

## The Promising and Diverse Therapeutic Effects of Metformin

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**ABSTRACT:** The repositioning of metformin represents a salient and intriguing area of research, serving as a valuable alternative to molecular target-based drug discovery through the implementation of an off-target strategy for therapeutic repurposing. The repurposing of an already approved anti-diabetic medication mitigates the substantial expenses associated with the protracted conventional drug development process related to the additional pharmacological applications mentioned. Metformin has demonstrated efficacy in inhibiting dyskinesia associated with Parkinson's disease, as well as in preventing cancer recurrence across various malignancies, including neuroendocrine tumors, colorectal carcinoma, prostate cancer, breast cancer, pancreatic cancer, cholangiocarcinoma, and fibrosarcoma; Furthermore, metformin is also reported to enhance the healing process for liver injuries and improve cardiovascular health. This positions

it as a potential treatment for conditions like cardiovascular disease and Fragile X syndrome.

Metformin exhibits significant benefits for neurodegenerative disorders, particularly Alzheimer's disease, as it upregulates neurotrophic factors and mitigates dopaminergic neuronal death in models of Parkinson's disease. Being one of the most prevalently prescribed oral antidiabetic agents, metformin also ameliorates serum lipid profiles, emphatically impacts hemostatic functions, alleviates cognitive impairments, and possesses notable anti-inflammatory characteristics. Findings from numerous clinical studies affirm that the prolonged administration of metformin in diabetic cohorts correlates with enhanced cognitive function, in comparison to individuals utilizing alternative antidiabetic therapies. The repositioning of metformin is presented as a cost-effective strategy, as it avoids the lengthy and expensive process of developing new drugs from scratch. This makes it an attractive option for addressing various health issues. This evidences substantiates the status of metformin as a preferred treatment and suggests its potential advantages for non-diabetic populations.

In conclusion, this paper presents metformin as a promising multi-therapeutic agent with a wide range of potential applications, particularly in neurodegenerative diseases, cancer treatment, and cognitive health, while also highlighting its cost-effectiveness in drug repositioning.

**Keywords:** *Metformin, repurposing, anti-cancer, anti-aging, anti-stroke, anti-psychotic, and anti-neurodegenerative.*

## **Introduction**

Metformin (1,1-dimethyl biguanide hydrochloride) is a synthetic analog of the naturally occurring guanidine compound derived from *G. officinalis*, a plant utilized in traditional herbal medicine. First introduced as an antihyperglycemic agent in 1957, Metformin received approval from the US Food and Drug Administration (FDA) in 1995 for the treatment of type 2 diabetes (Jason and Robert 2023). It has a history spanning over a century, has evolved from its initial use in diabetes management to a multi-target therapeutic agent with diverse applications. Its ability

to modulate various biological pathways has made it a promising candidate for treating metabolic disorders, aging-related conditions, cardiovascular diseases, and cancer (Froldi 2024).

Metformin, exhibits a range of therapeutic effects beyond its primary use, including anti-inflammatory, anti-cancer, anti-aging, anti-stroke, anti-psychotic, and anti-neurodegenerative properties (Top et al., 2022). These effects are attributed to its ability to modulate various cellular pathways and molecular targets, making it a promising candidate for repurposing in the treatment of diverse diseases. The following sections detail the specific benefits of metformin in these areas. Recent research indicates that metformin is not only essential for diabetes management but also offers potential advantages for cardiovascular health, cancer prevention, and cognitive function, warranting its continued use and further research (Top et al., 2022). This review examines the therapeutic potential of metformin, supported by recent research findings.

## **METFORMIN IN METABOLIC DISORDERS**

### ***Type 2 Diabetes Mellitus (T2DM)***

Metformin is the preferred treatment for T2DM, primarily due to its hepatic glucose production lowering ability and improving insulin sensitivity. It switches on AMP-activated protein kinase (AMPK), a crucial regulator of energy metabolism, leading to reduced gluconeogenesis and enhanced glucose uptake in skeletal muscles (Ala & Ala, 2021; Dutta et al., 2023; Sirtori et al., 2024). Additionally, metformin's effects on mitochondrial function and lipid metabolism contribute to its therapeutic efficacy in managing T2DM (Apostolova et al., 2020; Zhu et al., 2023).

### **Obesity and Weight Management**

Beyond glycemic control, metformin aids in weight loss by suppressing appetite and enhancing fat oxidation. Its role in activating AMPK also contributes to improved lipid profiles, making it beneficial for managing obesity-related metabolic disorders (Lv & Guo, 2020; Jaiswal et al., 2023; Sirtori et al., 2024).

## **Polycystic Ovary Syndrome (PCOS)**

In PCOS, metformin improves insulin sensitivity, restores menstrual cyclicality, and reduces hyperandrogenism. These effects are attributed to its insulin-sensitizing properties and modulation of androgen production (Lv & Guo, 2020; Yan et al., 2020; Ala & Ala, 2021).

## **ANTI-AGING PROPERTIES AND LONGEVITY**

### ***Anti-Aging and Longevity***

Metformin activates AMPK, which slows down cell aging and regulates intracellular signaling, contributing to its anti-aging effects. It may reduce age-associated inflammation and has been linked to lifespan prolongation through mechanisms like telomere prolongation (Sirtori et al., 2024).

### **Cellular Senescence and Telomere Length**

Metformin exhibits senolytic activity, reducing the burden of senescent cells that contribute to aging and age-related diseases. It also promotes telomere elongation by activating mitochondrial respiratory factors and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 $\alpha$ ) (Piskovatska et al., 2019; Chen et al., 2022; Sirtori et al., 2024).

### **Inflammation and Oxidative Stress**

Metformin is mainly known for its ability to lower glucose effects in type 2 diabetes. However, recent studies have suggested that it also possesses anti-inflammatory properties. The current paper builds on this by demonstrating that metformin can regulate specific microRNAs and proteins involved in inflammation,

Metformin regulates microRNAs such as miR-451, which in turn modulates inflammatory proteins like CXCL16, reducing inflammation in conditions like osteoarthritis (Alimoradi et al., 2024). Metformin simultaneously increases miR-451 level of expression with pain reduction. Unlike microRNA-15b, the expression of microRNA-451 increased with metformin treatment, suggesting that metformin's regulatory effects on microRNAs may be selective. It also decreases the serum levels

of BCL-2 and CXCL16 in patients with OA (Alimoradi et al., 2024). This distinction is important for understanding the specific molecular pathways by which metformin demonstrates its therapeutic effects in osteoarthritis (OA). The analgesic effects of metformin can be linked to various factors, such as its anti-inflammatory and anti-aging characteristics, indicating that metformin may alleviate pain and inflammation in OA patients by modulating miR-451/CXCL16 and BCL-2 (Alimoradi et al., 2024). Metformin activates AMPK, which helps control inflammatory conditions and improve oxidative status (Goel et al., 2022).

Aging is mostly followed by chronic inflammation (inflammaging) and oxidative stress. Metformin mitigates these processes by switching on nuclear factor erythroid 2-related factor (Nrf2) and suppressing pro-inflammatory pathways, like NF- $\kappa$ B ("The Gut Microbiome, Metformin, and Aging", 2022; Chen et al., 2022; Sirtori et al., 2024).

## **NEUROPROTECTION AND COGNITIVE HEALTH**

### ***Anti-Neurodegenerative Effects***

Metformin, recognized as one of the primary hypoglycemic agents, exhibits cardioprotective, anti-inflammatory, and anticancer properties, alongside its established hypoglycemic effects (Du et al., 2022). Moreover, the potential of metformin in both preventing and treating neurodegenerative diseases has garnered significant attention. An increasing body of research indicates that metformin may inhibit the advancement of neurodegenerative conditions. In recent years, numerous studies have explored the neuroprotective effects of metformin in the context of neurodegenerative diseases. Findings suggest that metformin can serve a neuroprotective function by modulating energy metabolism, oxidative stress, inflammatory responses, and protein accumulation within cells, thereby preventing neuronal dysfunction and cell death (Du et al., 2022). Metformin demonstrates neuroprotective capabilities through its regulation of energy metabolism, oxidative stress, and inflammatory responses, all of which are vital in averting neurodegenerative diseases (Du et al., 2022). Additionally, metformin has shown

potential in the management of severe neurological conditions like amyotrophic lateral sclerosis and frontotemporal dementia (Sirtori et al., 2024).

Recent studies indicate that metformin could postpone the onset of cognitive decline associated with aging and neurodegenerative diseases, such as Alzheimer's and Parkinson's disease. Its neuroprotective properties are associated with enhanced mitochondrial function, decreased oxidative stress, and the modulation of amyloid-beta pathology (Rotermund et al., 2018; Chen et al., 2022; Sirtori et al., 2024).

## **CARDIOVASCULAR BENEFITS**

### ***Lipid Metabolism and Atherosclerosis***

Metformin reduces the risk of cardiovascular events through its LDL cholesterol, triglycerides, and free fatty acids lowering capabilities. It also inhibits the progression of atherosclerosis by improving endothelial function and reducing oxidative stress (Apostolova et al., 2020; Lv and Guo, 2020; Zhu et al., 2023).

### **Blood Pressure Regulation**

The drug exerts antihypertensive effects by enhancing nitric oxide production and reducing vascular smooth muscle cell proliferation. These effects contribute to improved cardiovascular outcomes in diabetic and non-diabetic patients (Ala & Ala, 2021; Zhu et al., 2023).

### **Cardiomyocyte Protection**

Metformin protects cardiomyocytes from ischemic injury by activating AMPK and reducing apoptosis. Its antioxidant and anti-inflammatory properties further enhance its cardioprotective effects (Apostolova et al., 2020; Zhu et al., 2023).

### **Cardioprotective Potential**

The cardioprotective potentials of Metformin goes beyond its glucose-lowering effects, demonstrating significant benefits in reducing cardiovascular events, improving endothelial function, combating inflammation, and protecting myocardial tissue (Bu, et al., 2022). It's cardioprotective and neuroprotective potentials make it

suitable for treating a variety of human diseases, including those with epigenetic components (Roberts et al., 2024).

Metformin is linked to a decreased likelihood of significant harmful cardiac events like cardiac death, myocardial infarction, and heart failure in both diabetic and nondiabetic patients. Research indicates that it can slow the progression of atherosclerosis, enhance endothelial function, and diminish markers of systemic inflammation and oxidative stress, such as C-reactive protein, IL-6, and TNF-alpha (Bu et al., 2022; Jason and Roberts, 2023). Metformin also improves cardiac metabolic and functional parameters in heart failure patients and may precondition the heart against ischemia-reperfusion injury (Jason and Roberts, 2023). Clinical trials, including the UKPDS revealed a 30% reduction in macrovascular complications and sustained cardiovascular benefits in metformin-treated diabetic patients, independent of glycemic control (Varjabedian et al., 2018; Bu et al., 2022).

While metformin's diverse therapeutic effects are promising, some studies suggest it may have a dual role, potentially accelerating the progression of certain neurodegenerative diseases (Du et al., 2022). This highlights the need for further research to fully unravel its mechanisms and optimize its use across different conditions. Thus, metformin has garnered attention for its potential cardioprotective and neuroprotective effects. Research indicates that metformin may offer significant benefits beyond glycemic control, making it a candidate for repurposing in various diseases.

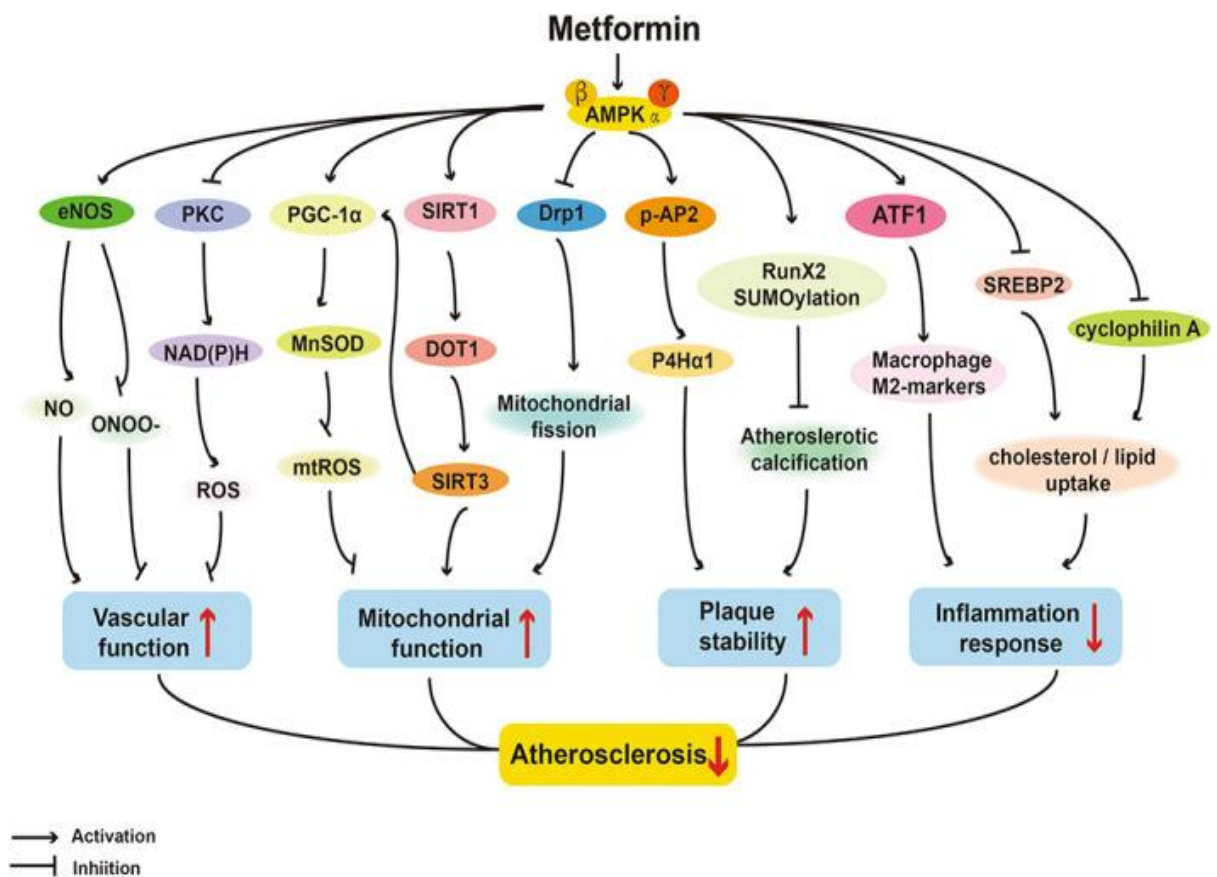
### **Mechanisms of Action**

Metformin exhibits multifaceted cardioprotective effects through mechanisms primarily involving AMPK activation, enhanced endothelial function, anti-inflammatory actions, and mitochondrial protection, supported by robust preclinical and clinical evidence indicating a reduction in cardiovascular morbidity and mortality beyond its antidiabetic role (Driver et al., 2018).

The activation of AMP-activated protein kinase (AMPK) is central to metformin's cardioprotective effects. AMPK activation leads to improvement of endothelial function and nitric oxide (NO) production via phosphorylation of endothelial nitric

oxide synthase (eN OS). Reduced oxidative stress and suppression of mitochondrial reactive oxygen species (ROS). Modulation of inflammatory pathways, lowering inflammatory cytokines in cardiovascular tissues, which are critical factors in cardiovascular health (Varjabedian et al., 2018; Bu et al., 2022; Jason and Roberts, 2023).

Sirtuin signaling (Sirt2 and Sirt3) is also implicated in metformin-induced AMPK activation and myocardial protection, representing a novel molecular target for heart failure and ischemic heart disease. Lastly, metformin also promotes autophagy and mitochondrial function which contribute to cardiac remodeling and protection after ischemic injury (Jason and Roberts, 2023).



**Figure 1:** AMPK-dependent actions of protective effects of metformin on atherosclerosis. eNOS, endothelial nitric oxide synthase; NO, nitric oxide; PKC, protein kinase C; PGC-1 $\alpha$ , peroxisome proliferator-activated receptor gamma coactivator-1 $\alpha$ ; MnSOD, manganese superoxide dismutase; mtROS, mitochondrial reactive oxygen species; SIRT1, sirtuin-1; DOT1, disruptor of telomeric silencing-1

*like protein or Kmt4; SIRT3, sirtuin-3; Drp1, dynamin-related protein; p-AP2, phosphorylation of activator protein 2 alpha; P4Ha1, prolyl-4-hydroxylase alpha 1; Runx2, Runt-related transcription factor 2; SUMO, small ubiquitin-like modifier; ATF1, activating transcription factor 1; SREBP2, Sterol regulatory element-binding protein 2 (Bu et al., 2022)*

### **Clinical Evidence:**

Several randomized controlled trials (RCTs), including the UK Prospective Diabetes Study (UKPDS), the CODYCE study, and others, confirm metformin's benefits on cardiovascular outcomes and inflammation reduction in patients with or without diabetes (Bu et al., 2022; Jason and Roberts, 2023). The CODYCE study demonstrated that metformin significantly improved coronary endothelial function and decreased oxidative stress markers over 24 months in patients with stable angina and coronary artery stenosis (Jason and Roberts, 2023).

Meta-analyses and long-term follow-ups demonstrate metformin's ability to reduce all-cause mortality, reinfarction, and major cardiovascular events, highlighting benefits that extend beyond glucose regulation (Varjabedian et al., 2018; Bu et al., 2022). Ongoing trials like VA-IMPACT and MET-HEFT aim to further validate metformin's cardiovascular benefits in various high-risk populations (Jason and Roberts, 2023).

### **Broader Implications**

The beneficial side effect profile and affordability of metformin render it a feasible choice for the prevention of cardiovascular diseases in non-diabetic populations (Zheng et al., 2023). Metformin has been demonstrated to decrease the risk of cardiovascular mortality in individuals with type 2 diabetes, especially among those who are obese. This was evidenced by the UK Prospective Diabetes Study (UKPDS), which revealed significant reductions in diabetes-related outcomes and overall mortality among users of metformin (Griffin et al., 2017). Furthermore, metformin may improve endothelial function, which are the inner lining of blood vessels. Enhanced endothelial function can lead to improved blood circulation and a reduced

risk of cardiovascular events. Several studies have linked metformin with improvements in markers of endothelial function (Ding et al., 2021).

## NEUROPROTECTIVE POTENTIAL

Metformin has demonstrated significant neuroprotective potential through multiple mechanisms, including modulation of mitochondrial function, reduction of oxidative stress, anti-inflammatory effects, and neural regeneration. Metformin promotes expression of neuroprotective genes such as *Bcl-2* and *CREB*, and mitochondria-associated genes like *PGC1 $\alpha$* , leading to improved neuronal survival and function in various neurological disorder models, including stroke, epilepsy, chemotherapy-induced cognitive impairment, and meningitis (Loan et al., 2024).

Metformin may encourage the growth of new neurons, studies have demonstrated it activation of certain pathways that promote neurogenesis, potentially helping to counteract some of the cognitive deficits associated with PD (Sritawan et al., 2020). Metformin also activates endogenous neural stem and progenitor cells, promoting neurogenesis and remyelination, thus enhancing spatial memory and cognition after brain injury or radiation (Loan et al., 2024). Metformin helps protect brain cells by improving mitochondrial function. Mitochondria, being the cell's energy factories, hence their dysfunction can be linked to Parkinson's disease (PD). It reduces reactive oxygen species (ROS) and helps maintain the health of mitochondria, which is crucial for the survival of dopaminergic neurons, the cells affected in PD (Ay et al., 2024).

Metformin also reduces tau protein phosphorylation and  $\alpha$ -synuclein accumulation a protein that forms toxic aggregates in PD (Paudel et al., 2020). By reducing the amount of this protein and its harmful effects, metformin may help protect neurons from damage, ameliorating dopaminergic neuron loss, thus showing disease-modifying potential in conditions like Parkinson's and Huntington's diseases (Rotermund et al., 2018; Sportelli et al., 2020; Dutta et al., 2023). It reduces infarct size and brain tissue apoptosis post-stroke and improves recovery outcomes in animal models as well as epidemiological observations in diabetic patients (Loan et al., 2024).

Metformin may also protect neurons by modulating energy metabolism, reducing oxidative stress, and mitigating inflammatory responses, which are pivotal in neurodegenerative diseases (Du et al., 2022). Studies suggest metformin slows the development of certain neurodegenerative disorders, including Parkinson's, by targeting pathways involved in neuronal health (Sportelli et al., 2020). Ongoing trials are exploring metformin's efficacy in early-stage neurodegenerative conditions, emphasizing its neuroprotective agent prospect (Piskovatska et al., 2019).

Metformin promotes autophagy, which can help remove toxic proteins and damaged organelles from cells. This action is particularly beneficial in PD, where the accumulation of damaged proteins contributes to cell death. By activating autophagy, metformin may help maintain cellular health and function (Lu et al., 2021).

Metformin has been shown to have positive effects on various neurological conditions such as major depressive disorder (MDD), Alzheimer's disease (AD), and Fragile X syndrome (FXS). However, its exact mode of action within the brain remains unclear. Emerging research indicates that metformin may influence not only synaptic transmission and plasticity under disease states but also modulate the balance between neuronal excitation and inhibition (E/I balance) within neural circuits (Li et al., 2022).

Metformin is known to have effects that may slow down aging processes. Since aging is a significant risk factor for PD, metformin's ability to target age-related cellular changes could provide additional neuroprotective benefits. It has been linked to improved health outcomes in various age-related diseases, suggesting it may also help in managing PD (Sportelli et al., 2020). While metformin shows promise in both cardio-protective and neuroprotective roles, some studies suggest it may have dual effects, potentially exacerbating certain neurodegenerative conditions in specific contexts (Du et al., 2022). This highlights the need for further research to fully understand its therapeutic potential and limitations.

### **Possible Mechanisms of Action**

Metformin activates AMPK, a critical energy sensor that helps regulate cellular energy metabolism, mitochondrial biogenesis, and autophagy, which collectively

protect neurons from metabolic stress (Sportelli et al., 2020; Du et al., 2022; Dutta et al., 2023; Loan et al., 2024).

By inhibiting mitochondrial complex I, metformin reduces excessive reactive oxygen species (ROS) production, alleviating oxidative stress, a major source of neuronal damage. It also promotes PGC-1 $\alpha$  expression, a key factor in mitochondrial biogenesis and function stress (Sportelli et al., 2020; Dutta et al., 2023; Loan et al., 2024).

Metformin reduces ROS levels by enhancing antioxidant pathways, such as increasing eNOS coupling and downregulating NADPH oxidase components, thereby protecting neurons from oxidative damage (Du et al., 2022). It inhibits NF- $\kappa$ B signaling and reduces production of pro-inflammatory cytokines, consequently dampening neuroinflammation that contributes to neurodegeneration. It also affects microglial activation and inflammatory pathways like NLRP3 inflammasome (Du et al., 2022; Loan et al., 2024). Metformin also influences other pathways such as PP2A (related to tau dephosphorylation), histone acetylation, and MAPK signaling, further contributing to neuroprotection and reduced neurotoxic protein aggregation (Du et al., 2022).

## **CANCER PREVENTION AND ANTITUMOR EFFECTS**

### ***Anti-Cancer Properties***

Metformin, a century-old molecule, has expanded from its initial use in diabetes treatment to demonstrate anti-cancer and life-prolongation potential, with mechanisms that involve insulin resistance, mitochondrial activity, and senolytic effects, offering hope for the treatment of age-related diseases and severe neurological disorders (Sirtori et al., 2024). A growing body of evidence indicates that metformin might possess both neuroprotective and anticancer properties. This means that, beyond diabetes management, metformin plays a part in reducing the risk of certain cancers and psychological decline, which is particularly relevant as the population ages (Top et al., 2022).

Metformin's role in combating cancer is connected to its effects on mitochondrial function and the resistance to phosphatidylinositol 3-kinase, which are vital in specific malignant tumors (Sirtori et al., 2024). Metformin's anti-cancer activity may also be linked to its tumor cell proliferation inhibition ability and induction of apoptosis, particularly in diabetic patients (Azizah et al., 2024). It acts on insulin receptors and mitochondrial pathways, which are crucial in cancer metabolism (Sirtori et al., 2024). Metformin may also influence cancer progression through epigenetic modifications, like histone modification and DNA methylation (Sirtori et al., 2024).

### **Mechanisms of Antitumor Action**

Metformin inhibition of cancer cell proliferation and apoptosis induction via numerous pathways, including AMPK activation, mTOR inhibition, and suppression of insulin/IGF-1 signaling. It also targets the tumor microenvironment by reducing inflammation and glycolysis (Amin et al., 2019; Kuznetsov et al., 2022; Sirtori et al., 2024).

### **Specific Cancers**

Metformin reduces breast cancer risk by inhibiting aromatase expression and improving insulin sensitivity (Amin et al., 2019; "Metformin", 2023). It suppresses the growth of colorectal cancer cells by inhibiting the Wnt/ $\beta$ -catenin pathway (Amin et al., 2019; Kuznetsov et al., 2022). Metformin's antiproliferative effects are linked to its ability to activate AMPK and induce apoptosis in endometrial cancer cells (Amin et al., 2019; "Metformin", 2023).

### **Clinical Evidence**

While preclinical studies strongly support metformin's anticancer effects, clinical trials have shown mixed results. The inconsistency may be ascribed to variance in metformin dosages between experimental and clinical settings (Amin et al., 2019; Kuznetsov et al., 2022).

Table: Therapeutic Effects of Metformin Across Diseases

| Disease/Condition         | Mechanism of Action                                                             | Citation                                                           |
|---------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------|
| Type 2 Diabetes Mellitus  | Activates AMPK, reduces hepatic gluconeogenesis, improves insulin sensitivity   | (Ala and Ala, 2021; Dutta et al., 2023; Sirtori et al., 2024)      |
| Obesity                   | Suppresses appetite, enhances fat oxidation, improves lipid metabolism          | (Lv and Guo, 2020; Jaiswal et al., 2023; Sirtori et al., 2024).    |
| Polycystic Ovary Syndrome | Restores menstrual cyclicality, reduces hyperandrogenism                        | (Lv and Guo, 2020; Yan et al., 2020; Ala and Ala, 2021).           |
| Alzheimer's Disease       | Reduces amyloid-beta pathology, improves mitochondrial function                 | (Rotermund et al., 2018; Chen et al., 2022; Sirtori et al., 2024). |
| Breast Cancer             | Inhibits aromatase expression, activates AMPK                                   | (Amin et al., 2019; "Metformin:", 2023)                            |
| Cardiovascular Diseases   | Lowers LDL cholesterol, inhibits atherosclerosis, enhances endothelial function | (Apostolova et al., 2020; (Lv and Guo, 2020; Zhu et al., 2023)     |

## Conclusion

Metformin's therapeutic potential extends beyond its role in diabetes management. Its ability to modulate AMPK, mitochondrial function, and inflammatory pathways makes it a versatile drug for treating metabolic disorders, aging-related diseases, cardiovascular conditions, and cancer. While further clinical trials are required to fully explore its effectiveness in non-diabetic populations, the existing evidence underscores metformin's promise as a multi-target therapeutic agent.

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