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Repurposing Metformin: A New Frontier in Cancer Therapy

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Abstract: *Metformin, a first-line medication for type 2 diabetes, has attracted considerable attention for its potential anticancer properties. In addition to its role in regulating blood glucose, emerging evidence suggests that metformin can disrupt cancer cell metabolism, suppress cell growth, and promote programmed cell death. These effects appear to involve several molecular pathways, particularly the activation of AMP-activated protein kinase (AMPK) and the suppression of the mammalian target of rapamycin (mTOR) signaling pathway. Furthermore, by lowering systemic insulin levels, metformin may reduce insulin-mediated tumor progression. Given its well-established safety record, affordability, and widespread clinical use, metformin is being actively explored as a repurposed therapeutic option in oncology. This paper summarizes recent research, mechanistic insights, and ongoing clinical studies that support metformin's emerging role as an anticancer agent.*

Keywords: Metformin, Cancer Treatment, Drug Repositioning, AMPK Pathway, mTOR Suppression, Antitumor Mechanisms, Oncology Studies, Cancer Cell Metabolism, Type 2 Diabetes Mellitus, Cell Apoptosis

I. INTRODUCTION

Metformin, primarily used to treat type 2 diabetes, has recently gained attention for its potential role in cancer management. Research indicates that it can hinder tumor development by influencing cellular energy pathways, particularly through AMPK activation, mTOR inhibition, and modulation of insulin-related signaling. While experimental studies show encouraging results, clinical findings remain variable. Due to its proven safety, affordability, and metabolic benefits, metformin is being explored as a promising option for cancer therapy repurposing.

Metformin (N′, N′-dimethyl biguanide) is an oral hypoglycemic drug from the biguanide class and is one of the most widely prescribed medications for the management of type 2 diabetes mellitus, benefiting nearly 120 million patients globally (1). It primarily works by enhancing insulin sensitivity and reducing hepatic glucose production. Beyond its glucose-lowering effects, metformin is also employed in the treatment of gestational diabetes mellitus and has been reported to play a beneficial role in preventing preeclampsia among affected patients. Moreover, emerging evidence suggests that metformin may contribute to lifespan extension (2). Recent epidemiological and experimental studies have highlighted metformin's potential in cancer prevention and therapy (3, 4). While observational data first indicated a reduced incidence of certain cancers among metformin users, subsequent molecular and interventional research has provided insight into its possible antineoplastic mechanisms. The exploration of metformin as an anticancer agent is particularly appealing because it is already an established, safe, and cost-effective drug for diabetes management. Repurposing such existing drugs—an approach known as *drug repositioning*—offers a more efficient and economical strategy than developing entirely new anticancer compounds. The widespread use of metformin, along with its favorable safety profile and FDA approval, facilitates the transition from observational findings to controlled clinical trials (5). Growing interest in metformin's antitumor potential stems from its observed ability to inhibit tumor growth independently of its glucose-lowering effects. These properties have been examined in various *in vitro* and *in vivo* models and are currently under clinical evaluation as an adjunct to standard chemotherapy. Notably, the concept of biguanides exerting anticancer activity is not new. Earlier research on phenformin—a related biguanide later withdrawn due to its higher risk of lactic acidosis—demonstrated its ability to enhance tumor cell inhibition both alone and in combination with conventional chemotherapeutic drugs (6–7)

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1.1 A Brief History of Biguanides

The biguanide class of drugs, including metformin, phenformin, and buformin, originates from the plant *Galega officinalis* (commonly called French lilac, Goat's Rue, or Italian Fitch). Historically, infusions made from French lilac were used in ancient Egypt and medieval Europe to alleviate frequent urination (polyuria) and sweet-smelling breath—symptoms now recognized as signs of diabetes (9–11). In the 1920s, scientific studies identified the active compounds in French lilac as biguanides, paving the way for their therapeutic development in the 1950s (9, 11, 12). Although phenformin and buformin were later withdrawn in the 1970s due to a high risk of lactic acidosis, metformin (N′,N′-dimethylbiguanide) has remained widely prescribed and is currently used in nearly 120 million treatments annually worldwide (13). Metformin received regulatory approval for treating hyperglycemia in the United Kingdom in 1958, Canada in 1972, and the United States in 1995. Beyond diabetes, metformin has demonstrated efficacy in managing polycystic ovary syndrome and is under investigation for antiviral and anticancer applications (13–15). The investigation of biguanides in cancer therapy began with studies exploring altered metabolic pathways in non-diabetic patients [16–18]. More recent research has linked metformin use to lower cancer incidence and mortality among diabetic patients, with its insulin-lowering properties believed to contribute to these anticancer effects (13, 19–21). This review examines the current understanding of metformin's role in oncology and the mechanisms by which it may inhibit tumor growth.

1.2 Mechanism of Metformin

At the cellular level, metformin exerts its effects primarily through activation of AMP-activated protein kinase (AMPK), a key regulator of cellular energy homeostasis that is sensitive to changes in intracellular AMP levels (22, 23). Metformin indirectly stimulates AMPK by inhibiting complex I of the mitochondrial respiratory chain, which reduces ATP production and increases the AMP:ATP ratio within the cell (24). Elevated AMP levels promote AMPK activation through several mechanisms: AMP allosterically enhances AMPK activity, facilitates phosphorylation of the catalytic subunit at Thr172 by the upstream kinase liver kinase B1 (LKB1, also known as STK11, a tumor suppressor mutated in Peutz-Jeghers syndrome), and protects Thr172 from dephosphorylation by protein phosphatases (25). Once activated, AMPK modulates numerous downstream targets, promoting ATP-generating catabolic pathways such as glycolysis and fatty acid β-oxidation, while suppressing energy-consuming processes including gluconeogenesis, protein and fatty acid synthesis, and cholesterol biosynthesis (26, 27). In the context of diabetes, metformin lowers blood glucose levels primarily by inhibiting hepatic gluconeogenesis and enhancing glucose uptake in skeletal muscle (28, 29). These effects are mediated by AMPK-dependent transcriptional regulation of genes involved in glucose metabolism, including peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) in the liver and glucose transporter type 4 (GLUT4) in muscle tissue (13, 30, 31). Through these mechanisms, metformin improves insulin sensitivity and reduces fasting blood glucose and insulin levels.

1.3 Mechanisms of Action in Cancer

Although numerous studies have reported that metformin exhibits anticancer effects, the precise mechanisms underlying these effects are not yet fully understood. Recent research has begun to uncover potential pathways through which metformin may exert its anticancer activity in various cancer types (34). A central player in metformin's mechanism is AMP-activated protein kinase (AMPK), which regulates cellular energy balance and metabolism (32). The anticancer effects of metformin can be broadly categorized into directand indirectmechanisms**.** Direct effects of metformin involve both AMPK-dependent and AMPK-independent pathways (32, 35). Through AMPK activation, metformin stabilizes tuberous sclerosis complex 2 (TSC2), leading to inhibition of mTORC1 signaling and suppression of protein synthesis. Additionally, metformin can inhibit mTOR independently of AMPK and TSC2 (35). AMPK-dependent actions also include downregulation of mTOR, folate metabolism, c-MYC, and NF-κB, alongside upregulation of p53 phosphorylation (33, 36). AMPK-independent effects include reduction of reactive oxygen species (ROS) and cyclin D1, and promotion of mTORC1 activity, autophagy, and apoptosis in cancer cells (35). Metformin has also been shown to inhibit DeltaNp63α, a member of the p53 family, thereby inducing apoptosis in human squamous cell carcinoma (36). Indirect effects of metformin are mediated through systemic metabolic changes. By

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lowering blood glucose, insulin, and insulin-like growth factor 1 (IGF-1) levels, metformin reduces activation of receptor tyrosine kinases and PI3K signaling pathways (33, 34). It also modulates the immune response by reducing proinflammatory cytokines and NF-κB activity, which can enhance anticancer immunity (33). Oxidative stress is a key contributor to both type 2 diabetes and cancer progression . Metformin has been reported to decrease oxidative stress and ROS levels, which may contribute to its protective effects against tumor development (36). Collectively, these multiple mechanisms highlight metformin's potential as a multifaceted anticancer agent.

1.4 Specific Cancers

Metformin has shown potential benefits in both the prevention and treatment of various cancer types.

1.4.1 Colorectal Cancer- Several studies indicate that metformin may help prevent or treat colorectal cancer. A meta-analysis found improved overall survival in diabetic patients with colorectal cancer using metformin (HR 0.75; 95% CI 0.65-0.87).(37)In a retrospective study, diabetic colorectal cancer patients on metformin had better 2-yr survival vs those on other treatments. (38) Some studies note that metformin mitigates Notch1/Hes1 pathway overactivation in diabetic colorectal cancer patients; other research suggests use of metformin together with chemopreventive agents. However, conflicting studies exist.

1.4.2 Pancreatic Cancer- In diabetic patients with pancreatic cancer, metformin use has been associated with improved survival: one seminal study found a 32% lower risk of death (HR 0.68) in metformin users with non-metastatic disease. (39) A more recent meta-analysis of 21 studies (38,772 patients) found HR = 0.83 (95% CI 0.74-0.91) for overall survival. (40) Mechanistic studies suggest that metformin's effect may involve reducing desmoplasia and enhancing the action of gemcitabine via AMPK-mediated pathways.

1.4.3 Prostate Cancer- Some observational studies indicate that metformin may have beneficial effects in prostate cancer. For example, in an Asian diabetic cohort on androgen-deprivation therapy, metformin use was associated with lower prostate cancer-related mortality (wHR 0.49) and all-cause mortality (wHR 0.53). (41)

1.4.4 Renal Cancer- Metformin has been linked to a reduced likelihood of renal cancer in patients with type 2 diabetes mellitus. Studies show that metformin can up-regulate miR-34a, resulting in inhibition of renal cancer cell growth and induction of cell cycle arrest. (42, 43)

1.4.5 Cervical Cancer- Cervical cancer is one of the most prevalent cancers among women, contributing to considerable morbidity and mortality. Research indicates that metformin use in diabetic women is associated with a lower risk of developing cervical cancer (44). Additionally, metformin has demonstrated moderate effectiveness in reducing tumor cell proliferation and promoting apoptosis in cervical cancer cells. Synergistic anticancer effects have also been observed when metformin is combined with nelfinavir in treatment regimens (45). In patients with both cervical cancer and type 2 diabetes, metformin improved five-year disease-free survival, although it did not significantly affect overall survival (46). Further long-term studies are necessary to validate these findings.

1.4.6 Endometrial Cancer- Overexpression of STAT3 has been identified in endometrial cancer and is linked to elevated glucose levels. Metformin has been shown to inhibit STAT3 expression, suggesting a potential role in preventing endometrial cancer (47). Short-term metformin treatment in patients with endometrial cancer has demonstrated beneficial effects, including a reduction in Ki-67 expression, a marker of cell proliferation (48, 49). Furthermore, metformin use has been associated with improved survival outcomes in these patients (50).

1.4.7 Gastric Cancer- In diabetic patients, metformin use has been correlated with a decreased risk of developing gastric cancer (51). The drug appears to inhibit the sonic hedgehog signaling pathway, which plays a crucial role in gastric cancer development. This mechanism may underlie metformin's potential preventive and therapeutic effects in gastric cancer (52).

1.4.8 Lung Cancer- Metformin has demonstrated beneficial effects across various types of lung cancer (53). Clinical trials have shown that metformin can reduce adenoma formation and may be effective in both early and late stages of lung cancer (55). However, combining metformin with pioglitazone does not appear to provide additional benefits. Meta-analyses indicate that metformin use improves survival rates in diabetic patients with lung cancer (54).

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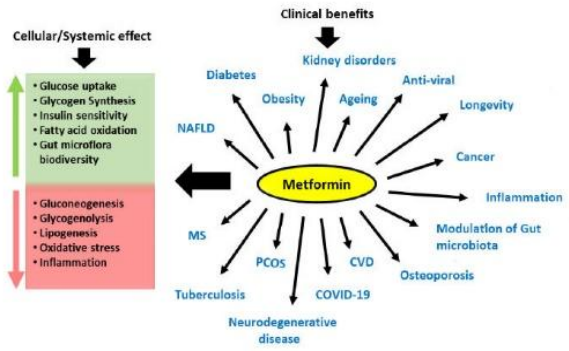

Fig.no. 2 therapeutic potential of metformin

Overall therapeutic potential of metformin: The diagram illustrates the clinical benefits of metformin on the right and its cellular and systemic effects on the left. Green arrows indicate enhanced effects, while red arrows indicate reduced effects. Abbreviations: CVD, cardiovascular diseases; MS, multiple sclerosis; PCOS, polycystic ovarian syndrome; NAFLD, non-alcoholic fatty liver disease; COVID-19, coronavirus disease 2019. (A high-resolution or color version of this figure is available in the electronic version of the article.)

1.5 Clinical Studies

Prospective and ongoing clinical trials are investigating the safety and efficacy of metformin in cancer patients, regardless of diabetic status, to evaluate its potential as a chemopreventive agent and to understand its biological effects. More than fifty studies on metformin in cancer patients are currently registered at major clinical trial registries. Most of these trials are phase II studies in breast cancer, which include biomarker analyses and the administration of metformin either alone or in combination with other treatments (56, 57). Limited clinical trials have been published to date. One study conducted a preoperative, "window of opportunity" randomized trial in which metformin was administered to non-diabetic breast cancer patients prior to surgery, and the antitumor effects were compared with untreated controls. While no measurable changes in tumor size were observed after 2–3 weeks of treatment, tumor biopsy analysis revealed decreased insulin levels and reduced Ki67 staining, a marker of proliferation, suggesting potential biological effects on tumor tissues (56). In contrast, another study found that presurgery treatment with metformin did not alter Ki67 levels compared to placebo in non-diabetic breast cancer patients. However, subgroup analysis revealed that metformin's effects on Ki67 depended on insulin resistance levels, with greater effects in patients with lower insulin resistance. Similar patterns were noted in women who were overweight, had abdominal obesity, or consumed moderate amounts of alcohol . Observational studies have indicated that elevated peptide-C levels are associated with poor outcomes in non-diabetic breast cancer patients. Additional research has shown that standard-dose metformin reduced insulin levels in non-diabetic breast cancer survivors without relapse. In further neoadjuvant studies, predictors of metformin benefit included elevated BMI, physical inactivity, high fasting insulin, tumor immunopositivity for Ki67 and TUNEL staining, and the presence of OCT1 and LKB1. Metabolic changes following metformin treatment correlated with increased TUNEL staining and decreased Ki67 expression (57). A short-term clinical trial evaluated metformin's chemopreventive potential in patients with rectal aberrant crypt foci (ACF), an endoscopic surrogate marker for colorectal cancer. Treatment with metformin significantly reduced the number of ACF after one month and decreased colonic epithelial proliferative activity, although no significant apoptotic changes were detected. A prospective randomized controlled trial has been registered to further assess metformin's chemopreventive effects in metachronous colorectal polyps and non-diabetic post-polypectomy patients (58).

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1.6.1 Monotherapy

Standard treatments for most cancers, such as surgery, chemotherapy, and radiation, are often effective in slowing tumor growth and improving patient survival. However, relying on a single treatment modality can have limitations. Monotherapy may lead to higher toxicity, the development of drug resistance, tumor metastasis, and disease recurrence. These challenges highlight the need for alternative strategies to enhance treatment outcomes. (59)

1.6.2 Combination Therapy

Combination therapy involves using two or more treatment approaches together, such as chemotherapeutic drugs, natural compounds, or targeted therapies. This strategy offers several advantages over monotherapy:

Increased efficacy – combining treatments can improve overall outcomes and reduce the chances of metastasis and relapse.

Synergistic effects – drugs used together can be administered at lower doses while maintaining high effectiveness.

Reduced toxicity – lower doses of individual drugs minimize adverse side effects.

Prevention of resistance – using multiple agents reduces the likelihood of cancer cells developing resistance.

Metformin has gained attention as part of combination therapy because it targets cancer cell metabolism, induces energy stress, and has minimal toxicity. Studies have explored its use alongside chemotherapeutic drugs or natural compounds, showing potential to enhance anti-cancer effects through multiple molecular mechanisms. (60)

II. CONCLUSION

Metformin's well-established safety record, defined pharmacodynamic profile, and affordability make it an appealing candidate for cancer prevention and treatment (Pollak, 2012) (61). Extensive epidemiological, clinical, and laboratory studies have shown promising anticancer properties of metformin, although many of these findings are derived from retrospective research in diabetic populations, limiting their applicability to the general cancer population (Evans et al., 2005) (65).Preclinical investigations have revealed that metformin can inhibit cancer cell growth through the suppression of mTORC1 signaling and downregulation of cyclin D1; however, these studies often use non-physiological doses and artificial conditions (Zakikhani et al., 2008) (63). Overall, evidence suggests that metformin exerts its anticancer effects via both insulin-dependent and insulin-independent pathways. Patients with elevated insulin levels and tumors expressing insulin receptor, LKB1, and TSC2 may benefit the most from metformin treatment (Dowling et al., 2011) (62).

Future Directions

Future research should aim to create physiologically relevant models that better reflect human metabolic conditions and tumor microenvironments, enabling a more accurate understanding of metformin's mechanisms of action (Pollak, 2012) (61). Identifying biomarkers that predict metformin response—such as insulin receptor, LKB1, and TSC2 expression—will be essential for personalizing cancer therapy (Dowling et al., 2011) (62). Further studies should include non-diabetic cancer patients to distinguish between metformin's systemic metabolic and direct anticancer effects (Evans et al., 2005) (65). Ongoing and upcoming clinical trials in various cancers—including prostate, breast, endometrial, and pancreatic—will provide critical data on metformin's therapeutic potential. A notable example is the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) MA.32 phase III trial involving over 3,500 women with early-stage breast cancer (Goodwin et al., 2011) (64). Integrating data from mechanistic and translational research with clinical findings will be key to determining metformin's effectiveness and establishing its role as a safe, low-cost anticancer therapy (Pollak, 2012) [61].

Abbreviation

Abbreviation	Full Form
FDA	Food and Drug Administration
AMP	Adenosine Monophosphate

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ATP	Adenosine Triphosphate
AMPK	AMP-Activated Protein Kinase
Thr172	Threonine 172
STK11	Serine/Threonine Kinase 11
PGC-1α	Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha
GLUT4	Glucose Transporter Type 4
LKB1	Liver Kinase B1
IGF-1	Insulin-Like Growth Factor 1
c-MYC	Cellular Myelocytomatosis Oncogene
ROS	Reactive Oxygen Species
T2DM	Type 2 Diabetes Mellitus
P53	Tumor Protein 53
mTOR	Mechanistic Target of Rapamycin
OCT1	Organic Cation Transporter 1
HOMA	Homeostasis Model Assessment
TUNEL	Terminal Deoxynucleotidyl Transferase dUTP Nick End Labeling
Ki-67	Ki-67 Antigen
ACF	Aberrant Crypt Foci
NCIC	National Cancer Institute of Canada

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