WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Metformin Beyond Diabetes: Mechanistic Insights, Therapeutic Repurposing, and Translational Potential in Cancer, Aging, and Neurodegeneration

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ABSTRACT

Metformin, a first-line oral hypoglycemic agent for type 2 diabetes mellitus, has emerged as a promising pleiotropic drug with therapeutic potential far beyond glycemic control. Epidemiological studies and clinical trials suggest its protective roles in cancer, aging, and neurodegenerative diseases. In oncology, metformin exhibits anti-proliferative, pro-apoptotic, and anti-angiogenic effects, largely mediated through AMP-activated protein kinase (AMPK) activation, mTOR inhibition, and modulation of insulin/IGF-1 signaling, with evidence linking its use to reduced cancer incidence and improved survival. In geroscience, metformin acts as a caloric restriction mimetic, improving mitochondrial function, reducing oxidative stress, and attenuating chronic inflammation. The ongoing TAME (Targeting Aging with Metformin) trial aims to establish its efficacy in extending healthspan. Additionally, growing preclinical and clinical evidence supports its neuroprotective properties in Alzheimer's and Parkinson's disease, where it enhances neuronal resilience, promotes autophagy, reduces β-amyloid accumulation, and modulates acetylcholinesterase activity. Despite these promising findings, conflicting results highlight the dualistic nature of metformin's actions in certain neurodegenerative contexts, necessitating careful patient stratification and optimized dosing. Overall, metformin is transitioning from a conventional anti-diabetic agent to a versatile candidate for cancer prevention, healthy aging, and neuroprotection, representing a paradigm shift in therapeutic repurposing.

Keywords: Metformin; Type 2 Diabetes Mellitus; AMPK; mTOR; Cancer Therapy; Geroscience; Aging; Caloric Restriction Mimetic; Autophagy; Oxidative Stress; Neurodegeneration; Alzheimer's Disease; Parkinson's Disease ;β-amyloid; Insulin/IGF-1 Signaling; Inflammation; Mitochondrial Function; TAME

1. Introduction

Type 2 diabetes mellitus is a global health challenge, characterized by insulin resistance, impaired glucose metabolism, and increased cardiovascular risk. Metformin, introduced in the late 1950s, remains the first-line pharmacotherapy for type 2 diabetes owing to its efficacy, safety, and low cost. Historically, metformin was confined to its glucose-lowering properties. However, epidemiological evidence and mechanistic discoveries have transformed its perception from a metabolic drug to a versatile agent with applications in oncology, anti-aging research, and neurodegenerative disorders. Repurposing metformin holds profound significance for modern pharmacology, as it represents a safe, inexpensive, and widely available drug capable of addressing multifactorial chronic diseases.

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder driven by insulin resistance, impaired hepatic glucose output, and β-cell dysfunction, and it remains a principal global contributor to cardiovascular morbidity and premature mortality. Since its introduction in the late 1950s, metformin—a biguanide derived from Galega officinalis—has become the first-line pharmacotherapy for T2DM because of its efficacy in lowering hepatic gluconeogenesis, its weight-neutral profile, a favorable safety signal, and low cost. Beyond glycemic control, accumulating population-level and mechanistic evidence over the last two decades has reframed metformin as a pleiotropic agent with potential roles in oncology, geroscience, and neuroprotection (Frontiers in Endocrinology, 2018; Pharmaceuticals, 2023).

At the mechanistic core, metformin activates AMP-activated protein kinase (AMPK) and dampens mTOR signaling, thereby shifting cellular programs from anabolic growth toward catabolic maintenance and stress resistance. AMPK-mTOR crosstalk links energy sensing to growth control, protein synthesis, autophagy, and inflammation—processes central to cancer biology, aging hallmarks, and neurodegeneration. Additional targets—including partial inhibition of mitochondrial complex I, modulation of lysosomal v-ATPase–Ragulator signaling, and effects on redox tone and NF-κB activity—offer a coherent biochemical rationale for metformin's multi-system actions (Frontiers in Physiology, 2021; Pharmaceuticals, 2023).

In oncology, epidemiological cohorts initially noted lower cancer incidence and improved cancer-specific survival among metformin-treated diabetics compared with those on insulin or sulfonylureas. Preclinical studies subsequently demonstrated anti-proliferative, pro-apoptotic, and anti-angiogenic actions, as well as metabolic reprogramming of the tumor microenvironment that can sensitize cancer cells to chemotherapy and targeted agents. These converging lines of evidence have motivated trials testing metformin as an adjuvant or neoadjuvant in breast, colorectal, prostate, endometrial, and ovarian cancers, including in non-diabetic populations (Frontiers in Endocrinology, 2018; Pharmaceuticals, 2023).

In aging research, metformin is frequently described as a caloric-restriction mimetic that can attenuate several hallmarks of aging—mitochondrial dysfunction, deregulated nutrient sensing, loss of proteostasis, and chronic low-grade inflammation ("inflammaging"). By enhancing autophagic flux and improving mitochondrial efficiency, metformin may extend healthspan rather than lifespan per se, potentially delaying the co-onset of age-related multimorbidity. The Targeting Aging with Metformin (TAME) trial was conceived to operationalize this concept at the clinical level by testing whether metformin delays incident age-related diseases in at-risk older adults (concept summaries in Frontiers in Endocrinology, 2018; Pharmaceuticals, 2023).

In neurodegeneration, metabolic dysfunction links T2DM with elevated risks of Alzheimer's disease (AD) and Parkinson's disease (PD). Metformin's neuroprotective hypotheses include enhancement of neuronal energy metabolism via AMPK, promotion of autophagy and clearance of toxic protein aggregates, attenuation of neuroinflammation and oxidative stress, reduced β-amyloidogenesis through BACE1 modulation, and potential acetylcholinesterase inhibition relevant to cholinergic deficits in AD. Yet clinical data are mixed, with signals of cognitive benefit in some diabetic cohorts and neutral or context-dependent outcomes in others, raising the possibility of a double-edged effect influenced by dose, duration, B12 status, and patient phenotype (Frontiers in Endocrinology, 2018; Pharmaceuticals, 2025).

A further layer of complexity involves mitochondrial gatekeeping via voltage-dependent anion channel 1 (VDAC1). Reviews have proposed VDAC1 as a unifying node through which metformin can tilt cells toward apoptosis in cancer while promoting survival in stressed neurons—an apparent paradox that reflects disease-specific energy demands and death-signaling thresholds (Frontiers in Physiology, 2021). This target-context dependency underscores the importance of patient stratification and mechanistic biomarkers in repurposing strategies.

Concurrently, advances in drug-delivery science are addressing metformin's pharmacokinetic constraints—variable absorption, gastrointestinal intolerance, and limited tissue targeting. Novel platforms such as nanoparticles, pH-responsive hydrogels, and microneedle systems aim to enhance bioavailability, improve hepatic or CNS delivery, and mitigate adverse effects, thereby broadening metformin's therapeutic window in non-diabetic indications (Drug Delivery and Translational Research, 2025).

Despite promising signals, key controversies remain. Benefits observed in diabetic cohorts do not always generalize to non-diabetic populations; long-term therapy can cause vitamin B12 deficiency with neurocognitive implications; and the directionality of AMPK–mTOR modulation may differ across tissues and disease stages. Addressing these gaps will require carefully powered, multicenter randomized trials, mechanistically informed endpoints, and combination strategies that pair metformin with cytotoxics, targeted therapies, or anti-amyloid agents (Frontiers in Endocrinology, 2018; Pharmaceuticals, 2023/2025).

In summary, metformin has evolved from an antihyperglycemic workhorse to a multifaceted therapeutic candidate that interfaces with fundamental biology of cancer, aging, and neurodegeneration. Its long safety record, low cost, and well-mapped signaling effects make it an attractive anchor for drug repurposing and preventive pharmacology, provided its use is guided by precision approaches that match mechanism to patient context.

2. Mechanisms of Action of Metformin: A Detailed, Multi-Journal Synthesis

- Cellular Entry, Distribution, and Transporters
- Hydrophilic cation: Metformin requires transporters to enter cells; passive diffusion is minimal.
- Hepatic uptake: Primarily via OCT1 (SLC22A1); pharmacogenetic variants alter glycemic response and GI intolerance. Renal elimination occurs via OCT2 (basolateral) and MATE1/2-K (apical) in proximal tubules.
- Tissue targeting: High hepatic and intestinal exposure underlies dominant effects on gluconeogenesis and gut-mediated glucose handling (Pharmaceuticals, 2023; Drug Deliv Transl Res, 2025).
- Energy Sensing: AMP/ADP • AMPK • mTORC1 Axis
- Mitochondrial complex I attenuation: Lowers ATP and raises AMP/ADP, producing an energetic stress signal at therapeutically relevant hepatic concentrations (Pharmaceuticals, 2023).
- AMPK activation: Upstream kinase LKB1 phosphorylates AMPK (Thr172) when AMP/ADP rise; AMPK then:
- Phosphorylates ACC1/2 → ↓ malonyl-CoA → ↑ fatty-acid oxidation, ↓ lipogenesis.
- Phosphorylates TSC2 and Raptor → inhibits mTORC1, reducing protein synthesis/proliferation and promoting autophagy via ULK1.
- mTORC1 downregulation links metformin to anti-tumor, anti-aging, and neuroprotective effects (Front Endocrinol, 2018; Pharmaceuticals, 2023/2025).
- Lysosomal AMPK Activation (ATP-independent arm)

- Beyond energy stress, metformin can activate AMPK at the lysosomal surface through a v-ATPase–Ragulator platform; reports indicate interaction via PEN2/ATP6AP1 leading to AMPK activation and mTORC1 suppression even with modest AMP changes. This provides a second node for AMPK control (summarized in Pharmaceuticals, 2023).
- Suppression of Hepatic Gluconeogenesis (Direct and Hormonal)
- Direct metabolic constraints
- Reduced mitochondrial NADH/NAD+ balance and ATP availability limit energy-intensive steps of gluconeogenesis.
- Allosteric AMP inhibits FBP1, restraining fructose-1,6-bisphosphate hydrolysis.
- Debate persists around mitochondrial glycerophosphate dehydrogenase (mGPD) inhibition: some studies report that metformin impairs the glycerophosphate shuttle, limiting gluconeogenesis from lactate/glycerol; others failed to replicate, so this remains controversial (Pharmaceuticals, 2023)
- Counter-glucagon signaling
- By elevating AMP, metformin inhibits adenylate cyclase, lowering cAMP–PKA activity and blunting glucagon action; downstream, CREB–CRTC2–driven transcription of PCK1 (PEPCK) and G6PC (glucose-6-phosphatase) falls (Front Endocrinol, 2018; Pharmaceuticals, 2023).
- Transcriptional remodeling
- AMPK and redox changes modulate SIRT1/PGC-1α, ChREBP, and SREBP1c, collectively reducing gluconeogenic and lipogenic gene programs.
- Intestinal Mechanisms (Often Under-appreciated)
- First-pass intestinal action increases anaerobic glucose utilization in enterocytes and reduces net glucose appearance.
- GLP-1 enhancement: Metformin raises L-cell GLP-1 secretion and/or slows degradation, improving insulinotropic tone.
- Bile-acid–FXR/TGR5 signaling: Altered bile acid pools in the gut contribute to glucose and lipid effects.
- Microbiome remodeling: Increases in Akkermansia and other taxa correlate with improved metabolic and inflammatory profiles (Pharmaceuticals, 2023; Drug Deliv Transl Res, 2025).
- Together, these gut-centric actions explain early glycemic benefits and some GI adverse effects.
- Redox and Mitochondrial Effects
- Mild complex I inhibition lowers ROS production and stabilizes mitochondrial function under stress; in some contexts, transient ROS may act as signals to activate AMPK and adaptive pathways (Front Physiol, 2021; Pharmaceuticals, 2023).
- Mitophagy/autophagy are promoted via ULK1 activation and mTORC1 suppression, supporting proteostasis.
- Inflammation and Innate Immunity
- NF-κB pathway: AMPK-dependent and -independent suppression of IκB kinase reduces pro-inflammatory cytokines (TNF-α, IL-6).
- NLRP3 inflammasome: Metformin dampens priming/activation, decreasing IL-1β maturation; contributes to benefits in metabolic syndrome and vascular disease (Front Endocrinol, 2018; Pharmaceuticals, 2023).
- Macrophage polarization: Favors M2-like anti-inflammatory phenotype.
- Insulin/IGF-1 Signaling and Systemic Endocrine Effects
- Indirect insulin-lowering: By improving hepatic and peripheral insulin sensitivity and reducing hepatic glucose output, metformin lowers circulating insulin, decreasing IGF-1/PI3K–Akt–mTOR drive—highly relevant in cancer prevention and therapy (Front Endocrinol, 2018).
- GDF15 induction: Several studies show metformin raises GDF15, which acts via GFRAL to reduce appetite and weight; this may contribute to weight-neutral or modest weight-loss effects (Pharmaceuticals, 2023).
- Vascular and Endothelial Actions
- eNOS activation: AMPK phosphorylates eNOS (Ser1177) → ↑ nitric oxide, improved endothelial function, and anti-atherogenic effects.
- Anti-thrombotic and anti-oxidative effects in endothelium further support cardiovascular protection (Front Endocrinol, 2018).
- Cancer-Relevant Mechanisms (Direct and Indirect)
- Direct: Energetic stress → AMPK↑/mTORC1↓, reduced protein synthesis, cell-cycle arrest, and autophagy; decreased HIF-1α and VEGF signaling contributes to anti-angiogenesis; modulation of one-carbon metabolism and redox can reduce cancer cell fitness.

- Indirect: Systemic insulin/IGF-1 reduction decreases growth signaling in insulin-responsive tumors.
- Tumor microenvironment: Metabolic reprogramming in stromal and immune cells may enhance response to chemo/radiotherapy (Front Endocrinol, 2018; Pharmaceuticals, 2023/2025).

2. Neuroprotective Mechanisms

- Energy & autophagy: Neuronal AMPK activation enhances autophagic clearance of misfolded proteins; ULK1 signaling supports proteostasis.
- B-amyloid axis: Reports suggest BACE1 downregulation and reduced amyloidogenic processing; AChE inhibition has also been described in vitro, aligning with cholinergic support (Front Endocrinol, 2018; Pharmaceuticals, 2025).
- Neuroinflammation/oxidative stress: Microglial NF-κB/NLRP3 suppression and improved mitochondrial function may protect synapses.
- Context dependence: Clinical data are mixed; effects vary with B12 status, dose, disease stage, and comorbid insulin resistance—hence the "double-edged" narrative in reviews (Front Endocrinol, 2018; Pharmaceuticals, 2025).
- VDAC1 as a Unifying Gatekeeper (Hypothesis)
- Frontiers in Physiology (2021) reviews propose VDAC1 (outer mitochondrial membrane) as a convergent target: metformin's regulation of VDAC1 could promote apoptosis in cancer (where cell death is desired) while stabilizing stressed neurons by limiting maladaptive apoptosis—explaining apparent bidirectionality across diseases.
- Safety-Mechanism Links
- Vitamin B12 malabsorption: Thought to involve altered calcium-dependent uptake in the terminal ileum; clinically relevant for neuropathy risk—monitor long-term users.
- Lactic acidosis: Very rare; risk rises with advanced renal/hepatic failure due to reduced clearance/oxygenation, particularly with high doses.
- GI effects (nausea, diarrhea): Correlate with high gut exposure; extended-release formulations and microbiome adaptation may mitigate (Drug Deliv Transl Res, 2025).
- Delivery Science and Next-Gen Targeting
- Nanoparticles, pH-responsive hydrogels, microneedles aim to improve bioavailability, tissue targeting (liver/CNS), and tolerability—key for repurposing in non-diabetic indications (Drug Deliv Transl Res, 2025).
- One-Glance Summary (textual "table")
- Energy sensor: Complex I → AMP/ADP↑ → AMPK↑ → ACC↓, ULK1↑, mTORC1↓ → ↓lipogenesis, ↑autophagy, ↓protein synthesis.
- Gluconeogenesis: Energy limitation + AMP inhibition of FBP1 + ↓cAMP/PKA (anti-glucagon) + transcriptional suppression of PCK1/G6PC.
- Gut axis: ↑GLP-1, bile-acid/FXR modulation, microbiome remodeling, ↑enterocyte glucose use.
- Inflammation/ROS: NF-κB and NLRP3 suppression; ROS moderation; mitophagy↑.
- Cancer: Direct mTORC1 blockade + indirect insulin/IGF-1 lowering + anti-angiogenesis.
- Neuro: AMPK-autophagy, BACE1↓, AChE↓, microglial inflammation↓ (context dependent).
- VDAC1 hypothesis: Disease-specific tilt between survival and apoptosis.
- Safety: B12↓ (monitor/replace), rare lactic acidosis in high-risk states, GI intolerance (formulation/slow titration help).
- Delivery advances: Nanocarriers/hydrogels/microneedles to enhance targeting.
- Metformin exerts multifaceted effects at molecular and cellular levels. Primary metabolic effects include AMPK activation, inhibition of hepatic gluconeogenesis, and suppression of the mTOR pathway. Secondary effects include anti-inflammatory actions, mitochondrial regulation, and modulation of insulin and IGF-1 signaling.
- Table 1. Mechanisms of action of metformin
- Primary effects include AMPK activation, inhibition of hepatic gluconeogenesis, and mTOR suppression. Secondary effects include anti-inflammatory pathways, mitochondrial regulation, and insulin or IGF-1 modulation.
- Primary EffectsActivation of AMPK LKB1–AMPK pathway Promotes catabolic metabolism, enhances fatty acid oxidation, improves insulin sensitivity

- Inhibition of hepatic gluconeogenesis Mitochondrial complex I inhibition, AMP/ATP ratio ↑Decreased hepatic glucose output, improved glycemic control
- Suppression of mTOR signaling AMPK–TSC2–mTOR axis Reduced protein synthesis, inhibition of uncontrolled cell proliferation

- Secondary Effects Anti-inflammatory actions NF-κB inhibition, cytokine modulation (IL-6, TNF-α)Decreased systemic and vascular inflammation
  - Mitochondrial regulation Complex I inhibition, ROS reduction Improved mitochondrial efficiency, reduced oxidative stress
  - Insulin/IGF-1 pathway modulation PI3K–Akt–mTOR, IGF-1 receptor signaling Reduced growth signaling, protective in cancer and aging
  - Enhanced autophagy AMPK–ULK1–Beclin1 pathway Clearance of damaged proteins and organelles, neuroprotection
  - Modulation of gut microbiota Increased Akkermansia spp., SCFA production Improved metabolic and inflammatory profile

3. Metformin in Cancer Therapy — Detailed Extract (multi-journal synthesis)

- Epidemiological and observational evidence
- Multiple large cohort studies and meta-analyses reported lower cancer incidence and cancer-specific mortality among people with type 2 diabetes treated with metformin compared with those treated with other glucose-lowering agents (e.g., insulin, sulfonylureas). Early pharmaco-epidemiologic signals first spurred laboratory investigations and clinical interest. Observational datasets suggest the strongest and most consistent associations for colorectal, hepatocellular, and endometrial cancers and notable signals in breast and prostate cancer, although heterogeneity across studies (confounding by indication, immortal time bias, dose/duration differences) tempers causal inferences (Rotermund et al., Front Endocrinol. 2018; Isop et al., Pharmaceuticals. 2023).
- Key epidemiologic observations:
  - Reduced incidence and improved survival in metformin users in many retrospective cohorts.
  - Dose- and duration-related gradients observed in some studies (longer exposure → larger effect), but not universally reproduced.
  - Effect estimates attenuate in carefully controlled prospective designs, arguing for cautious interpretation and need for randomized data.
- Molecular and cellular mechanisms relevant to anti-cancer activity
- Metformin exerts both direct (cell-autonomous) and indirect (host-mediated) anticancer actions:
  - Direct (intratumoral / cellular) mechanisms
    - Energetic stress via complex I attenuation: Metformin partially inhibits mitochondrial complex I, lowering ATP/raising AMP — activating AMPK and eliciting metabolic stress that is particularly deleterious for rapidly proliferating tumor cells with high anabolic demand (Isop et al., 2023).
    - AMPK activation / mTOR suppression: AMPK activation and downstream inhibition of mTORC1 reduce protein translation, cell growth and proliferation, and increase autophagy, which can blunt tumor growth or sensitize cells to other agents (Rotermund et al., 2018; Kruczkowska et al., 2025).
    - Cell cycle arrest and pro-apoptotic signaling: Through p53/p21 and other stress pathways, metformin can induce cell-cycle arrest and increase apoptosis in certain cancer cell lines.
    - Inhibition of cancer stem-like cells: Several models report decreased clonogenicity and stemness markers after metformin exposure, suggesting impairment of tumor-initiating cells.
    - Anti-angiogenic effects: Metformin lowers HIF-1α stabilization and VEGF expression in hypoxic tumor microenvironments, reducing angiogenesis (Rotermund et al., 2018).
  - Indirect (systemic, host-mediated) mechanisms
    - Insulin/IGF axis modulation: By improving insulin sensitivity and lowering circulating insulin and IGF-1, metformin reduces systemic mitogenic drive that can fuel insulin-responsive tumors (e.g., breast, endometrium). This is a major hypothesized mediator of observational associations (Isop et al., 2023).
    - Anti-inflammatory and immune-modulatory effects: Metformin dampens NF-κB signaling, reduces pro-inflammatory cytokines and NLRP3 inflammasome activity, and may shift macrophage polarization toward an anti-tumor phenotype, modifying the tumor microenvironment (Sulong et al., 2025).

- Metabolic reprogramming of stroma and immune cells: By altering stromal and immune cell metabolism, metformin can change nutrient availability and immune competence within tumors, potentially synergizing with immunotherapies.

■ Context and target dependency

- Mechanistic reviews highlight that metformin's anti-tumor efficacy is highly context-dependent — dependent on tumor genotype (e.g., LKB1 status), microenvironment nutrient supply, drug exposure at tumor sites (OCT1 expression), and host metabolic state (hyperinsulinemia vs normoinsulinemia) (Frontiers reviews 2018–2023).
- Preclinical evidence (in vitro and in vivo)
- Preclinical work shows reproducible anti-proliferative effects across many cancer cell lines and tumor xenograft models, with stronger effects seen when metformin is combined with cytotoxic agents, targeted inhibitors, or radiation. Notable preclinical patterns:
  - Synergy with standard therapies: Metformin potentiates chemotherapy and targeted agents in breast, colorectal, and ovarian cancer models, frequently via metabolic synthetic lethality or enhancement of autophagy/apoptosis.
  - Dose/exposure dependence: In vitro concentrations that exert direct cytotoxicity are often supra-pharmacologic relative to human plasma levels; beneficial effects in vivo often rely on host-mediated insulin reduction or tumor microenvironment changes rather than direct cytotoxicity at clinically achievable doses (Isop et al., 2023).
  - Biomarker associations: Tumors with intact LKB1/AMPK signaling may be more susceptible; tumors overexpressing OCT transporters have greater intracellular metformin accumulation. VDAC1-related mitochondrial vulnerabilities have been proposed as an explanatory axis for differential tumor responses (Shoshan-Barmatz et al., Front Physiol. 2021).
- Clinical trials: completed and ongoing (landscape and lessons)
- Randomized and translational clinical trials have focused on two main strategies: (A) repurposing metformin as an adjunct to improve outcomes in established cancers and (B) using metformin in cancer prevention or adjuvant settings, often in non-diabetic patients.
- Key findings and trial types:
  - Adjuvant/neoadjuvant trials (breast, endometrial, prostate): Mixed results to date — some small trials show improved pathologic response or biomarker shifts (reduced proliferation markers like Ki-67), whereas larger, well-powered trials are needed to confirm clinical benefit.
  - Combination with chemotherapy/targeted therapy: Several phase I/II combination trials indicate safety and potential efficacy signals; response appears context-dependent and more pronounced in hyperinsulinemic patients.
  - Prevention trials: Observational benefits suggest potential for chemoprevention; however, randomized prevention trials are limited and face feasibility, duration, and endpoint definition challenges.
  - Biomarker-driven designs: Emerging trials stratify by metabolic phenotype, tumor genotype, or transporter expression, aiming to identify responders.
- Limitations in clinical translation:
  - Heterogeneity of trial design: Variation in patient selection (diabetic vs non-diabetic), metformin formulation/dose/regimen, endpoints (biomarker vs survival), and background therapies complicates synthesis.
  - Pharmacokinetics and tumor exposure: Oral metformin achieves modest plasma levels; tumor penetration varies, affecting capacity for direct cytotoxic effects. New delivery approaches (see below) are being explored to improve tumor exposure (Sulong et al., 2025).
- Translational innovations and drug-delivery approaches
- To overcome PK limitations and GI tolerability, recent work (Drug Deliv Transl Res, 2025) explores targeted delivery systems: liver-directed nanoparticles for hepatocellular carcinoma, tumor-penetrant formulations, and mucosal/controlled-release systems to modulate gut-mediated effects while reducing systemic dosing. These strategies aim to reach intratumoral concentrations closer to those used in preclinical experiments while minimizing systemic toxicity.
- Predictive biomarkers and patient selection
- Effective repurposing requires precision: candidate biomarkers include baseline insulin/IGF-1 levels (patients with insulin resistance may benefit most from indirect effects), tumor LKB1/AMPK pathway integrity, OCT1 expression (drug uptake), and metabolic signatures (glycolytic vs oxidative tumors). Trials increasingly incorporate genomic and metabolic profiling to enrich for likely responders (Isop et al., 2023; Kruczkowska et al., 2025).
- Safety considerations specific to oncology populations

- Metformin's safety profile is favorable, but oncology populations have unique vulnerabilities: concomitant nephrotoxic chemotherapies raise lactic acidosis risk in patients with renal impairment; long-term use is associated with vitamin B12 deficiency which may confound neuropathy assessment in patients receiving neurotoxic chemotherapies; GI side effects can compromise tolerability in heavily pretreated patients. Careful monitoring and dose adjustment are essential (Rotermund et al., 2018; Sulong et al., 2025).
- Current evidence synthesis and clinical recommendations
    - Evidence strength: Compelling mechanistic rationale and consistent preclinical signals justify continued clinical evaluation, but randomized trial evidence demonstrating clear survival benefit across cancers is not yet conclusive.
    - Where metformin seems most promising: Tumors with insulin-responsive biology (e.g., endometrial, some breast cancers), settings where metabolic modulation augments therapy (chemo/radiation sensitization), and prevention settings in high-risk metabolic populations.
    - Trial design recommendations: Future trials should (1) stratify by metabolic phenotype and tumor genotype, (2) incorporate translational biomarkers (insulin, IGF-1, tumor OCT1/LKB1), (3) evaluate combination regimens with mechanistic endpoints, and (4) consider novel delivery platforms to achieve therapeutic intratumoral concentrations.
- Key controversies and research gaps
    - Mechanism vs concentration paradox: Many in vitro antiproliferative concentrations exceed clinically achievable plasma levels, raising questions whether observed clinical effects are direct tumor cell killing or host-mediated metabolic modulation.
    - Heterogeneity of response: Genetic and microenvironmental determinants of sensitivity are incompletely defined.
    - Optimal dose/regimen for oncology use: Standard anti-hyperglycemic dosing may be suboptimal for direct anti-tumor action; higher doses raise tolerability and safety concerns.
- Concluding synthesis (practical takeaways)
- Metformin remains one of the most attractive drug-repurposing candidates in oncology because of its favorable safety profile, low cost, mechanistic plausibility (AMPK–mTOR and insulin/IGF axis), and supportive preclinical and observational data. However, translation to routine oncologic use requires rigorously designed randomized trials with biomarker-based patient selection and, potentially, improved delivery systems to achieve effective tumor exposure. Until such data mature, metformin's role in cancer therapy should be considered investigational outside of clinical trials, with the most rational use in trials targeting metabolically defined subgroups or combination regimens where mechanistic synergy is clear.
- Metformin is regarded as a caloric restriction mimetic with geroprotective potential. It enhances mitochondrial energy efficiency, reduces reactive oxygen species production, downregulates inflammaging, and influences senescence pathways such as p53 and SASP. The TAME trial is assessing metformin's ability to delay multimorbidity and extend healthspan.

4. Metformin in Neurodegenerative Disorders – Short Review Extract

- Alzheimer's Disease (AD):
- Metformin enhances neuronal survival via AMPK activation and reduction of amyloid-β accumulation.
- It modulates tau hyperphosphorylation and improves synaptic plasticity.
- Some clinical evidence suggests improved cognition, though results remain mixed due to variability in insulin resistance status. (Journal of Alzheimer's Disease, 2022; Frontiers in Aging Neuroscience, 2023)
- Parkinson's Disease (PD):
- Protects dopaminergic neurons by reducing mitochondrial oxidative stress and enhancing autophagy.
- Animal studies show metformin lowers α-synuclein aggregation and improves motor function.
- Potential synergy with L-DOPA therapy is under investigation. (Neuropharmacology, 2021; Pharmaceuticals, 2024)
- Huntington's Disease (HD):
- Metformin improves mitochondrial biogenesis and reduces mutant huntingtin (mHTT) protein aggregation.
- In preclinical models, it delays neuronal dysfunction and prolongs survival. (Molecular Neurobiology, 2020; CNS Drugs, 2022)
- Amyotrophic Lateral Sclerosis (ALS):
- Evidence is limited, but preclinical studies suggest neuroprotection through AMPK–mTOR regulation and autophagic clearance of misfolded proteins. (Neurotherapeutics, 2021)

- Cognitive Impairment & Aging:
- Beyond specific diseases, metformin shows anti-inflammatory and vascular protective effects, lowering dementia risk in diabetic populations.
- It influences neurogenesis in the hippocampus and reduces neuroinflammation via NF-κB inhibition. (Frontiers in Pharmacology, 2023; Drug Discovery Today, 2024)
- Type 2 diabetes is a recognized risk factor for Alzheimer's disease and Parkinson's disease. Metformin may mitigate this risk by enhancing neuronal energy metabolism via AMPK activation, promoting autophagy, reducing beta-amyloid accumulation via BACE1 inhibition, inhibiting acetylcholinesterase activity, and reducing inflammation and oxidative stress. Preclinical studies show strong neuroprotection, while clinical outcomes remain mixed, highlighting metformin's double-edged role in neurodegeneration.

5. Challenges and Controversies

- Key challenges include contradictory outcomes in diabetic versus non-diabetic populations, risk of vitamin B12 deficiency with long-term use, potentially harmful effects in some neurodegenerative contexts, and poor bioavailability with limited tissue specificity.
- Challenges and Controversies in Metformin Beyond Diabetes
- Although metformin has emerged as a promising candidate for cancer therapy, aging intervention, and neurodegenerative disease management, significant challenges and controversies remain that limit its universal acceptance as a pleiotropic therapeutic agent.
- Inconsistent Clinical Evidence
- Cancer: Epidemiological studies often report reduced cancer incidence and mortality among diabetic patients taking metformin. However, randomized controlled trials (RCTs) have yielded mixed results, with some showing no significant benefits in cancer progression or survival.
- Aging: While animal studies demonstrate lifespan extension, human studies remain inconclusive. The Targeting Aging with Metformin (TAME) trial aims to address this, but results are pending.
- Neurodegeneration: Evidence of neuroprotection in Alzheimer's and Parkinson's disease is promising, yet some studies show neutral or even adverse cognitive effects, raising controversy.
- Dose and Bioavailability Issues
- Standard antidiabetic doses may not achieve therapeutic concentrations in tumor or brain tissues.
- High-dose regimens raise safety concerns such as gastrointestinal intolerance and rare but serious lactic acidosis.
- Tissue-specific bioavailability, especially in the central nervous system, remains poorly understood.
- Patient Population Variability
- Genetic polymorphisms in metformin transporters (OCT1, OCT2, MATE1) influence drug absorption, distribution, and efficacy.
- Differences between diabetic and non-diabetic populations may affect outcomes, complicating trial design and interpretation.
- Mechanistic Uncertainty
- AMPK activation and mTOR inhibition are widely accepted mechanisms, but metformin's full spectrum of action—including mitochondrial regulation, gut microbiota modulation, and insulin/IGF-1 signaling—is still under debate.
- It remains unclear whether observed benefits in cancer and aging are direct drug effects or secondary to systemic metabolic improvements.
- Safety Concerns in Non-Diabetic Use
- While metformin is considered safe in type 2 diabetes, long-term use in non-diabetic populations raises concerns regarding vitamin B12 deficiency, gastrointestinal side effects, and unknown off-target risks.
- Use in elderly populations, a primary target for anti-aging therapy, may be limited by renal function decline.

6. Future Perspectives

- Metformin may be repurposed as a multi-disease preventive agent. Personalized approaches using genetic and metabolic profiling, combination therapies with anti-cancer and anti-amyloid drugs, and advanced delivery systems such as nanoparticles and microneedles are promising. Large-scale, multicentric trials remain essential.
- Metformin's transformation from a decades-old antihyperglycemic agent into a candidate multi-disease therapeutic raises pragmatic and scientific opportunities as well as important requirements for rigorous translation. The following future-perspective roadmap synthesizes translational

priorities, trial and biomarker strategies, therapeutic combinations, delivery innovations, regulatory and ethical considerations, and implementation issues needed to determine whether metformin can safely and effectively be repurposed for cancer, aging, and neurodegeneration.

- Precision repurposing: define who benefits
- Identify biological and clinical responder phenotypes rather than pursuing one-size-fits-all trials. Candidate enrichment strategies include metabolic phenotype (hyperinsulinemia/insulin resistance), tumor genotype (LKB1/AMPK pathway integrity; OCT transporter expression), inflammatory/metabolomic signatures, microbiome profiles (e.g., Akkermansia abundance), and age-related biomarker panels. Integrating multi-omic baseline profiling (genomic, transcriptomic, metabolomic, microbiome) with clinical covariates will allow targeted, biomarker-driven trials that maximize the chance of detecting true effects and limit exposure of non-responders.
- Mechanistically informed trial designs
- Future randomized trials should test clearly articulated biological hypotheses with mechanistic endpoints alongside clinical outcomes. Example approaches: adaptive platform trials that test metformin across multiple indications (adjuvant cancer cohorts, cognitively impaired elders, frailty/prevention arms) with shared control groups; randomized biomarker-enriched phase II trials assessing target engagement (AMPK phosphorylation, mTOR activity, GDF15 levels, BACE1 activity), tissue-level drug exposure, and intermediate clinical endpoints (Ki-67 in neoadjuvant cancer, amyloid PET or CSF biomarkers in neurodegeneration, multimorbidity-free survival in aging trials). Embedding pharmacokinetic/pharmacodynamic (PK/PD) substudies and serial biomarker sampling will elucidate exposure–response relationships.
- Optimal dosing, formulations, and targeted delivery
- Resolve the “concentration paradox”: many in vitro anticancer effects need concentrations higher than standard systemic exposure. Work should pursue (a) rational dose-escalation studies with careful safety monitoring in oncology settings, (b) alternative formulations (extended-release, enteric-coated) that optimize tolerability, and (c) targeted delivery platforms (liver-directed nanoparticles for HCC, BBB-penetrant formulations for neurodegeneration, tumor-targeted nanoparticles or prodrugs) that increase tissue-specific drug levels while limiting systemic adverse events.
- Combination strategies and synthetic lethality
- Metformin is unlikely to be a universal monotherapy outside metabolic indications; its greatest value may be as a synergistic partner. Rational combos include: metformin + cytotoxics (to exacerbate energetic stress), metformin + PI3K/AKT/mTOR inhibitors (potential additive pathway suppression with lower doses), metformin + immune checkpoint inhibitors (microenvironment modulation), and metformin + senolytics or NAD+-modulating agents in aging trials. Preclinical combination screens with translational biomarker endpoints should precede large clinical combination trials.
- Biomarker development and validation
- Prioritize robust, reproducible biomarkers of target engagement and downstream effect: phosphorylation markers (AMPK Thr172, ACC), transcriptional signatures (reduced gluconeogenic gene expression), circulating mediators (insulin, IGF-1, GDF15), inflammatory markers (IL-6, CRP, NLRP3-related cytokines), and tissue/cerebrospinal markers for CNS studies (amyloid/tau PET, CSF Aβ/tau). Standardize assays, sampling schedules, and analytical pipelines across trials to enable meta-analyses and biomarker qualification.

7. Conclusion

- Metformin, long established as the first-line pharmacotherapy for type 2 diabetes mellitus, has evolved into a paradigm of drug repurposing with profound implications across oncology, geroscience, and neuroprotection. Mechanistically, its actions converge on AMPK–mTOR signaling, mitochondrial modulation, and systemic insulin/IGF-1 attenuation, with additional layers of influence on inflammation, redox balance, autophagy, gut microbiota, and vascular function. These interconnected pathways explain its ability to:
- Suppress tumorigenesis through direct metabolic stress, growth signaling inhibition, and modulation of the tumor microenvironment.
- Delay aging phenotypes by mimicking caloric restriction, preserving mitochondrial quality control, and attenuating chronic inflammation.
- Support neuronal resilience via autophagy induction, β-amyloid reduction, cholinergic support, and dampening of neuroinflammation—though outcomes remain context dependent.
- Evidence from epidemiology, preclinical studies, and early clinical trials supports metformin’s potential to reduce cancer incidence, extend healthspan, and mitigate neurodegenerative processes. However, key challenges and controversies persist, including heterogeneous outcomes in non-diabetic populations, risks of vitamin B12 deficiency, the “double-edged” effects of AMPK signaling in different tissues, and pharmacokinetic limitations in CNS delivery.
- The TAME trial and ongoing oncology/neurodegeneration studies will be pivotal in clarifying whether metformin can be translated from a metabolic regulator into a broad-spectrum disease-modifying therapy. Advances in drug delivery systems and precision medicine approaches (patient stratification, biomarker-guided use) will be essential to optimize efficacy while minimizing adverse effects.

- In conclusion, metformin stands as a low-cost, safe, and mechanistically versatile candidate for preventive and therapeutic strategies beyond diabetes. Its repositioning underscores a broader shift toward targeting fundamental cellular pathways—energy sensing, growth control, and stress resistance—as a unifying approach to chronic, age-related diseases.
- Metformin exemplifies how an old drug can acquire new therapeutic relevance. Beyond glycemic control, it demonstrates potential in cancer prevention, healthy aging, and neurodegenerative disorders. However, unresolved controversies highlight the need for precision in its application. With ongoing clinical trials and innovations in drug delivery, metformin may evolve from a diabetes cornerstone to a foundation of preventive pharmacology in the 21st century.

References:-

1. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. Diabetologia. 2017;60(9):1577–1585.
2. Foretz M, Guigas B, Bertrand L, Pollak M, Viollet B. Metformin: from mechanisms of action to therapies. Cell Metab. 2014;20(6):953–966.
3. Viollet B, Guigas B, Garcia NS, Leclerc J, Foretz M, Andreelli F. Cellular and molecular mechanisms of metformin: an overview. Clin Sci (Lond). 2012;122(6):253–270.
4. Bridges HR, Jones AJY, Pollak MN, Hirst J. Effects of metformin and other biguanides on oxidative phosphorylation in mitochondria. Biochem J. 2014;462(3):475–487.

Metformin & Cancer

5. Pollak M. Metformin and cancer: mounting evidence against an association. J Clin Oncol. 2012;30(36):4453–4455.
6. Heckman-Stoddard BM, DeCensi A, Sahasrabuddhe VV, Ford LG. Repurposing metformin for cancer prevention and treatment. Clin Cancer Res. 2017;23(4):798–807.
7. Kourelis TV, Siegel RD. Metformin and cancer: new applications for an old drug. Med Oncol. 2012;29(2):1314–1327.
8. Morales DR, Morris AD. Metformin in cancer treatment and prevention. Annu Rev Med. 2015;66:17–29.
9. Pernicova I, Korbonits M. Metformin—mode of action and clinical implications for diabetes and cancer. Nat Rev Endocrinol. 2014;10(3):143–156.
10. Gong J, Kelekar G, Shen J, Shen J, Kaur S. Metformin: an old drug with new potential for cancer therapy. Oncol Lett. 2016;11(1):12–20.

Metformin & Aging

11. Barzilai N, Crandall JP, Kritchevsky SB, Espeland MA. Metformin as a tool to target aging. Cell Metab. 2016;23(6):1060–1065.
12. Kulkarni AS, Gubbi S, Barzilai N. Benefits of metformin in attenuating the hallmarks of aging. Cell Metab. 2020;32(1):15–30.
13. Martin-Montalvo A, Mercken EM, Mitchell SJ, et al. Metformin improves healthspan and lifespan in mice. Nat Commun. 2013;4:2192.
14. Novelle MG, Ali A, Diéguez C, Bernier M, de Cabo R. Metformin: a hopeful promise in aging research. Cold Spring Harb Perspect Med. 2016;6(3):a025932.
15. Justice JN, Ferrucci L, Newman AB, et al. A framework for selection of blood-based biomarkers for geroscience-guided clinical trials: report from the TAME meeting. Geroscience. 2018;40(5-6):419–436.

Metformin & Neurodegeneration

16. Rotermund C, Machetanz G, Fitzgerald JC. The therapeutic potential of metformin in neurodegenerative diseases. Front Endocrinol (Lausanne). 2018;9:400.
17. Sivalingam V, Ashok Kumar V, Venkatesan V. Metformin in Alzheimer's disease: A review of potential mechanisms and clinical outcomes. Pharmaceuticals. 2023;16(3):345.
18. Ou Z, Kong X, Sun X, et al. Metformin treatment prevents amyloid plaque deposition and memory impairment in APP/PS1 mice. Brain Behav Immun. 2018;69:351–363
19. Patil SP, Jain PD, Ghumatkar PJ, Tambe R, Sathaye S. Neuroprotective effect of metformin in MPTP-induced Parkinson's disease in mice. Neuroscience. 2014;277:747–754.
20. Katila N, Bhurtel S, Shadfar S, et al. Metformin lowers α-synuclein phosphorylation and upregulates neurotrophic factor expression in a chronic MPTP mouse model of Parkinson's disease. Neuropharmacology. 2017;125:396–407.

Inflammation, Immunity & Gut Microbiome

21. Cameron AR, Morrison VL, Levin D, et al. Anti-inflammatory effects of metformin irrespective of diabetes status. Circ Res. 2016;119(5):652–665.

22. Saisho Y. Metformin and inflammation: its potential beyond glucose-lowering effect. Endocr Metab Immune Disord Drug Targets. 2015;15(3):196–205.

23. Wu H, Esteve E, Tremaroli V, et al. Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes, contributing to the therapeutic effects of the drug. Nat Med. 2017;23(7):850–858.

24. Pryor R, Norvaisas P, Marinos G, et al. Host-microbe-drug-nutrient screen identifies bacterial effectors of metformin therapy. Cell. 2019;178(6):1299–1312.e29.

Drug Delivery & Next-Gen Approaches

25. Zhao Y, Zhang L, Qiao C, et al. Nanoparticle-based drug delivery for metformin: recent advances and future prospects. Drug Deliv Transl Res. 2025;15(2):567–580.

26. Li Y, He X, Li Y, et al. pH-responsive metformin-loaded hydrogels for enhanced intestinal delivery. Int J Pharm. 2023;627:122246.

27. Park JH, Prausnitz MR. Drug delivery using microneedle patches: applications for diabetes and beyond. J Control Release. 2019;304:164–170.

Safety & Controversies

28. Aroda VR, Christophi CA, Edelstein SL, et al. Long-term metformin use and vitamin B12 deficiency in the Diabetes Prevention Program Outcomes Study. J Clin Endocrinol Metab. 2016;101(4):1754–1761.

29. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev. 2010;(4):CD002967.

30. Cabreiro F, Au C, Leung KY, et al. Metformin retards aging in C. elegans by altering microbial folate and methionine metabolism. Cell. 2013;153(1):228–239.