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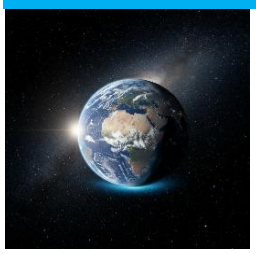

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Metformin as a Potential Geroprotective Agent: Mechanisms, Clinical Evidence and Implications for Healthy Aging

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Abstract

Background: Population aging represents a growing medical and socioeconomic challenge worldwide. The increasing prevalence of age-related diseases such as cardiovascular disorders, neurodegeneration, cancer, and metabolic dysfunction highlights the need for strategies aimed at extending healthspan rather than lifespan alone. In this context, pharmacological agents capable of modulating fundamental biological processes of aging have attracted significant scientific interest. Among them, metformin has emerged as a potential candidate beyond its established role in the treatment of type 2 diabetes mellitus.

Aim: The aim of this narrative review was to critically evaluate current evidence regarding the potential geroprotective properties of metformin, with particular emphasis on underlying molecular mechanisms and available clinical data.

Materials and Methods: A narrative literature review was performed using the PubMed database. Articles published between January 2015 and March 2025 were identified using combinations of the following keywords: “metformin”, “aging”, “longevity”, and “geroprotection”. Peer-reviewed original studies and review articles published in English were included. Case reports and non-peer-reviewed publications were excluded from the analysis.

Results: Current evidence indicates that metformin affects multiple biological pathways implicated in aging processes, including activation of AMP-activated protein kinase (AMPK), inhibition of the mechanistic target of rapamycin (mTOR), modulation of mitochondrial metabolism, reduction of oxidative stress, and attenuation of chronic low-grade inflammation. Observational studies suggest a potential association between metformin use and reduced incidence of certain age-related diseases, as well as improved survival outcomes. However, direct evidence supporting its use as an anti-aging intervention in non-diabetic populations remains limited.

Conclusions: Metformin demonstrates several biological properties consistent with a potential geroprotective effect. Nevertheless, further well-designed randomized controlled trials are required to determine its efficacy and safety in the context of healthy aging.

Keywords: metformin; aging; geroprotection; longevity; AMPK; mTOR; healthy aging

1. Introduction

Aging is a universal biological process characterized by the gradual decline of physiological functions and increased susceptibility to chronic diseases [1]. The growing proportion of elderly individuals in modern societies has led to a substantial rise in the burden of age-related conditions, including cardiovascular disease, type 2 diabetes, neurodegenerative disorders, and malignancies [2,3]. Consequently, contemporary research has increasingly focused on identifying interventions that may delay the onset of these disorders by targeting the underlying mechanisms of aging itself.

Current understanding of aging highlights several interconnected molecular pathways that contribute to functional decline over time. Dysregulated nutrient sensing, impaired mitochondrial function, accumulation of oxidative damage, chronic low-grade inflammation, and cellular senescence represent key biological processes involved in aging progression [4,5]. Therapeutic strategies capable of modulating these pathways are considered potential geroprotective approaches, aiming to extend healthspan rather than merely prolong lifespan [6].

Metformin, a biguanide widely prescribed as first-line therapy for type 2 diabetes mellitus, has attracted considerable scientific attention due to its pleiotropic biological effects [7]. Beyond its well-established role in improving insulin sensitivity and reducing hepatic glucose production, metformin has been shown to influence cellular energy metabolism, activate AMP-activated protein kinase (AMPK), inhibit the mechanistic target of rapamycin (mTOR) pathway, and modulate inflammatory responses [8,9]. These mechanisms overlap with pathways implicated in the regulation of aging processes.

Epidemiological observations suggest that individuals treated with metformin may exhibit lower mortality rates and reduced incidence of certain age-related diseases compared with diabetic patients receiving other therapies [10,11]. Such findings have led to the hypothesis that metformin may exert effects extending beyond glycemic control and potentially act as a pharmacological modulator of aging-related pathways. Nevertheless, the extent to which these effects translate into clinically meaningful anti-aging benefits remains to be fully elucidated.

The aim of this narrative review is to summarize current knowledge regarding the proposed geroprotective properties of metformin, with particular focus on its molecular mechanisms of action and evidence derived from human studies.

2. Materials and Methods

A narrative review of the literature was conducted using the PubMed database. The search strategy was designed to identify publications investigating the potential role of metformin in aging and age-related processes. The following combinations of keywords were used: “metformin AND aging”, “metformin AND longevity”, “metformin AND geroprotection”, and “metformin AND healthy aging”.

Articles published between January 2015 and March 2025 were considered. Additionally, selected landmark studies published before 2015 were included when essential for the conceptual and mechanistic framework of the review. Only peer-reviewed original research articles and review papers published in English were included. Studies conducted in human populations were prioritized; however, selected experimental studies were also considered when relevant to the understanding of biological mechanisms associated with aging.

Titles and abstracts were screened to assess relevance to the topic. Publications focusing exclusively on glycemic control without reference to aging-related pathways were excluded. Case reports, conference abstracts, and non-peer-reviewed publications were not included in the final analysis.

After screening and eligibility assessment, 34 articles met the inclusion criteria and were included in the final qualitative synthesis.

3. Biological Mechanisms of Metformin in Aging

Metformin exerts its biological effects through multiple interconnected molecular pathways that are closely associated with aging processes. Unlike drugs targeting a single receptor or signaling cascade, metformin modulates cellular energy sensing, mitochondrial metabolism, inflammatory signaling, and stress-response mechanisms. These pleiotropic effects overlap with several recognized hallmarks of aging, including dysregulated nutrient sensing and impaired cellular homeostasis [1,2]. Consequently, metformin has been proposed as a potential pharmacological agent capable of influencing fundamental biological processes involved in aging [5].

Among the various mechanisms attributed to metformin, modulation of AMP-activated protein kinase (AMPK) and inhibition of the mechanistic target of rapamycin (mTOR) pathway are considered central to its proposed geroprotective effects [5,7].

3.1 AMPK and mTOR signaling

AMP-activated protein kinase (AMPK) is a key cellular energy sensor that regulates metabolic homeostasis in response to changes in intracellular energy status. Activation of AMPK promotes catabolic pathways that generate adenosine triphosphate (ATP) while inhibiting anabolic processes that consume energy. Dysregulation of nutrient-sensing pathways, including AMPK signaling, has been recognized as one of the major hallmarks of aging [1,2].

Metformin indirectly activates AMPK primarily through inhibition of mitochondrial complex I, leading to a mild reduction in ATP production and an increase in the AMP/ATP ratio [7,12]. This shift in cellular energy balance results in AMPK activation, which subsequently influences multiple downstream targets involved in metabolism, autophagy, and cellular stress resistance. Activation of AMPK has been associated with improved insulin sensitivity, enhanced fatty acid oxidation, and modulation of inflammatory responses [12,13].

One of the most important downstream effects of AMPK activation is inhibition of the mechanistic target of rapamycin (mTOR) pathway. The mTOR complex plays a central role in regulating cell growth, protein synthesis, and nutrient signaling. Hyperactivation of mTOR has been linked to accelerated aging and increased susceptibility to age-related diseases [1,2]. By suppressing mTOR signaling, metformin may promote autophagy, enhance cellular repair mechanisms, and reduce cellular senescence [5,13].

Experimental studies have demonstrated that modulation of AMPK and mTOR signaling pathways is associated with lifespan extension in various model organisms [5,14]. Although direct extrapolation to humans remains limited, these findings provide a mechanistic rationale supporting the hypothesis that metformin may exert geroprotective effects through nutrient-sensing pathways.

Collectively, the ability of metformin to activate AMPK and indirectly inhibit mTOR signaling represents one of the most extensively studied mechanisms underlying its potential role in aging modulation.

3.2 Mitochondrial function and oxidative stress

Mitochondrial dysfunction is widely recognized as a central feature of the aging process [1,2]. With advancing age, mitochondrial efficiency declines, leading to impaired oxidative phosphorylation, increased production of reactive oxygen species (ROS), and reduced cellular energy availability. Accumulation of oxidative damage to proteins, lipids, and DNA contributes to progressive cellular dysfunction and has been implicated in the pathogenesis of numerous age-related diseases.

Metformin exerts part of its biological activity through interaction with mitochondrial metabolism. The drug partially inhibits complex I of the mitochondrial respiratory chain, resulting in a mild reduction in ATP synthesis and alterations in cellular energy balance [7,12]. Although this effect may appear detrimental at first glance, moderate inhibition of mitochondrial respiration can trigger adaptive stress responses that enhance cellular resilience.

By reducing excessive mitochondrial ROS production, metformin may limit oxidative damage and improve redox homeostasis [12,15]. Furthermore, activation of energy-sensing pathways promotes improved metabolic efficiency and may support maintenance of mitochondrial integrity. Experimental models have demonstrated that metformin can improve mitochondrial function and reduce markers of oxidative stress, suggesting a potential protective role against age-associated mitochondrial decline [14,15].

Importantly, mitochondrial modulation by metformin does not appear to induce severe energetic failure under therapeutic conditions. Instead, the mild metabolic stress induced by the drug may activate compensatory mechanisms that enhance cellular survival pathways. This concept aligns with the theory of mitohormesis, in which low-level stress promotes adaptive responses that ultimately increase cellular robustness [16].

Overall, the influence of metformin on mitochondrial metabolism and oxidative stress represents another plausible mechanism through which the drug may contribute to modulation of aging-related processes.

3.3 Inflammation and cellular senescence

Chronic low-grade inflammation, often referred to as "inflammaging," is a hallmark of aging and plays a significant role in the development of cardiovascular disease, metabolic disorders, neurodegeneration, and cancer [1,2]. Aging tissues frequently exhibit elevated levels of pro-inflammatory cytokines and persistent activation of inflammatory signaling pathways, contributing to progressive functional decline.

Metformin has been shown to exert anti-inflammatory effects through several mechanisms. Activation of AMPK can inhibit pro-inflammatory transcription factors and reduce the production of inflammatory mediators [12,17]. Additionally, modulation of metabolic pathways may indirectly suppress inflammatory signaling by improving insulin sensitivity and reducing metabolic stress.

Another critical aspect of aging is the accumulation of senescent cells. Cellular senescence is characterized by irreversible cell cycle arrest and the development of a senescence-associated secretory phenotype (SASP), which promotes local and systemic inflammation [1,2]. The presence of senescent cells has been linked to tissue dysfunction and age-related pathologies.

Emerging evidence suggests that metformin may influence cellular senescence by modulating nutrient-sensing pathways and improving metabolic homeostasis [5,17,18]. Although it is not considered a direct senolytic agent, metformin may attenuate the pro-inflammatory environment associated with senescent cells and reduce the deleterious effects of SASP.

Taken together, the modulation of inflammation and cellular senescence further supports the hypothesis that metformin may act on multiple interconnected hallmarks of aging rather than targeting a single pathway.

4. Clinical Evidence in Humans

While experimental and mechanistic studies provide a biological rationale supporting the potential geroprotective properties of metformin, evaluation of its impact on human aging relies primarily on clinical and epidemiological data [5,14]. Importantly, most available evidence originates from studies conducted in individuals with type 2 diabetes mellitus, rather than from trials specifically designed to assess aging-related outcomes.

Several large observational cohort studies have reported that metformin use is associated with reduced all-cause mortality compared with other glucose-lowering therapies [6,19]. In some analyses, patients treated with metformin demonstrated survival outcomes comparable to or even exceeding those observed in matched non-diabetic control populations [6]. These findings have generated considerable interest in the hypothesis that metformin may exert protective effects beyond glycemic regulation, potentially influencing fundamental aging-related processes.

Cardiovascular disease represents one of the most prevalent age-related conditions, and a substantial body of evidence supports the cardioprotective effects of metformin [20,21]. Improvements in endothelial function, reductions in systemic inflammation, modulation of lipid metabolism, and enhanced insulin sensitivity may collectively contribute to lower cardiovascular risk. Although these benefits are well documented in diabetic populations, it remains uncertain to what extent they reflect direct anti-aging mechanisms versus improved metabolic control.

In addition to cardiovascular outcomes, epidemiological studies have suggested a potential association between metformin use and reduced incidence of certain malignancies [22,23]. Proposed mechanisms include decreased circulating insulin levels, inhibition of mTOR signaling, and modulation of cellular proliferation pathways. However, randomized controlled trials evaluating cancer prevention or progression as primary endpoints have produced mixed results, and definitive conclusions cannot yet be established.

Cognitive decline and neurodegenerative diseases are also closely linked to aging. Some observational data suggest that metformin may influence cognitive outcomes, potentially through improved metabolic regulation and reduced inflammatory signaling [24]. Nevertheless, findings remain inconsistent, with certain studies indicating neutral or even adverse associations in specific subgroups. These discrepancies highlight the complexity of translating metabolic interventions into measurable neuroprotective effects.

Importantly, direct clinical evidence evaluating metformin as an anti-aging intervention in non-diabetic individuals remains limited. Most clinical trials involving metformin have focused on metabolic parameters such as glycemic control, weight reduction, or insulin resistance rather than validated biomarkers of biological aging [5,25]. Therefore, although epidemiological observations are encouraging, they cannot establish causality or confirm that metformin directly modifies the biological rate of aging.

A major development in this field is the proposed Targeting Aging with Metformin (TAME) trial, designed to assess whether metformin can delay the onset of multiple age-related diseases in older adults without diabetes [5,26]. This innovative trial conceptualizes aging as a modifiable risk factor and aims to evaluate composite outcomes related to cardiovascular disease, cancer, cognitive decline, and mortality. Although the final results are still pending, the design of the TAME study reflects a paradigm shift toward treating aging itself as a therapeutic target.

Taken together, current clinical evidence suggests that metformin may confer benefits that extend beyond glycemic control, potentially influencing multiple age-related conditions. However, most data are observational and subject to confounding variables, including differences in baseline health status, treatment selection, and lifestyle factors [19,22]. Consequently, while metformin represents a promising candidate in the context of geroprotection, robust

randomized controlled trials specifically designed to assess aging-related outcomes are necessary before its role in promoting healthy aging can be definitively established.

5. Safety and Limitations

Despite the growing interest in metformin as a potential geroprotective agent, its safety profile and the limitations of currently available evidence must be carefully considered. Although metformin has been widely used for several decades and is generally regarded as safe, particularly in the treatment of type 2 diabetes mellitus [20,27], extrapolating its use to broader aging-related indications requires cautious evaluation.

Metformin is most commonly associated with mild gastrointestinal adverse effects, including nausea, abdominal discomfort, and diarrhea. These symptoms are usually transient and dose-dependent [27]. However, long-term therapy has also been linked to vitamin B12 deficiency, which may contribute to anemia and neurological symptoms, particularly in older adults [28]. Given that elderly individuals may already be at risk of nutritional deficiencies and cognitive decline, monitoring of vitamin B12 levels should be considered in long-term users.

Another safety concern historically associated with metformin is lactic acidosis. Although the absolute risk is very low in appropriately selected patients, the risk increases in the presence of severe renal impairment, hepatic dysfunction, or advanced heart failure [27,29]. As renal function often declines with age, careful dose adjustment and regular monitoring are essential when considering metformin therapy in older populations.

Beyond pharmacological safety, an important limitation lies in the interpretation of clinical evidence. The majority of data supporting potential anti-aging effects derive from observational studies in diabetic populations [6,19]. Such studies are inherently subject to confounding factors, including differences in baseline disease severity, comorbidities, lifestyle behaviors, and treatment allocation. Patients prescribed metformin may differ systematically from those receiving alternative therapies, which can influence observed outcomes.

Furthermore, aging itself is a complex and multifactorial biological process that cannot be adequately captured by single clinical endpoints [1,2]. Many available studies assess surrogate markers such as mortality, cardiovascular events, or cancer incidence rather than validated biomarkers of biological aging or comprehensive healthspan measures [25]. Consequently, it remains unclear whether the observed benefits reflect true modulation of aging mechanisms or secondary effects of improved metabolic control.

Another limitation concerns the heterogeneity of study populations. Most clinical investigations focus on individuals with type 2 diabetes, obesity, or metabolic syndrome [6,20]. Evidence in non-diabetic, otherwise healthy older adults remains limited. Therefore, generalizing potential geroprotective effects to the broader aging population should be approached with caution.

Finally, the concept of pharmacologically targeting aging raises ethical and regulatory considerations [26]. Aging is not currently classified as a disease in many healthcare systems, which complicates the design, approval, and interpretation of clinical trials aiming to evaluate anti-aging interventions. Until large, well-designed randomized controlled trials specifically targeting aging-related outcomes are completed, the use of metformin solely for the purpose of lifespan extension cannot be formally recommended.

In summary, while metformin has an established safety record in metabolic disease management and demonstrates promising mechanistic and epidemiological signals, significant limitations remain. Careful interpretation of existing evidence and further rigorous clinical research are required before metformin can be definitively considered a geroprotective therapy.

6. Future Perspectives

The growing body of experimental and epidemiological evidence has positioned metformin as one of the most promising pharmacological candidates in the field of geroscience [5,18]. Nevertheless, translating mechanistic insights into clinically meaningful anti-aging interventions remains a complex challenge requiring further investigation.

One of the most important future directions involves the identification and validation of reliable biomarkers of biological aging [30]. Current clinical studies often rely on traditional endpoints such as mortality or disease incidence, which may not accurately reflect the biological rate of aging. The development of composite aging biomarkers, including epigenetic clocks, inflammatory profiles, metabolic signatures, and functional assessments, may allow more precise evaluation of whether metformin truly modifies aging-related processes [30,31].

Large-scale randomized controlled trials specifically designed to assess aging-related outcomes are essential [26,30]. The Targeting Aging with Metformin (TAME) trial represents a pioneering step in this direction by conceptualizing aging as a modifiable risk factor rather than focusing on a single disease [5,26]. Future trials may further explore optimal dosing strategies, treatment duration, and patient selection criteria, particularly in non-diabetic older adults.

Another important area of research concerns combination therapies. Aging is driven by multiple interconnected biological pathways; therefore, it is unlikely that a single pharmacological agent will fully address all hallmarks of aging [1,2]. Future strategies may investigate the synergistic effects of metformin with other interventions, such as caloric restriction mimetics, senolytic agents, or lifestyle modifications including physical activity and dietary optimization [32].

Personalized approaches to geroprotection also warrant attention. Genetic variability, metabolic status, and baseline inflammatory profiles may influence individual responses to metformin [18,33]. Identifying subgroups of patients who are most likely to benefit from treatment could improve both efficacy and safety.

Finally, ethical and regulatory frameworks will need to evolve alongside scientific progress [26]. As research increasingly targets aging as a modifiable biological process, healthcare systems may need to reconsider how aging-related interventions are classified, evaluated, and implemented. Clear clinical guidelines and long-term safety data will be essential before widespread use of metformin for geroprotection can be recommended.

In summary, while metformin represents a compelling candidate within the emerging field of geroscience, future research must focus on rigorous clinical trials, validated aging biomarkers, and personalized therapeutic strategies. Only through such comprehensive efforts can the true potential of metformin in promoting healthy aging be fully determined.

7. Conclusions

The concept of pharmacologically targeting aging represents a paradigm shift in modern medicine, moving beyond the treatment of individual diseases toward modulation of fundamental biological processes. Within this context, metformin has gained considerable attention due to its well-established safety profile, pleiotropic metabolic effects, and ability to influence multiple hallmarks of aging.

Preclinical data provide a strong mechanistic rationale supporting the hypothesis that metformin may modulate nutrient-sensing pathways, mitochondrial function, oxidative stress, inflammation, and cellular senescence. Observational human studies suggest associations with reduced mortality and lower incidence of selected age-

related diseases. Nevertheless, these findings do not establish causality, and definitive evidence demonstrating a direct impact on biological aging is still lacking.

At present, metformin should not be considered a confirmed anti-aging therapy, but rather a promising candidate within an evolving field of geroscience. Ongoing and future randomized controlled trials, including studies specifically designed to assess aging-related endpoints, will be crucial in clarifying its role in promoting healthy aging.

Until such data are available, the use of metformin for geroprotection should remain grounded in scientific evidence and clinical judgment. The continued integration of molecular research, epidemiology, and well-designed clinical trials will ultimately determine whether metformin can fulfill its potential as a therapeutic strategy targeting aging itself.

Disclosure

Author Contributions

Conceptualization: P.K.
Writing – original draft preparation: P.K.
Writing – review and editing: K.B., M.R., K.F., N.B.-K., S.Z., P.P., O.W., Ł.S., A.B.
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