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# *EXPLORING THE DIVERSE THERAPEUTIC BENEFITS OF METFORMIN: FROM ANTI-CANCER TO ANTI-INFLAMMATION AND PCOS MANAGEMENT*

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***ABSTRACT***
**Background:** Metformin is widely prescribed for type 2 diabetes mellitus and is recognized for its therapeutic benefits beyond glycemic control. This review summarizes current data on metformin's diverse roles in various therapeutic contexts, including treating polycystic ovarian syndrome (PCOS), anti-inflammatory effects, and cancer prevention. **Method:** This comprehensive examination highlights the multifaceted applications of metformin in modern medicine and its potential to enhance the treatment of inflammatory diseases, cancer, and reproductive disorders. **Results and Discussion**: Metformin's anti-inflammatory properties may benefit autoimmune disorders, neurological diseases, and cardiovascular illnesses. In women with PCOS, metformin aids in restoring menstrual regularity, inducing ovulation, and improving reproductive outcomes by enhancing insulin sensitivity, modulating ovarian function, and reducing hyperandrogenism. Additionally, emerging evidence suggests that metformin may reduce cancer incidence and mortality in diabetic individuals by modulating cellular metabolism, inducing apoptosis, and inhibiting tumor cell proliferation. **Conclusion**: Our review suggests promising evidence for metformin's role in cancer prevention, reducing inflammation, and managing PCOS. However, further research is required to identify patient subgroups that will benefit most from metformin therapy, elucidate its mechanisms of action, and optimize dosing regimens.

## *INTRODUCTION*

Metformin is a typical medication suggested for managing type 2 diabetes mellitus, although its uses have expanded beyond what is usually thought to be possible. Within the previous 15 years, a growing number of inquiries demonstrated the many therapeutic advantages of metformin in a range of clinical contexts, going well beyond glycemic control [1]. Researchers

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and physicians are particularly interested in its possible use in managing polycystic ovarian syndrome (PCOS), controlling inflammation, and preventing and treating cancer [2]. Effective preventative and treatment techniques are desperately needed since cancer continues to be one of the major causes of morbidity and death globally [3]. Metformin usage might be linked to a lower prevalence and mortality of cancer in diabetic people, according to preclinical research and epidemiological data [4]. Numerous processes, including cellular metabolic control, apoptosis activation, and decreased tumor cell proliferation, are responsible for metformin's anti-cancer effects [5]. Research on the effectiveness of metformin as a second line of treatment for many cancer types has been sparked by these discoveries, which have the potential to enhance the lives of patients [6] greatly. Apart from its potential anti-cancer properties, metformin has strong anti-inflammatory properties that might have implications for various inflammatory conditions [7].

Several illnesses, such as autoimmune disorders, neurological diseases, and cardiovascular ailments, are linked to chronic inflammation. By inhibiting the production of pro-inflammatory cytokines via AMP-activated protein kinase (AMPK) and other signaling pathways, metformin's actions enhance immunological homeostasis and have anti-inflammatory characteristics [8]. Given that metformin possesses anti-inflammatory properties beyond its ability to manage diabetes, it may find new use in treating inflammatory diseases [9]. Finally, PCOS, a prevalent endocrine condition affecting women in their reproductive years, has made metformin a key component of treatment. Infertility, irregular menstruation, and metabolic problems are the results of PCOS, which is characterized by hormone abnormalities, insulin resistance, and ovarian dysfunction [10]. Menstrual regularity can be restored, ovulation can be induced, and reproductive outcomes can be improved in women with PCOS by taking metformin, which lowers hyperandrogenism and improves insulin sensitivity. Its value goes beyond glycemic control, as evidenced by its first-line pharmaceutical therapy for PCOS [11].

There are still several unanswered concerns and difficulties despite the increasing awareness of metformin's many therapeutic advantages. Studies are still being conducted to understand better the processes underlying the drug's varied effects, optimize dosage schedules, and pinpoint patient subgroups who stand to gain the most from metformin therapy [12]. In addition, concerns regarding possible adverse effects, medication interactions, and long-term safety profiles need to be carefully taken into account, especially in populations without diabetes. This review aims to provide a thorough summary of the available data on the therapeutic advantages of metformin in various clinical settings, such as its ability to prevent cancer, reduce inflammation, and help control PCOS. We seek to summarize results from preclinical investigations, clinical trials, and epidemiological data to provide insight into the underlying processes, clinical consequences, and possible uses of metformin as a flexible therapeutic agent in modern medicine beyond its conventional application.

## *MATERIALS AND METHODS*

For this review, we used various sources, including PubMed, Google Scholar, and the Directory of Open Access Journals (DOAJ). The search was conducted using combinations of the following keywords and/or their equivalents: metformin, antiinflammation, anti-cancer, and PCOS.

Studies examining the many therapeutic advantages of metformin, such as its use in treating cancer, inflammatory diseases, and polycystic ovarian syndrome (PCOS), satisfied the inclusion criteria for this publication. The study encompassed observational and experimental studies looking at how metformin affects different elements of health. Conversely, studies with a population outside the purview of this investigation, an inadequate design, or no relevance to the primary research question are examples of exclusion criteria.

### Anti-cancer potential role of metformin

Innovative preventative and treatment approaches are required since cancer is still a major worldwide health concern. The oral hypoglycemic medication metformin has gained traction as a viable option for treating and preventing cancer, providing a novel perspective to enhance current patient care strategies. Beyond controlling blood sugar, metformin also has many other impacts [13]. These include altering how cells metabolize their resources, preventing cell growth, triggering cell death, and blocking signaling pathways supporting tumor growth [6].

Metformin is a commonly accessible medicine that has sparked attention to its potential for oncological applications due to the increasing body of research supporting its anti-cancer properties [12]. There is optimism for better treatment results and increased

patient survival due to ongoing clinical trials assessing the effectiveness of metformin as monotherapy or in conjunction with traditional anti-cancer medicines across various cancer types [14]. Figure 1 provides an immediate description of anti-cancer and classical processes.

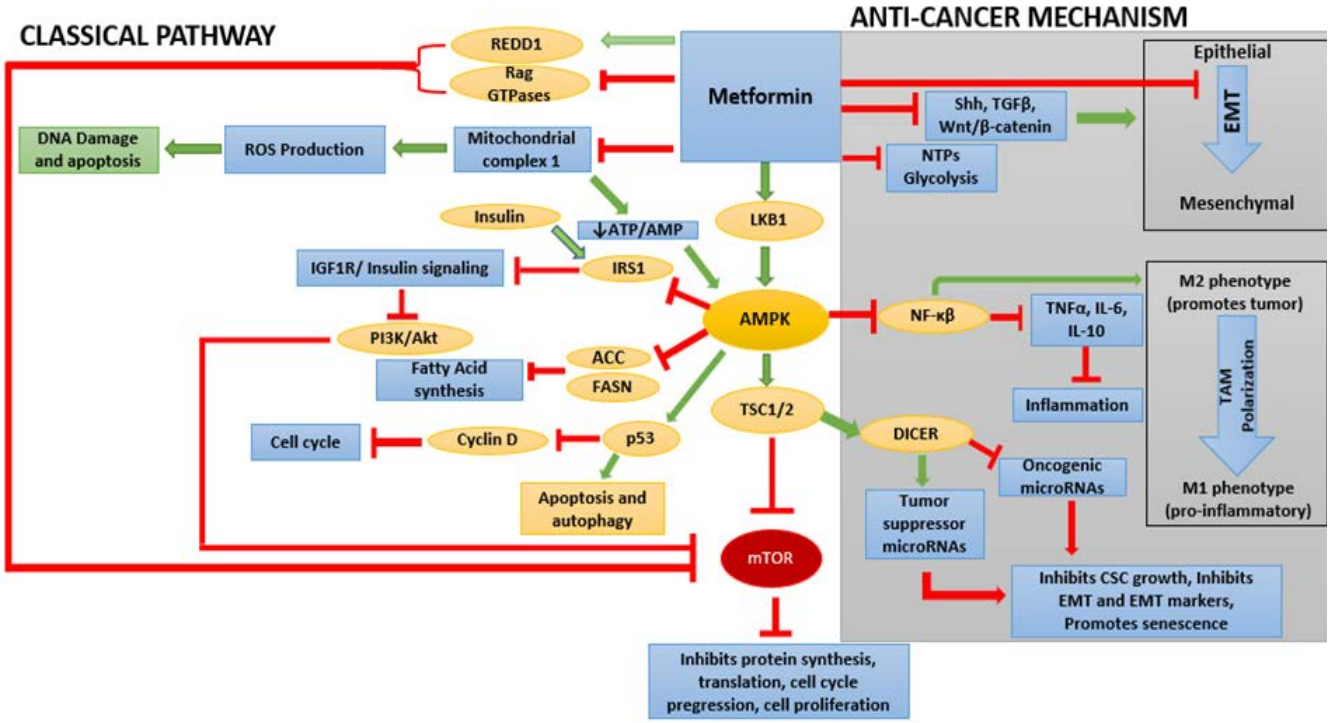


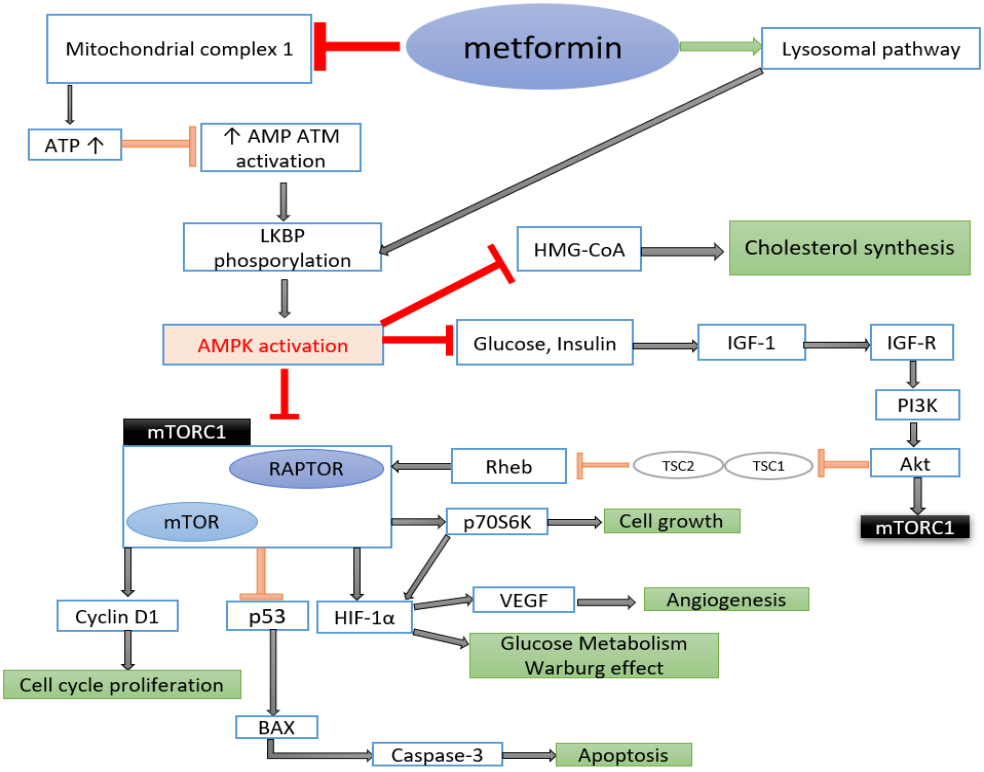

**Figure 1: Molecular mechanisms associated with classical anti-cancer and anti-CSC effects of metformin, adapted from Saini and Yang (2018) [14]**

The classical cancer prevention and anti-CSC processes are presented as solid line arrows when metformin is activated; the routes it inhibits are shown as dotted lines. Terminologies: ACC (acetyl-coA carboxylase); Akt (protein kinase B); AMP (adenosine monophosphate); ATP (adenosine triphosphate); AMPK (AMP-activated protein kinase); EMT (epithelial to mesenchymal transition); FASN (fatty acid synthase); IGF1R (insulin growth factor-1 receptor); IL (interleukin); IRS1 (insulin receptor substrate-1); LKB1 (liver kinase B1); mTOR (mammalian target of rapamycin); NF-κB (nuclear factor kappa-light-chain-enhancer of activated B-cells); NTPs (nucleotide triphosphates); PI3K (phosphatidylinositol-4,5-bisphosphate 3-kinase); REDD1 (regulated in development and DNA damage response 1); ROS (reactive oxygen species); Shh (sonic hedgehog); TAM (tumor-associated macrophage); TGFβ (transforming growth factor beta); TNFα (tumor necrosis factor-alpha); TSC1/2 (tuberous sclerosis 1 and 2) [14]. The effects of metformin in patients with pancreatic cancer are being investigated in phase II clinical research. Metformin may enhance progression-free survival, according to preliminary data [15].

Optimizing dose schedules, determining which patient groups may benefit the most, and addressing potential resistance mechanisms are still difficult tasks. Metformin modulates angiogenesis, extracellular matrix remodeling, and immunological responses, affecting the tumor microenvironment. Metformin's anti-inflammatory properties help the immune system eliminate cancer cells by inhibiting the generation of pro-inflammatory cytokines and boosting anti-tumor immunity [4]. Additionally, metformin alters the extracellular matrix's structure and function, impairing tumor-stromal connections and inhibiting angiogenesis by downregulating VEGF production [15].

Targeting basic metabolic pathways, especially those involved in glucose and lipid metabolism, is how metformin affects cancer cells. Metformin disrupts ATP synthesis by blocking mitochondrial respiratory complex I, which activates AMPK and causes an energy shortage. Following AMPK activation, anabolic pathways are inhibited, and catabolic pathways are encouraged, suppressing cancer cell development and multiplication [16]. Metformin prevents the development of

cancer cells by interfering with crucial signaling pathways involved in the regulation and survival of the cell cycle [17]. Metformin stops cancer cells by blocking the mTOR (mammalian target of rapamycin) pathway, which stops protein synthesis and cell division [18]. Metformin also causes apoptosis using AMPK-dependent and -independent pathways, which increases sensitivity to apoptotic stimuli and causes caspase-mediated cell death [19]. Figure 2 illustrates the metformin route, which aids the body's metabolism and prevents carcinogenesis.




**Key**

**Decreasing mechanism or inhibition**

**Main decreasing mechanism or inhibition by AMPK activation**

**Increasing mechanism or activation**

**Figure 2.** MTF's function in the AMPK/mTOR signaling pathway's metabolism and carcinogenesis, these pathways adapted from Lucafo et al. (2021) [21]

By inhibiting mTORC1, AMPK activation increases apoptosis, lowering angiogenesis, the Warburg effect, and cell proliferation. ATM ataxia telangiectasia mutated, LKB1 liver kinase B1, AMPK adenosine-monophosphate-activated protein kinase, ATP adenosine-triphosphate, AMP adenosine-monophosphate, Coenzyme A β-Hydroxy β-methylglutaryl-coenzyme A, The IGF-R insulin-like growth factor receptor, IGF-1 insulin-like growth factor 1, Phospholipase 3 kinase, or PI3K B-protein kinase Akt, Rheb Ras homolog abundant in the brain, TSC1,2 tuberous sclerosis complex 1,2, and mTORC1 mammalian target of rapamycin complex 1, VEGF, or vascular endothelial growth factor, HIF-1α, hypoxia-inducible factor 1α, p53 tumor suppressor protein, RAPTOR regulatory-related protein of mTOR, mTOR mammalian target of rapamycin, and BAX, or BCL-2 associated X protein [16]. Metformin modulates several signaling pathways inside the body, with AMPK (AMP-activated protein kinase) and mTOR (rapamycin's mucosal target) as primary targets. The metabolic regulation enzyme AMPK is triggered when AMP (adenosine monophosphate) is high and ATP (adenosine triphosphate), a source of cell energy, is low [20]. This enzyme controls the utilization of glucose and the synthesis of energy. Metformin activates AMPK, enhancing muscle cell absorption of glucose and fatty acid oxidation, decreasing the liver's synthesis of glucose [23].

On the other hand, the mTOR signaling pathway is inhibited by metformin as well and is accountable for cell division. Protein synthesis and cell proliferation are decreased by this pathway,

which involves suppression of the mTORC1 complex. Metformin slows down the aging process of cells and helps shrink tumors by blocking mTOR [24]. Metformin's actions on AMPK activation and mTOR inhibition point to possible benefits for regulating glucose metabolism, enhancing insulin sensitivity, and lowering the risk of aging-related disorders and cancer [25]. Clarifying metformin's therapeutic mechanisms across various clinical situations, from diabetes to cancer prevention, requires a thorough knowledge of the drug's interactions with various signaling pathways.

**Anti-inflammatory role of Metformin**

Transcription regulators implicated in inflammation include NF-κB. This factor can interfere with many inflammatory pathways, cell death, and tissue degradation through the regulation of signaling [20]. Upon examination of a traumatic spinal cord injury in mice, these circumstances were shown to cause complex reactions of local inflammation in addition to phagocyte infiltration, microglia development and activation, and increased production of preinflammatory cytokines. Metformin's anti-inflammatory action, achieved by lowering NF-kB expression, can limit neuronal damage and its impairments in the early stages. Metformin prevents monocytes from differentiating into macrophages by blocking the phosphorylation of STAT by activating AMPK. Metformin was shown to inhibit the activity of NF-kB-dependent genes. This involves preinflammatory molecules that are adhesion molecules like intercellular binding molecule-1 (ICAM-1), vessel adhesion to cell molecule-1 (VCAM-1), selectin E, and monocyte chemoattractant protein-1 (MCP-1) [21].

Aldosterone was shown to activate TRAF3-engaging protein (TRAF3IP2) mediators of inflammation in a study assessing the anti-fibrotic properties of metformin in heart muscle cells [22], alerting pathological stress and causing oxidative stress. This increases the release of cytokines that promote inflammation, such as IL-6, IL-17, and IL-18 [23]. In response to oxidative stress, TRAF3IP2 is a cytoplasmic adaptor molecule that promotes the synthesis of many transcription factors, including NF-kB, AP-1, and C/EBPβ, and it plays a role in the development of inflammatory mediators [24].

Conversely, studies have demonstrated that metformin can block the AMPK from being activated by the aldosterone-induced TRAF3IP2 molecule. It may also aim to block the pathway that triggers the transcription factors NF-kB or C/EBPβ, which reduces or stops the generation of inflammatory cytokines [25]. Ultimately, the risk of cardiac fibrosis is mitigated, and cardiac fibroblast migration and proliferation are decreased [24]. Metformin reduces inflammation in atherosclerosis by preventing the phosphorylation of transcription factors P38, JNK, and AKT in smooth muscle cells, which IL-1 triggers. Furthermore, it downregulates the synthesis of IL-6 and IL-8 by macrophages and epithelial cells, which are cytokines that promote monocyte recruitment and epithelial cell adhesion [22].

According to another research, a meta-analysis involving 20 trials representing 433 women with polycystic ovarian syndrome validated the decrease in CRP plasma levels induced by metformin, particularly in women who are obese. Another systematic review of 216 studies found that metformin significantly reduced CRP in women with polycystic ovarian syndrome but had no appreciable effect on IL-6 [26]. A major inflammatory cytokine that can lead to tissue damage and fibrosis is called tumor necrosis factor-alpha (TNF-α). It is generated by viral and bacterial infections in the body [29]. Similarly, a different study found that metformin might lower the level of the inflammatory marker YKL-40. Additionally, metformin decreases the generation of inflammatory cytokines associated with sepsis generated by monocytes and neutrophils, such as TNF-α, IL-1β, and IL-6 [30,31].

TNF-α, IL-8, and insulin sensitivity were among the inflammatory markers that metformin was shown to reduce in an obese 6- to 12-year-old research [29]. Metformin has been shown in several studies to offer protection against inflammatory stress-related cardiovascular diseases (CVD), including endothelial dysfunction [30], myocardial infarction [34], acute myocarditis [35], and chronic heart failure [33]. Figure 2 shows how metformin can reduce the effects of inflammation by transcriptionally suppressing ICAM-1, MCP-1, and E-selectin in HUVECs. It can also stop TNFα-induced NF-κB activation [34]. Particularly harmful effects can arise from persistent inflammation of the neurological system or neuroinflammation. Both the central [e.g., Alzheimer's disease (AD), Parkinson's disease (PD), ischemia and traumatic brain injury [35], multiple sclerosis, motor neuron disease [36], and depression] and peripheral [e.g., neuropathic pain, fibromyalgia] nervous systems are significantly influenced by neuroinflammation in the developmental process of disease [37]. The role of

inflammation in the development of tumors has long been recognized [41]. Many cancers start as infections, chronic irritants, or inflammatory sites [9].

Additionally, the main agent in the formation of the tumor's environment is the inflammatory cell, a crucial component of the neoplastic process that fosters the proliferation, continued existence, and motility of tumor cells [39]. Colorectal cancer cells (HCT-116 and Caco-2 cells) undergo apoptosis when metformin and 5-aminosalicylic acid (5-ASA) work together to reduce cell growth [43]. By reducing the production of IL-1β, IL-6, COX-2, TNF-α, and TNF receptors in cancer cells, metformin bolsters the anti-inflammatory properties of 5-ASA. The combination also exhibits metastasis-inhibitory effects by reducing the enzymatic activity of matrix metalloproteinase (MMP)-2 and MMP-9 [44]. Clinical studies show that individuals with metformin-treated ovarian cancer had less IL6 expression in their tumor stroma [42]. Metformin inhibits inflammation in several additional situations by a mechanism particular to each condition [46].

**Metformin in PCOS Management**

The main symptoms of PCOS, a widespread endocrine condition that affects women of reproductive age worldwide, include insulin resistance, ovarian malfunction, and elevated hormone levels [10]. Glycemic control is not the only benefit that metformin, a first-line treatment for type 2 diabetes mellitus, offers. It has become a mainstay in the treatment of PCOS [47]. To optimize the use of metformin and enhance clinical results, it is important to comprehend the processes behind its therapeutic actions in PCOS [48]. One of PCOS's main characteristics is insulin resistance, which fuels hyperandrogenism and hyperinsulinemia. Metformin primarily increases peripheral tissues' insulin sensitivity, lowers insulin levels, and lessens compensatory hyperinsulinemia [46].

PCOS model was studied in vitro at the Animal Experimental Center of Sun Yat-sen University Medical College (SCXK, Guangdong). To the Metformin group (MF), MF 300 mg/kg/d was administered daily. Subcutaneous injection of Exenatide group (EX) (10μg/kg•d) was done daily for the EX group. Four weeks of continuous administration were followed by assessments of fasting blood glucose, serum testosterone, luteinizing hormone, and other biochemical markers. Through the use of Western and real-time PCR techniques, the expression of SIRT1 with AMPKα in the reproductive systems of each group was measured. Metformin and exenatide significantly improve the fertility and hormonal health of PCOS-affected rats via the AMPKα-SIRT1 pathways. This strategy may serve as a target for treatments and could be the molecular process affecting IR in PCOS [49]. Metformin enhances glucose absorption and utilization via AMPK activation and decreases hepatic gluconeogenesis. This lowers ovarian androgen production and restores regular menstrual periods. Metformin directly affects the ovarian tissue, affecting ovulatory function, steroidogenesis, and folliculogenesis [48]. Metformin inhibits ovarian androgen production and promotes follicular maturation by activating AMPK and blocking the mTOR pathway [50]. In addition, metformin helps PCOS-afflicted women conceive more successfully by reestablishing the proper equilibrium between granulosa cell growth and apoptosis [49].

An important aspect of PCOS is hyperandrogenism, which fuels hirsutism, acne, and irregular menstruation [51]. By improving the liver's production of hepatic sex hormone-binding globulin (SHBG) and reducing the quantity of testosterone generated by the ovaries and adrenal glands, metformin reduces hyperandrogenism [52]. Because it balances excess androgen and restores the hypothalamic-pituitary-ovarian axis, metformin helps women with PCOS suffer fewer of the clinical symptoms associated with hyperandrogenism [53]. Metformin treatment for PCOS has shown promise in promoting ovulation, regulating menstrual cycles, and increasing reproductive results. Additionally, metformin may aid in weight loss and reduce the risk of gestational diabetes in women with PCOS who are expecting, among other metabolic advantages [54]. However, further research is needed to determine the best dosage schedules, length of therapy, and patient selection standards to enhance therapeutic efficacy and reduce side effects.

***DISCUSSION***

Metformin side effects include nausea and diarrhea, as well as the uncommon but dangerous risk of lactic acidosis [57]. This is in addition to its many therapeutic advantages, which include anti-cancer, anti-inflammatory, and control of PCOS. Chronic liver illness, significant renal impairment, and circumstances that increase the risk of lactic acidosis are examples of contraindications. The reduced efficacy of metformin therapy in individuals with impaired renal function and the possibility of pharmacological interactions with other medications that raise

lactic acid levels are two of its side effects [58]. The novel aspects of this review are briefly discussed, highlighting recent advancements in our knowledge of metformin's potential therapeutic uses beyond glycemic control. In addition to helping control diabetes, metformin also shows promise in treating cancer, inflammation, and PCOS. This review incorporates fresh research supporting these claims. The application of metformin in many clinical and therapeutic situations is being further explored with the help of fresh findings from recent research and a deeper knowledge of the drug's mechanisms of action.

## *CONCLUSION*

Metformin has great potential in many medical fields as a repurposed medicinal drug. Further study is needed to validate the advantages and find the best dosages and treatment plans for metformin's drug-repurposing strategy. This review offers important insights that might help develop safer and more effective treatments for metformin in cancer, inflammatory diseases, and PCOS.

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## *CONFLICT OF INTEREST*

The authors declare no conflict of interest.

## *AUTHOR CONTRIBUTION*

Nurul Azizah contributed to Conceptualization, Visualization, and Writing-Original Draft. Annisa Abdi Ghifari contributed to visualization, writing, review, & editing. Wirawan Adikusuma contributed by writing, reviewing & editing the manuscript and following the methodology. Darmawi Darmawi contributed to the manuscript's conceptualization, writing, review & editing, and Supervision. Muhammad Yulis Hamidy contributed to Funding Acquisition, Project administration, Writing - Review, & Editing.

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