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REPURPOSING METFORMIN IN ONCOLOGY: FROM GLYCEMIC CONTROL TO CANCER CARE

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ABSTRACT: Cancer remains a leading cause of mortality worldwide, with an increasing burden projected in India by 2025. Despite advances in surgery, radiotherapy, and immunotherapy, chemotherapy continues to be cornerstone of cancer treatment; however, its utility is often limited by drug resistance and severe toxicity. This highlights the need for novel, safer, and more cost and therapeutically effective approaches. Drug repurposing is exploring new indications for already approved drugs that have emerged as a promising strategy, offering advantages such as established safety profiles, reduced costs, and shorter development timelines. Metformin, a first-line therapy for type 2 diabetes, has gained significant attention due to its metabolic links with cancer and favorable safety profile. Metformin exerts antitumor effects through multiple mechanisms, including AMPK activation, inhibition of mTOR signaling, reduction of insulin/IGF-1 signaling, modulation of the tumor microenvironment, suppression of inflammatory mediators, ROS-mediated apoptosis, and inhibition of cancer stem cells and epithelial–mesenchymal transition. Preclinical studies consistently demonstrate its anticancer potential, while observational studies in diabetic populations suggest reduced cancer incidence and improved outcomes. However, randomized controlled trials have yielded mixed results, with benefits observed only in specific subgroups. Overall, metformin represents a cost-effective and well-tolerated candidate for adjunct cancer therapy. Future research should focus on biomarker-driven patient selection, optimized dosing strategies, and rational combinations with immunotherapy and targeted agents. Large, well-designed clinical trials are needed to validate its role in oncology and integrate it into precision medicine approaches.

Keywords: *Drug repurposing, Cancer, Metformin, Antitumor, Cost-effective*

INTRODUCTION

Cancer is a serious and complex disease affecting millions of lives worldwide and remains the leading cause of death globally. The most common cancers are breast, lung, colorectal, and prostate cancers. In India, it is anticipated that there will be 1,569,793 cancer patients by 2025 [1]. One in nine people in India are likely to develop cancer in their lifetime. Among males, lung cancer is the most common type, while in females, breast cancer predominates. In children aged 0–14 years, lymphoid leukemia is the leading type of cancer (boys: 29.2% and girls: 24.2%). The incidence of cancer cases in India is estimated to rise by 12.8% in 2025 compared to 2020 [2].

Drug therapy continues to remain the cornerstone of cancer treatment, despite significant advancements in surgical, radiotherapeutic, and immunotherapeutic approaches. However, the development of drug resistance and the onset of severe toxic side effects often restrict the efficacy of conventional chemotherapy. Therefore, there is an urgent need to find new therapeutic agents for the treatment of cancer.

One of the innovative and highly promising strategy that has gained attention is drug repurposing, also known as drug repositioning or drug re-profiling. It is the process of identifying new therapeutic uses for existing, clinically approved drugs. In this approach, drugs originally developed for a specific disease or a condition is tested for efficacy in other conditions, often leveraging into previously unknown therapeutic efficacies. This strategy offers several advantages, including established safety profiles, reduced development costs, and significantly shorter timelines, as it bypasses preclinical phases required for entirely new drugs [3,4,5].

The concept of repurposing existing drugs to combat different diseases has gained prominence, with various pharmacological classes being explored for their potential anticancer effects. Metformin, an antidiabetic medication from the biguanide class and widely used as a first-line treatment for type 2 diabetes, has emerged as a particularly promising candidate for repurposing due to the well-established metabolic links between diabetes and cancer [5]. Originally approved for its glucose-lowering effects, metformin has gained the focus of numerous studies revealing its potential role in cancer prevention and treatment.

MECHANISM OF ACTION OF METFORMIN

Metformin, an oral glucose lowering agent used as First-line treatment for type 2 diabetes mellitus (T2DM). It primarily acts by lowering blood glucose by decreasing hepatic gluconeogenesis and improving insulin sensitivity. It decreases both basal and postprandial plasma glucose without causing hypoglycemia or hyperinsulinemia [6,7]. Metformin extend pleiotropic effects beyond glucose control, including weight neutrality, lipid profile modulation, cardio-protection, and regulation of inflammatory markers [6,8].

The Principal target of metformin is liver; a major mechanism involves activation of adenosine monophosphate-activated protein kinase (AMPK), a key regulator of energy metabolism. Metformin increases the AMP/ATP ratio by inhibiting mitochondrial respiratory chain complex I, which leads to phosphorylation of AMPK via its upstream kinase, LKB1. Activated AMPK downregulates gluconeogenic genes such as PEPCK and G6Pase through transcriptional co-repressors including small heterodimer partner (SHP) and inhibition of HNF4α, FoxO1, and CREB-CBP-CRTC2 transcriptional complexes. AMPK also phosphorylates acetyl-CoA carboxylases (ACC1 and ACC2), reducing malonyl-CoA levels, thereby inhibiting hepatic lipogenesis and improving insulin resistance [9].

Metformin enhances peripheral glucose uptake and utilization in skeletal muscle and adipose tissue, contributing to improved insulin sensitivity [7,8]. This effect, while secondary to hepatic action, plays a role in lowering circulating glucose and mitigating insulin resistance.

The gut has emerged as another important site of metformin action. Preabsorptive metformin activates duodenal mucosal AMPK, which communicates with the liver to suppress gluconeogenesis [9]. Moreover, metformin increases GLP-1 secretion and modifies the composition of gut microbiota. Randomized controlled trials and animal studies demonstrate that altered microbiota, particularly an increased abundance of Lactobacillus, contributes to improved glucose metabolism and regulation of SGLT1 expression [9].

Beyond glycemic control, metformin exerts beneficial Pleiotropic effects on weight regulation, lipid metabolism, and inflammatory signaling. The UKPDS trial reported a significant reduction in myocardial infarction among metformin-treated patients, highlighting its cardioprotective role [6]. Observational studies

have also noted a reduced incidence of cancer in metformin users, generating interest in its repurposing for oncology [8].

PHARMACOKINETICS AND SAFETY PROFILE OF METFORMIN

Absorption:

After oral administration, metformin is absorbed primarily in the small intestine. The drug exhibits an onset of action of approximately 1.5 hours, with a plasma half-life ranging between 2 and 3 hours. Its duration of action varies depending on the formulation: immediate-release forms provide activity for 6–8 hours, while extended-release formulations extend this duration up to 10 hours. Therapeutic dosing generally ranges from 250 to 2550 mg/day, resulting in plasma concentrations of 5–20 μM in patients with type 2 diabetes mellitus (T2DM) [3,6,10].

Distribution:

Metformin is rapidly distributed throughout the body. Unlike many other drugs, it does not bind to plasma proteins, which contributes to its distinct pharmacokinetic behavior and low risk of drug–drug displacement interactions [3,6,10].

Metabolism:

Metformin is not metabolized in the liver. It remains chemically unchanged in the systemic circulation, thereby minimizing pharmacokinetic interactions with other agents metabolized by cytochrome P450 enzymes [3,6,10].

Excretion:

Metformin is primarily eliminated unchanged via the kidneys**.** Renal function plays a key role in its clearance; impaired renal function can markedly reduce elimination and increase the risk of lactic acidosis, a rare but potentially fatal complication. Due to this risk, metformin is contraindicated in patients with serum creatinine ≥1.4 mg/dL (females) and ≥1.5 mg/dL (males) [3,6,10].

Safety and Tolerability:

Overall, metformin is considered safe and well tolerated. The most common adverse effects include gastrointestinal disturbances such as nausea, diarrhea, anorexia, metallic taste, and flatulence, particularly during the early phase of therapy. These effects are usually transient and may be minimized by gradual dose titration or taking the drug with meals. With prolonged use, vitamin B12 deficiency has been reported, possibly due to altered enterohepatic circulation, reduced intrinsic factor secretion, bacterial overgrowth, and impaired calcium-dependent binding of the intrinsic factor–vitamin B12 complex to the cubilin receptor [3,6,10].

ANTICANCER ACTIVITY OF METFORMIN

The antitumor activity of metformin is attributed to multiple interrelated molecular and cellular mechanisms that collectively inhibit cancer initiation and progression. The major mechanisms are summarized below.

Cell cycle arrest:

The normal cells in the body proliferate through the cell cyclein a regulated manner, G0/G1, S, G2 and M phases. Metformin has been shown to regulate the G0/G1 phase in tumor cells, leading to arrest and inhibition of phase progression. Studies in ovarian and breast cancer cells have also revealed arrest at the S and G2/M phases, thereby preventing DNA replication or mitosis. By halting the cycle at these checkpoints, metformin reduces tumor cell proliferation and promotes apoptotic pathways [11,12].

Activation of AMPK Pathway:

A central mechanism of metformin involves inhibition of mitochondrial respiratory chain complex I, leading to reduced intracellular ATP production. This energy stress activates AMP-activated protein kinase (AMPK), primarily via liver kinase B1 (LKB1) phosphorylation at threonine 172. Activated AMPK regulates key processes including cell growth, proliferation, apoptosis, and autophagy. One of the downstream effects is inhibition of mammalian target of rapamycin complex 1 (mTORC1) through tuberculous sclerosis complex 1 and 2 (TSC1/TSC2) activation, resulting in reduced protein synthesis and suppression of tumor growth. Since mTOR hyperactivation is common in many malignancies and associated with poor prognosis, its inhibition via the AMPK/LKB1 axis represents an important anticancer effect of metformin [13,14,15].

Reduction in insulin/IGF-1 signaling:

Insulin and insulin-like growth factor-1 (IGF-1) drive cell survival and proliferation through activation of the IGF-1R/PI3K/AKT signaling pathway. Over expression of insulin and IGF-1 receptors has been observed in several cancers, including breast, liver, colon, and pancreatic malignancies. Metformin decreases circulating insulin levels by improving insulin sensitivity and suppresses IGF-1 signaling, thereby limiting mitogenic stimuli to cancer cells. Moreover, when combined with IGF-1R inhibitors, metformin enhances cytotoxicity through synergistic inhibition of this pathway. By lowering hyperinsulinemia, especially in patients with diabetes, metformin further reduces the risk of cancer development and progression [11,13].

Modulation of Tumor Microenvironment (TME):

The tumor microenvironment, characterized by hypoxia, chronic inflammation, and immune suppression, plays a critical role in tumor progression and therapeutic resistance. Metformin alleviates hypoxic stress, reduces inflammatory cytokine levels, and improves immune surveillance within the TME. This reprogramming of the tumor niche not only limits cancer cell survival but also enhances response to conventional therapies [11].

Regulation of Inflammatory Mediators:

Cancer progression is closely associated with chronic inflammation. Patients with malignancies often exhibit elevated levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), C-reactive protein, and other pro-inflammatory cytokines. Metformin reduces these inflammatory mediators, thereby suppressing tumor-promoting inflammation and contributing to its anticancer properties [11].

ROS-Mediated Apoptosis and FOXO3a Activation:

Metformin induces accumulation of reactive oxygen species (ROS), which can damage DNA, RNA, and proteins, ultimately leading to apoptosis in cancer cells. While tumor cells often upregulate antioxidant defenses, excessive ROS can overwhelm these systems. Additionally, metformin increases the expression of pro-apoptotic transcription factor FOXO3a, which regulates cell proliferation, DNA damage response, and apoptosis. FOXO3a activation is facilitated by AMPK activation, AKT inhibition, and ROS accumulation, all of which are influenced by metformin treatment [12].

Inhibition of Cancer Stem Cells and EMT:

Epithelial-to-mesenchymal transition (EMT) not only enhances tumor invasiveness but also contributes to the generation of cancer stem-like cells, which are implicated in recurrence and drug resistance. Metformin inhibits EMT, thereby limiting both metastatic potential and cancer stem cell maintenance. This suppression of cancer stemness is considered an important mechanism for long-term disease control [12].

Chemopreventive Effects:

Metformin also exerts chemopreventive actions by reducing hepatic glucose production and lowering systemic insulin requirements. Through AMPK-dependent mechanisms, metformin disrupts ATP synthesis, suppresses IGF-1 receptor signaling, and inhibits the mTOR pathway. Together, these actions decrease the availability of metabolic and hormonal drivers essential for tumor initiation and progression [14].

METFORMIN IN CANCER: A SUMMARY OF STUDY OUTCOMES

Table 1: Metformin in Cancer: A Summary of Study Outcomes

Author(s)	Year	Cancer Type	Study Design	Outcome / Key Findings
Alimova I N *et al.* [15]	2009	Breast Cancer (cell lines: MCF-7, BT-474, SKBR-3)	Preclinical, in vitro	Metformin inhibited proliferation, reduced colony formation, induced partial G1 arrest, suppressed Cyclin D1 and E2F1, and inhibited MAPK, AKT, and mTOR signaling.
DeCensi A *et al.* [16]	2010	Multiple Cancers (systematic review in diabetics)	Systematic review & meta-analysis of 11 studies	Metformin use associated with 31% reduction in overall cancer risk. Significant reduction for pancreatic and HCC; non significant for breast, prostate, and colon.
Bodmer M *et al.* [17]	2010	Breast cancer	Nested case–control study	Long- term metformin use (≥5 years; ≥40 prescriptions) was associated with a significantly reduced risk of breast cancer. Short-term metformin use and other oral antidiabetic drugs showed no significant association with breast cancer risk.
Rocha G Z *et al.* [18]	2011	Breast (MCF-7), Lung (A549)	Preclinical (cell lines, xenograft mouse models)	Metformin + paclitaxel synergistically enhanced AMPK activation, inhibited mTOR signaling, increased apoptosis, induced G2/M arrest, and reduced tumor growth compared with single agents.
Shi W-Y *et al.* [19]	2012	Lymphoma (B- and T-cell, Hodgkin's)	Preclinical (cell lines, primary patient samples, xenograft mice)	Metformin activated AMPK → inhibited mTOR pathway → induced autophagy; suppressed lymphoma growth in vitro and in vivo; enhanced sensitivity to doxorubicin and temsirolimus. Demonstrated tumor-specific effect with minimal toxicity to normal hematopoietic

Frouws M A *et al.* [20]	2017	Pancreatic Cancer	Observational cohort study (Netherlands Cancer Registry)	No significant association between metformin use and overall survival in pancreatic cancer.
Yang X *et al.* [21]	2021	Ovarian Cancer (SKOV3 cell line)	Preclinical, in vitro	Metformin reduced mesothelin (MSLN), suppressed IL-6/STAT3 signaling, inhibited proliferation, migration, angiogenesis, stemness, and induced apoptosis.
Feng J *et al.* [22]	2022	Hepatocellular Carcinoma (HCC)	Preclinical (CRISPR screen, in vitro, in vivo, patient-derived organoids)	DOCK1 identified as determinant of metformin sensitivity; low DOCK1 expression associated with improved survival; DOCK1 inhibition synergized with metformin to suppress HCC growth.
Lord S R *et al.* [23]	2023	Multiple (overview: breast, endometrial, prostate, ovarian, H&N, cervical)	Perspective summarizing RCTs & pharmacodynamic studies	Despite strong preclinical rationale, large RCTs (e.g., MA.32) failed to show clear survival benefit; some subgroup signals (e.g., HER2+ breast cancer) noted. Pharmacodynamic studies show reduced Ki67, altered AMPK/mTOR signaling, but inconsistent across tumor types.
Goodwin P J *et al.* [24]	2023	Early Breast Cancer (MA.32 trial)	Phase III randomized double-blind trial	Metformin (850 mg BID, 5 yrs) did not reduce risk of new primary cancers vs placebo (HR 1.25, 95% CI 0.94–1.68). These findings did not support the use of metformin to reduce risk of new primary cancers in patients without diabetes who have high-risk breast cancer. Exploratory benefit in HER2+ subgroup with specific SNP genotype
Finisguerra V et al. [25]	2023	Multiple solid tumors (focus on hypoxic &	Preclinical (murine models, in vitro	Metformin rescued CD8+ T cells from hypoxia-induced apoptosis and dysfunction; improved proliferation,

		immunosuppressive tumors, including melanoma)	CD8+ T-cell assays)	cytokine production, and reduced exhaustion markers. Did not reduce tumor hypoxia directly but improved infiltration/survival of T cells in hypoxic tumor areas. Enhanced response to adoptive cell therapy and PD-1 blockade.
Orchard S *G et a.l* [14]	2023	Overall cancer incidence and cancer-related mortality	Randomized, double-blind, placebo-controlled clinical trial (ASPREE)	In older adults with diabetes, metformin use was associated with a reduced risk of incident cancer over 4.5 years of follow-up, though no clear benefit was observed for cancer mortality. The protective effect of metformin appeared attenuated in those with high fasting blood glucose levels (>150 mg/dL). Aspirin use was linked to increased cancer mortality among metformin users, but the interaction between metformin and aspirin was not statistically significant due to limited sample size.
Brown J *C et al*. [26]	2024	Breast & Colorectal	Phase II multi-centre factorial randomized trial	Exercise increased LIF and IL-15; Metformin decreased apelin and IL-15; exploratory evidence that exercise and metformin elicit distinct myokine responses warranting further study
Wang L *et al.* [27]	2024	13 Obesity-Associated Cancers (colorectal, pancreatic, liver, gallbladder, kidney, ovarian, endometrial, esophageal,	Retrospective cohort (EHR database study)	GLP-1RAs vs insulin → significantly reduced risk in 10/13 cancers (e.g., pancreatic, colorectal, liver, kidney, gallbladder, ovarian, myeloma, meningioma). Compared with metformin, GLP-1RAs showed no added reduction, and for kidney

		stomach, breast, thyroid, meningioma, multiple myeloma)		cancer risk was higher. Shows GLP-1RAs protective vs insulin, but metformin remains strong comparator.

CONCLUSION

The repurposing of metformin in oncology represents a promising, safe, and cost-effective therapeutic agent, with evidence supporting its potential role as an adjunctive therapy in various cancers types. While studies have provided mixed results, its potential as a cost-effective adjunct therapy is undeniable. Significant differences exist between observational studies and randomized controlled trials (RCTs), making it difficult to draw definitive conclusions. Key confounding factors include a lack of standardized dosage and duration protocols, as well as challenges in patient selection, particularly when comparing outcomes in diabetic versus non-diabetic populations. To overcome current limitations, future research should focus on identifying biomarkers to accurately predict which patients will respond to metformin therapy. Developing effective combination strategies, particularly with newer treatments like immunotherapy and targeted therapy, is crucial. Additionally, there is a clear need for more large-scale, well-designed RCTs to validate its efficacy. Ultimately, metformin holds a potential role in precision medicine, where its use could be tailored to specific patient and tumor characteristics for optimal therapeutic benefit. However, the existing data highlights the need for more rigorous, high-quality research to fully realize its therapeutic potential.

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