H.S. You, Y.E. Han, et al., Metformin usage and the risk of colorectal cancer: a national cohort study, Int. J. Colorectal Dis. 36 (2) (2021) 303–310.
[120] Q.L. Wang, G. Santoni, E. Ness-Jensen, J. Lagergren, S.H. Xie, Association between metformin use and risk of esophageal squamous cell carcinoma in a population-based cohort study, Am. J. Gastroenterol. 115 (1) (2020) 73–78.
[121] A. Misitzis, A.J. Stratigos, M. Beatson, G. Mastorakos, R.P. Dellavalle, M. A. Weinstock, The association of metformin use with keratinocyte carcinoma development in high-risk patients, Dermatol. Ther. 33 (6) (2020) e14402.
[122] M.J. Tsai, C.J. Yang, Y.T. Kung, C.C. Sheu, Y.T. Shen, P.Y. Chang, et al., Metformin decreases lung cancer risk in diabetic patients in a dose-dependent manner, Lung Cancer 86 (2) (2014) 137–143.
[123] T.K. Oh, I.A. Song, Metformin use and the risk of cancer in patients with diabetes: a nationwide sample cohort study, Cancer Prev. Res. 13 (2) (2020) 195–202.
[124] R. Dankner, N. Agay, L. Olmer, H. Murad, L. Keinan Boker, R.D. Balicer, et al., Metformin treatment and cancer risk: cox regression analysis, with time-dependent covariates, of 320,000 persons with incident diabetes mellitus, Am. J. Epidemiol. 188 (10) (2019) 1794–1800.
[125] J. Zheng, S.H. Xie, G. Santoni, J. Lagergren, Metformin use and risk of gastric adenocarcinoma in a Swedish population-based cohort study, Br. J. Cancer 121 (10) (2019) 877–882.
[126] F. Gaertner, S. Preissner, M. Heiland, R. Preissner, J. Wüster, Beneficial effect of metformin on the five-year survival in about 40,000 patients with head and neck cancer, Cancers 16 (5) (2024).
[127] A. Dulskas, A. Patasius, D. Linkeviciute-Ulinskiene, L. Zabuliene, V. Urbonas, G. Smailyte, Metformin increases cancer specific survival in colorectal cancer patients-National cohort study, Cancer Epidemiol. 62 (2019) 101587.
[128] B. Yuan, J. Ma, J. Wang, J. Hao, The effect of metformin usage on survival outcomes for hepatocellular carcinoma patients with type 2 diabetes mellitus after curative therapy, Front. Endocrinol. 13 (2022) 1060768.
[129] H.S. Seo, Y.J. Jung, J.H. Kim, H.H. Lee, C.H. Park, The effect of metformin on prognosis in patients with locally advanced gastric cancer associated with type 2 diabetes mellitus, Am. J. Clin. Oncol. 42 (12) (2019) 909–917.
[130] A. Dulskas, A. Patasius, D. Linkeviciute-Ulinskiene, L. Zabuliene, G. Smailyte, Cohort study of antihyperglycemic medication and pancreatic cancer patients survival, Int. J. Environ. Res. Public Health 17 (17) (2020).
[131] N. Sadeghi, J.L. Abbruzzese, S.C. Yeung, M. Hassan, D. Li, Metformin use is associated with better survival of diabetic patients with pancreatic cancer, Clin. Cancer Res. 18 (10) (2012) 2905–2912.
[132] Z. Wang, W.Y.F. Ong, T. Shen, J.H. Sng, R.M. Lata, R. Mahendran, et al., Beyond diabetes mellitus: role of metformin in non-muscle-invasive bladder cancer, Singap. Med. J. 63 (4) (2022) 209–213.
[133] A. Markowska, J. Stanislawiak-Rudowicz, T. Kasprzak, J. Markowska, M. Szarszewska, Metformin in selected malignancies in women, Ginekol. Pol. 93 (5) (2022) 416–421.
[134] S. Adeberg, D. Bernhardt, S. Ben Harrabi, T. Bostel, A. Mohr, C. Koelsche, et al., Metformin influences progression in diabetic glioblastoma patients, Strahl. Onkol. 191 (12) (2015) 928–935.
[135] K. Chen, W. Qian, Z. Jiang, L. Cheng, J. Li, L. Sun, et al., Metformin suppresses cancer initiation and progression in genetic mouse models of pancreatic cancer, Mol. Cancer 16 (1) (2017) 131.
[136] P. Zhu, M. Davis, A.J. Blackwelder, N. Bachman, B. Liu, S. Edgerton, et al., Metformin selectively targets tumor-initiating cells in ErbB2-overexpressing breast cancer models, Cancer Prev. Res. 7 (2) (2014) 199–210.
[137] X. Duan, B. Liao, X. Liu, R. Chen, Efficacy of metformin adjunctive therapy as the treatment for non-diabetic patients with advanced non-small cell lung cancer: a systematic review and Meta-analysis, J. Res. Med. Sci. 28 (2023) 45.
[138] G.R. Jones, M.P. Molloy, Metformin, microbiome and protection against colorectal cancer, Dig. Dis. Sci. 66 (5) (2021) 1409–1414.
[139] K. Skipar, T. Hompland, K.V. Lund, C.S. Fjeldbo, K. Lindemann, T.P. Hellebust, et al., Tolerability, safety and feasibility of metformin combined with chemoradiotherapy in patients with locally advanced cervical cancer: a phase II, randomized study, Acta Oncol. 64 (2025) 439–447.
[140] A. DeCensi, M. Puntoni, S. Gandini, A. Guerrieri-Gonzaga, H.A. Johansson, M. Cazzaniga, et al., Differential effects of metformin on breast cancer proliferation according to markers of insulin resistance and tumor subtype in a randomized presurgical trial, Breast Cancer Res. Treat. 148 (1) (2014) 81–90.
[141] E.P. Mofo Mato, M. Guewo-Fokeng, M.F. Essop, P.M.O. Owira, Genetic polymorphisms of organic cation transporter 1 (OCT1) and responses to metformin therapy in individuals with type 2 diabetes: a systematic review, Medicine 97 (27) (2018) e11349.
[142] V.D.A. Ningrum, A.H. Sadewa, Z. Ikawati, R. Yuliwulandari, M.R. Ikhsan, R. Fajriyah, The influence of metformin transporter gene SLC22A1 and SLC47A1 variants on steady-state pharmacokinetics and glycemic response, PLOS One 17 (7) (2022) e0271410.
[143] L.N. Al-Eitan, B.A. Almomani, A.M. Nassar, B.Z. Elsaqa, N.A. Saadeh, Metformin pharmacogenetics: effects of SLC22A1, SLC22A2, and SLC22A3 polymorphisms on glycemic control and HbA1c levels, J. Pers. Med. 9 (1) (2019).
[144] A. Angelopoulou, G. Theocharous, D. Valakos, A. Polyzou, S. Magkouta, V. Myrianthopoulos, et al., Loss of the tumour suppressor LKB1/STK11 uncovers a leptin-mediated sensitivity mechanism to mitochondrial uncouplers for targeted cancer therapy, Mol. Cancer 23 (1) (2024) 147.
[145] M. Foretz, S. Hébrard, J. Leclerc, E. Zarrinpashneh, M. Soty, G. Mithieux, et al., Metformin inhibits hepatic gluconeogenesis in mice independently of the LKB1/AMPK pathway via a decrease in hepatic energy state, J. Clin. Investig. 120 (7) (2010) 2355–2369.
[146] A. Bishnu, A. Sakpal, N. Ghosh, P. Choudhury, K. Chaudhury, P. Ray, Long term treatment of metformin impedes development of chemoresistance by regulating cancer stem cell differentiation through taurine generation in ovarian cancer cells, Int. J. Biochem. Cell Biol. 107 (2019) 116–127.
[147] A.M. Scherbakov, D.V. Sorokin, V.V. Tatarskiy Jr., N.S. Prokhorov, S.E. Semina, L. M. Berstein, et al., The phenomenon of acquired resistance to metformin in breast cancer cells: the interaction of growth pathways and estrogen receptor signaling, IUBMB Life 68 (4) (2016) 281–292.
[148] D.S. Seo, S. Joo, S. Baek, J. Kang, T.K. Kwon, Y. Jang, Metformin resistance is associated with expression of inflammatory and invasive genes in A549 lung cancer cells, Genes 14 (5) (2023).