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METFORMIN BEYOND DIABETES: A COMPREHENSIVE PHARMACOLOGICAL REVIEW OF THE ANTI-AGING AND ANTI-CANCER PLEIOTROPY, THE AMPK/MTOR AND MITOCHONDRIAL MECHANISMS, THE TAME TRIAL, AND THE CRITICAL APPRAISAL OF GERO PROTECTION AND ONCOLOGICAL REPURPOSING

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ABSTRACT
Metformin, a biguanide derived from *Galega officinalis* (French lilac), has been the first-line oral therapy for type 2 diabetes mellitus for decades. Beyond its glucose-lowering effects, metformin has attracted considerable scientific attention because of its potential anti-cancer and anti-aging (geroprotective) properties. Its pharmacological actions include inhibition of mitochondrial complex I, activation of AMP-activated protein kinase (AMPK), suppression of mechanistic target of rapamycin (mTOR) signaling, reduction of circulating insulin and insulin-like growth factor-1 (IGF-1) levels, modulation of the gut microbiome, and effects on growth/differentiation factor 15 (GDF15). These mechanisms influence pathways implicated in carcinogenesis and aging, providing biological plausibility for its broader therapeutic potential. Early observational studies reported associations between metformin use and reduced cancer incidence, lower cancer-related mortality, and improved overall survival, generating enthusiasm for its use beyond diabetes management. However, many of these findings are affected by important methodological limitations, particularly immortal time bias and time-window bias, which may have overstated the apparent benefits. Consistent with these concerns, randomized controlled trials evaluating metformin for cancer prevention and treatment have largely produced neutral or inconclusive results, warranting a more cautious interpretation of its anti-cancer effects. Metformin has also emerged as a leading candidate geroprotective agent. The Targeting Aging with Metformin (TAME) trial represents a landmark effort to determine whether metformin can delay the onset of multiple age-related diseases and modify the aging process in humans. This review critically examines the molecular mechanisms underlying metformin's pleiotropic actions, evaluates the evidence for its anti-cancer and anti-aging effects, discusses key methodological challenges, and summarizes safety considerations, the Indian perspective, and future research priorities. While metformin remains a promising candidate for broader clinical applications, definitive evidence will require well-designed randomized clinical trials.

KEYWORDS: Metformin; AMPK; mTOR; geroprotection; anti-aging; cancer prevention; drug repurposing; TAME trial; mitochondrial complex I; immortal time bias; IGF-1; hallmarks of aging.

1. INTRODUCTION

Metformin is one of the most extensively prescribed medications worldwide and remains the recommended first-line pharmacological therapy for type 2 diabetes mellitus because of its efficacy, favorable safety profile, weight neutrality, cardiovascular benefits, and low cost.[1,44,60] Derived from guanidine-related compounds identified in Galega officinalis (French lilac or goat's rue), metformin has been used in clinical practice for more than six decades and has accumulated an extensive record of safety and effectiveness.[1,2]

In recent years, interest in metformin has expanded beyond glycemic control. Experimental studies have shown that metformin influences multiple cellular pathways involved in energy metabolism, growth regulation, and cellular stress responses, including AMP-activated protein kinase (AMPK), mechanistic target of rapamycin (mTOR) signalling, mitochondrial function, and insulin/insulin-like growth factor (IGF-1) pathways.[2,19,20,21] These biological actions have prompted investigation of metformin in a range of conditions beyond diabetes, including cancer, cardiovascular disease, polycystic ovary syndrome (PCOS), non-alcoholic fatty liver disease (NAFLD), and age-related disorders.[5,41,42,56,61]

Among these emerging applications, the potential roles of metformin in cancer prevention and healthy aging have generated particular attention. Observational studies have reported associations between metformin use and favorable outcomes in several malignancies, while preclinical research has suggested that metformin may influence fundamental mechanisms implicated in the aging process.[31,32,36] However, interpretation of these findings remains challenging because observational studies are susceptible to methodological limitations, including confounding and time-related biases, and results from randomized clinical trials have not consistently supported the magnitude of benefit suggested by earlier reports.[3,9,10]

Similarly, growing interest in geroscience has led to the proposal that metformin may serve as a candidate geroprotective agent. The development of the Targeting Aging with Metformin (TAME) trial reflects an important effort to evaluate whether interventions can delay the onset of multiple age-related diseases and thereby influence healthspan in humans.[4,13,36]

Given the rapidly expanding literature and the continuing debate regarding the clinical significance of metformin's non-glycemic effects, a critical appraisal of the available evidence is warranted. This review examines the molecular mechanisms underlying metformin's pleiotropic actions, evaluates current evidence regarding its anti-cancer and anti-aging potential, discusses methodological considerations affecting interpretation of the literature, summarizes other clinically relevant effects and safety issues, and highlights implications for clinical practice and future research, with particular reference to the Indian healthcare context.

2. MOLECULAR MECHANISMS OF METFORMIN

2.1 Mitochondrial Targets and AMPK Activation

Metformin exerts its metabolic effects through multiple interconnected mechanisms, although its precise primary molecular target remains a subject of ongoing investigation. The classically proposed mechanism involves inhibition of mitochondrial respiratory chain complex I (NADH oxidoreductase), resulting in reduced mitochondrial ATP production and increased cellular AMP and ADP ratios. These changes activate AMP-activated protein kinase (AMPK), a key cellular energy sensor that shifts metabolism from anabolic (energy-consuming) to catabolic (energy-generating) processes. In the liver, AMPK activation contributes to suppression of gluconeogenesis and promotion of fatty acid oxidation, thereby improving metabolic homeostasis.[5,19,20,21]

However, the mechanism of metformin action remains incompletely resolved. Alternative and complementary mechanisms have been proposed, including inhibition of mitochondrial glycerophosphate dehydrogenase (mGPD), which may reduce hepatic gluconeogenesis by altering cellular redox balance. Current evidence suggests that metformin's metabolic effects likely arise from the combined influence of several mitochondrial and cellular targets rather than a single dominant mechanism. Nevertheless, alterations in cellular energy status and downstream AMPK signaling remain central components of current mechanistic models.[2,5,59]

2.2 mTOR Inhibition and Insulin/IGF-1 Signaling

AMPK activation by metformin inhibits mechanistic target of rapamycin complex 1 (mTORC1), a major regulator of cell growth, protein synthesis, and proliferation that **is** frequently dysregulated in cancer and implicated in aging. Inhibition of mTORC1 reduces cellular growth and proliferation while promoting autophagy, an essential cellular quality-control process involved in the removal of damaged proteins and organelles. These effects have been proposed as potential contributors to both anti-cancer and geroprotective actions.[6,36,47]

In addition, metformin improves insulin sensitivity and reduces hyperinsulinemia, leading to lower circulating insulin levels and attenuation of insulin-like growth factor-1 (IGF-1) signaling. Because insulin and IGF-1 promote cellular growth and proliferation, reductions in these pathways may contribute indirectly to the observed associations between metformin use and cancer-related outcomes. Together, modulation of the AMPK–mTOR axis and insulin/IGF-1 signaling forms a central framework for understanding the proposed pleiotropic effects of metformin.[6,58]

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2.3 Gut, Microbiome, and GDF15

Increasing attention has focused on the gastrointestinal actions of metformin. The drug accumulates at high concentrations within the intestine, where it influences glucose handling, enhances glucagon-like peptide-1 (GLP-1) secretion, and alters the composition and function of the gut microbiome. These effects contribute to glucose regulation and may also mediate broader systemic benefits.[22,56]

Metformin also increases circulating growth/differentiation factor 15 (GDF15), a stress-responsive cytokine that acts through receptors in the hindbrain to reduce appetite and food intake. This pathway appears to contribute to the weight-neutral or modest weight-reducing effects of metformin and may play a role in its metabolic benefits.[7]

Emerging evidence suggests that metformin may also exert favorable effects on metabolic dysfunction-associated steatotic liver disease (MASLD), the condition previously termed non-alcoholic fatty liver disease (NAFLD). Although the precise mechanisms remain under investigation, improvements in insulin sensitivity, hepatic metabolism, and inflammatory signaling may contribute to these effects. Collectively, gut-mediated, microbiome-related, and GDF15-dependent pathways highlight the complexity of metformin pharmacology and underscore that its actions extend beyond the traditional hepatic AMPK-centered model.[7,22,56]

3. ANTI-CANCER PLEIOTROPY: A CRITICAL APPRAISAL

3.1 The Mechanistic Rationale

The biological rationale for an anti-cancer effect of metformin is substantial. Through activation of AMP-activated protein kinase (AMPK) and inhibition of mechanistic target of rapamycin (mTOR) signaling, metformin may suppress cellular growth, proliferation, and protein synthesis pathways that are frequently dysregulated in cancer. In addition, by improving insulin sensitivity and reducing circulating insulin and insulin-like growth factor-1 (IGF-1) levels, metformin may attenuate the systemic mitogenic environment associated with obesity, insulin resistance, and increased cancer risk. Experimental studies have also suggested direct effects on tumor cell metabolism, cellular energetics, cancer stem cells, and the tumor microenvironment.[8,26,28,58] Collectively, these mechanisms provided a strong biological basis for investigating metformin as both a cancer-preventive agent and an adjunct to cancer therapy. An important limitation of the mechanistic evidence is that many in vitro studies demonstrating anti-cancer effects have used metformin concentrations in the millimolar (mM) range, whereas therapeutic plasma concentrations achieved in humans are typically in the micromolar (μM) range. Consequently, some experimentally observed anti-cancer effects may not be fully reproducible under clinically relevant conditions, and caution is required when translating preclinical findings into expectations of clinical benefit.[27,58,59]

3.2 The Observational Evidence and Its Biases

Early observational studies reported associations between metformin use and reduced cancer incidence and mortality among individuals with diabetes, generating considerable enthusiasm regarding its potential anti-cancer properties. However, subsequent methodological analyses identified several important biases that may have exaggerated these apparent benefits.[9,23,24,25]

Among these, immortal time bias has been particularly influential. In many early cohort studies, patients were classified as metformin users based on receiving a prescription sometime after cohort entry. The period between cohort entry and the first metformin prescription was frequently misclassified as exposed person-time, even though patients had not yet received the drug. Because individuals had to survive this interval to be categorized as metformin users, this "immortal" period artificially favored the metformin group and could produce a spurious survival advantage.[9] Additional sources of bias include time-window bias, confounding by indication, and differences in disease severity, whereby patients receiving metformin often differed systematically from those receiving insulin or other therapies. When these methodological issues are addressed through appropriate study design and time-dependent analyses, the magnitude of the observed protective association is substantially reduced and, in some studies, no longer statistically significant.[3,9]

3.3 Evidence from Randomized Controlled Trials

Randomized controlled trials provide the most reliable method for determining whether metformin has a causal anti-cancer effect. To date, the results have generally been neutral and have not confirmed the magnitude of benefit suggested by observational studies.[10]

In the treatment setting, randomized trials evaluating the addition of metformin to standard cancer therapy have largely failed to demonstrate meaningful improvements in clinical outcomes. The MA.32 trial, one of the largest studies in this field, evaluated metformin as an adjunct to standard adjuvant therapy in patients with early-stage breast cancer and did not demonstrate a significant improvement in invasive disease-free survival or other major clinical endpoints.[10]

Evidence for cancer prevention is similarly inconclusive. Randomized studies examining colorectal adenoma or polyp recurrence have reported mixed findings, with some demonstrating modest reductions in adenoma recurrence but insufficient evidence to establish a broad chemopreventive role for metformin. Likewise, diabetes prevention and cardiovascular outcome trials that collected cancer outcomes as secondary endpoints have

not consistently demonstrated reductions in cancer incidence or mortality.[10]

The divergence between observational and randomized evidence represents an important lesson in clinical epidemiology. A comparable pattern has been observed in the vitamin D–cancer literature, where observational studies suggested substantial protective effects, but large randomized trials generally failed to confirm corresponding reductions in cancer incidence or mortality. In both cases, biological plausibility and observational associations proved insufficient substitutes for randomized evidence.

Overall, the available data support a strong mechanistic rationale for anti-cancer effects but provide limited clinical evidence that metformin functions as an effective anti-cancer therapy or chemopreventive agent in unselected populations. While potential benefits in specific molecular subgroups or clinical contexts remain under investigation, current evidence does not support the broad anti-cancer claims that emerged from early observational studies. The metformin-cancer experience therefore underscores the importance of rigorous study design, careful interpretation of observational data, and the central role of randomized trials in establishing causality.[29]

4. ANTI-AGING AND GEROPROTECTION

4.1 The Hallmarks of Aging and Metformin

Aging is increasingly understood through the framework of the hallmarks of aging. The updated framework proposed by López-Otín and colleagues includes genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, impaired macroautophagy, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis.[11] These interconnected processes contribute to the progressive decline in physiological resilience and increase susceptibility to age-related diseases.

The geroprotection hypothesis proposes that targeting these fundamental biological mechanisms could delay or prevent multiple age-related disorders simultaneously, thereby improving healthspan rather than treating individual diseases in isolation. Metformin has attracted particular interest because it influences several pathways implicated in aging biology, including AMPK activation, mTOR inhibition, mitochondrial metabolism, inflammatory signaling, and nutrient-sensing pathways. Some of these effects resemble aspects of caloric restriction, one of the most robust interventions known to extend lifespan in experimental organisms.[11] Consequently, metformin has emerged as one of the leading candidate geroprotective agents for human investigation.[11,38,39,40]

4.2 Preclinical and Observational Evidence

Preclinical studies provide support for a potential geroprotective role of metformin, although results have not been uniformly consistent. Lifespan or healthspan extension has been reported in certain studies involving Caenorhabditis elegans (C. elegans) nematodes, Drosophila species (fruit flies), and rodent models, but effects vary according to species, genetic background, dose, and experimental conditions.[31,32,33] In some settings, high-dose metformin has produced neutral or even adverse effects, highlighting the complexity of translating findings across model systems.

Observational evidence has also generated interest in metformin as a candidate longevity intervention. A widely cited retrospective study by Bannister and colleagues reported lower all-cause mortality among patients with type 2 diabetes treated with metformin than among matched non-diabetic controls.[12] Although noteworthy, such findings remain vulnerable to residual confounding, selection bias, and other methodological limitations inherent to observational research. Consequently, the available preclinical and epidemiological evidence should be viewed as hypothesis-generating rather than definitive proof of a geroprotective effect.[13,37]

4.3 The TAME Trial

The Targeting Aging with Metformin (TAME) trial represents the most prominent effort to evaluate metformin as a geroprotective intervention in humans. Rather than focusing on a single disease, TAME was designed to assess whether metformin can delay the onset of age-related multimorbidity by measuring the time to occurrence of major age-related outcomes, including cardiovascular events, cancer, dementia, and death, in older adults without diabetes.[13]

Importantly, TAME was conceived not only as a test of metformin but also as a proof-of-concept for the broader strategy of targeting aging itself as a modifiable biological process. A positive result would provide evidence that interventions directed at fundamental aging mechanisms can delay multiple age-related diseases simultaneously and could help establish a regulatory framework for future geroprotective therapies.[13]

The trial also highlights the practical challenges of aging research, including lengthy follow-up requirements, large sample sizes, funding limitations associated with generic drugs, and the absence of established regulatory pathways for aging-based indications. As of manuscript submission (2026), TAME remains in the preparatory and funding phase, and definitive outcome data are not yet available. Therefore, metformin's role as a human geroprotector remains an important but unproven hypothesis requiring prospective clinical validation.[13]

Notably, some studies have suggested that metformin may attenuate certain physiological adaptations to

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exercise, particularly improvements in mitochondrial function and insulin sensitivity in older adults, raising important questions regarding potential interactions between pharmacological and lifestyle interventions.[34,35] These observations further underscore the complexity of metformin's biological effects and the need for carefully designed clinical studies.

5. OTHER PLEIOTROPIC EFFECTS

Beyond its proposed anti-cancer and anti-aging actions, metformin has been investigated in several other clinical contexts because of its effects on metabolism, inflammation, and cellular signaling pathways. Research has explored its potential role in cardiovascular disease, neurodegenerative disorders, metabolic dysfunction-associated steatotic liver disease (MASLD), and infectious diseases, although evidence for many of these applications remains limited or inconclusive.[30,45,46,47,57]

Particular interest has emerged regarding metformin's effects on COVID-19 outcomes. Observational studies initially suggested potential benefits, and subsequent randomized trials, including the COVID-OUT trial, investigated whether metformin could reduce disease severity and post-acute complications. While some findings have suggested possible reductions in the risk of long COVID, the overall evidence remains insufficient to support routine use of metformin specifically for COVID-19 prevention or treatment, and further research is required.[14]

Metformin has also been studied in patients with metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as non-alcoholic fatty liver disease (NAFLD). The term MASLD was adopted in 2023 to reflect the central role of metabolic dysfunction in disease pathogenesis and has largely replaced the older NAFLD nomenclature. Although metformin may improve certain metabolic parameters in affected patients, current evidence does not support its use as a specific treatment for MASLD independent of its established indications for diabetes and metabolic disorders.[43]

6. SAFETY CONSIDERATIONS

Metformin has an excellent safety profile established through decades of clinical use, contributing to its appeal as a potential pleiotropic agent. The most common adverse effects are gastrointestinal symptoms, including nausea, diarrhea, abdominal discomfort, and metallic taste, which are generally mild, dose-dependent, and often improve with gradual dose titration or the use of extended-release formulations. A clinically important long-term adverse effect is vitamin B12 deficiency due to impaired intestinal absorption, which may result in anemia and peripheral neuropathy; therefore, periodic monitoring is recommended, particularly in long-term users.[15,50,51]

The most serious potential adverse effect is metformin-associated lactic acidosis (MALA), a rare but potentially fatal complication. The reported incidence is approximately 3–10 cases per 100,000 patient-years, with most cases occurring in the presence of significant comorbidities rather than metformin use alone.[48,49] Current prescribing guidelines recommend avoiding metformin in patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² and using it with caution, including dose reduction and closer monitoring, when eGFR is between 30–45 mL/min/1.73 m². Additional caution is required in conditions associated with impaired lactate clearance or tissue hypoxia, such as severe hepatic dysfunction, acute illness, major surgery, or iodinated contrast administration.[48,49]

Although metformin's favourable safety profile supports continued investigation of its potential anti-cancer and anti-aging effects, its use for anti-aging in healthy individuals remains unsupported by current evidence. Long-term safety considerations, including vitamin B12 deficiency, possible interactions with exercise adaptations, and the uncertain risk-benefit balance in non-diabetic populations, require further evaluation. Therefore, metformin should not be used for anti-aging purposes outside well-designed clinical trials until clear evidence of benefit is established.[34,35]

7. INDIAN CONTEXT

India, often described as having one of the world's largest diabetes burdens, is home to more than 100 million people with diabetes and many more with prediabetes.[16] Metformin remains the first-line pharmacological therapy for type 2 diabetes and is among the most widely prescribed medications in the country because of its effectiveness, affordability, and availability as a low-cost generic. Consequently, any additional benefits or risks associated with metformin could have major public health implications in the Indian setting.[16,52,53,54,55]

The proposed anti-cancer and anti-aging effects of metformin have attracted considerable interest given India's growing cancer burden and rapidly aging population. However, despite strong mechanistic plausibility, current evidence does not support the use of metformin for cancer prevention or treatment outside established indications, and its anti-aging effects remain under investigation. Therefore, metformin should continue to be prescribed primarily for evidence-based indications, including type 2 diabetes, diabetes prevention in selected high-risk individuals, and polycystic ovary syndrome (PCOS).[17,41,42]

A particularly important consideration in India is the risk of vitamin B12 deficiency during long-term metformin therapy. Vitamin B12 deficiency is already prevalent in the Indian population, partly because dietary patterns with limited intake of animal-source foods are common,

and metformin may further reduce B12 absorption.[18] Regular monitoring of vitamin B12 status and appropriate supplementation should therefore be considered in long-term users. Future Indian research, including well-designed epidemiological studies and clinical trials, may help clarify metformin's broader health effects while avoiding the methodological limitations that have affected previous studies of its pleiotropic benefits.[18,50]

8. SUMMARY TABLES

Table 1: Metformin Mechanisms.

Mechanism	Effect	Relevance
Mitochondrial complex I inhibition	↑AMP:ATP ratio	Triggers AMPK; reduces hepatic energy
AMPK activation	Catabolic switch	Suppresses gluconeogenesis; pleiotropy
mTOR inhibition	↓growth/proliferation; ↑autophagy	Anti-cancer/anti-aging rationale
↓Insulin / IGF-1	Less mitogenic signaling	Indirect anti-cancer rationale
Gut/microbiome	↑GLP-1; microbiome shift	Metabolic effects
↑GDF15	Appetite reduction	Weight neutrality/loss

Table 2: Anti-Cancer Evidence — Critical Appraisal.

Evidence Type	Finding	Caveat
Mechanistic	Plausible (AMPK/mTOR, IGF-1)	Concentrations may exceed clinical levels
Observational	Reduced cancer incidence/mortality	Immortal time bias; confounding
Randomized (treatment)	Largely neutral (e.g. MA.32 breast)	Does not confirm benefit
Randomized (prevention)	No clear benefit	Rigorous standard not met
Conclusion	Not established as anti-cancer agent	Lesson in pharmacoepidemiology

Table 3: Anti-Aging / Geroprotection.

Aspect	Status
Hallmarks of aging engaged	Nutrient sensing (AMPK/mTOR), inflammation, mitochondria
Caloric restriction mimetic	Partial
Preclinical lifespan	Mixed (species/dose-dependent)
Observational (Bannister)	Diabetics on metformin outlived non-diabetics (confounded)
TAME trial	Tests multimorbidity endpoint; proof-of-concept for targeting aging
Status	Promising hypothesis under investigation; Not proven

Table 4: Pleiotropic Applications.

Application	Evidence Status
Type 2 diabetes	Established (first-line)
Diabetes prevention	Established (DPP)
PCOS (metabolic/ovulation)	Established
NAFLD/MASLD	Investigated; not primary therapy
Cancer prevention/treatment	Not supported by RCTs
Anti-aging/geroprotection	Unproven hypothesis (TAME)
Neuroprotection	Mixed/inconclusive (B12 confounder)

Table 5: Indian Context.

Element	**Status India**	**Notes**
Diabetic population	>100 million	'Diabetes capital'; huge metformin use
Metformin availability	Ubiquitous, very cheap	Few rupees/day generic
Established role	First-line diabetes, prevention, PCOS	High-value, evidence-based
Vitamin B12 deficiency	High background (vegetarian)	Compounded by metformin; monitor
Anti-cancer use	Not evidence-supported	Avoid off-label use
Anti-aging use	Unproven	Only in trials
Research opportunity	Large metformin population	Rigorous methodology essential
Teaching value	High	Drug repurposing, immortal time bias

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9. FUTURE DIRECTIONS

9.1 Clarification of Molecular Mechanisms

Although substantial progress has been made in understanding metformin pharmacology, the relative contributions of mitochondrial complex I inhibition, mitochondrial glycerophosphate dehydrogenase inhibition, AMPK activation, gut-mediated effects, and GDF15 signaling remain incompletely defined. Further mechanistic studies are needed to clarify the pathways responsible for both metabolic and potential pleiotropic effects.[2,5,59]

9.2 Identification of Responsive Subgroups

Future research should focus on identifying patient populations most likely to benefit from metformin beyond diabetes management. Precision medicine approaches incorporating molecular, metabolic, and genetic biomarkers may help identify subgroups that derive greater benefit from metformin-based interventions.[61]

9.3 Rigorous Evaluation of Anti-Cancer Effects

Given the limitations of observational studies, future oncology research should prioritize well-designed randomized controlled trials in carefully selected cancer subtypes and treatment settings. Particular attention should be paid to clinically relevant metformin concentrations and biologically plausible targets.[10,27,29]

9.4 Completion of Geroprotection Trials

The outcomes of the TAME (Targeting Aging with Metformin) trial and related studies will be critical in determining whether metformin can delay age-related multimorbidity and improve healthspan. These investigations may also establish a framework for evaluating future geroprotective therapies.[4,13,36]

9.5 Long-Term Safety and Drug–Lifestyle Interactions

Further research is required to evaluate long-term safety in non-diabetic populations, including vitamin B12 deficiency, potential effects on exercise adaptation, and the overall risk–benefit profile of prolonged metformin use for non-traditional indications.[34,35,48,50]

9.6 Methodologically Robust Pharmacoepidemiology

The metformin–cancer experience highlights the importance of addressing immortal time bias, time-window bias, and residual confounding in observational research. Future epidemiological studies should employ rigorous methodologies to ensure reliable estimates of treatment effects.

Collectively, these research priorities will help determine whether metformin's proposed pleiotropic effects can be translated into meaningful clinical benefits and will guide the future development of evidence-based drug repurposing strategies.[3,9]

10. CONCLUSION

Metformin, a widely used first-line antidiabetic drug derived from the French lilac, has attracted considerable attention for its potential effects beyond glucose control, particularly in cancer prevention and healthy aging. Its mechanisms—including inhibition of mitochondrial complex I, activation of AMPK, suppression of mTOR signaling, reduction of insulin/IGF-1 activity, and modulation of the gut microbiome—target key pathways involved in both cancer and aging, providing strong biological plausibility for these pleiotropic effects.[2,6,7,22]

Despite this mechanistic rationale, current evidence does not establish metformin as an effective anti-cancer agent. Many early observational studies reporting reduced cancer risk were affected by methodological limitations such as immortal time bias, while randomized controlled trials have largely produced neutral results.[10] Thus, metformin's anti-cancer potential remains unproven and highlights the importance of rigorous evidence appraisal in drug repurposing research.

The anti-aging hypothesis is currently being investigated through the landmark TAME (Targeting Aging with Metformin) trial,[4,13,36] which aims to determine whether metformin can delay the onset of multiple age-related diseases. Although promising, anti-aging benefits remain hypothetical and should not justify metformin use outside clinical trials. In India, where diabetes, prediabetes, and vitamin B12 deficiency are highly prevalent, metformin's established role in diabetes management remains paramount. Overall, metformin serves as an important example of both the promise of drug repurposing and the necessity for rigorous scientific validation of pleiotropic claims.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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