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Caloric restriction mimetics: effects of spermidine and berberine on healthy longevity and prevention of aging-associated diseases

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ABSTRACT

Introduction: Aging is a complex biological process associated with the accumulation of cellular damage, loss of proteostasis, and mitochondrial dysfunction, which contribute to the development of chronic diseases. Spermidine and berberine are natural compounds with complementary properties that promote healthy longevity by targeting key cellular pathways such as autophagy and mitochondrial biogenesis.

The objective of this review is to evaluate the mechanisms of action, benefits, and limitations of spermidine and berberine and to explore their synergistic potential as anti-aging agents in personalized medicine strategies.

Methods: A narrative review of the scientific literature was conducted to analyze the effects of spermidine and berberine in preclinical and clinical models. Relevant studies focusing on molecular mechanisms, therapeutic applications, and practical limitations were examined.

Results: Spermidine stimulates autophagy by inhibiting acetyltransferases, improving protein quality, and reducing toxic aggregates associated with cellular aging. Berberine activates AMPK and SIRT1, enhancing mitochondrial biogenesis and regulating energy metabolism. Both compounds have shown efficacy in animal models in improving cognitive function, reducing oxidative stress, and preventing metabolic diseases. However, their low bioavailability and the lack of longitudinal studies limit their clinical application.

Discussion: The complementary effects of spermidine and berberine address proteostasis and cellular bioenergetics simultaneously. Their combination represents a promising multifactorial approach but requires advances in formulations to optimize absorption and stability. Clinical trials are essential to validate their safety and efficacy in humans.

Conclusions: Spermidine and berberine have significant potential as therapeutic agents in anti-aging medicine. Their integration into personalized therapies could improve quality of life and prevent chronic diseases, although additional studies are needed to overcome current limitations.

KEYWORDS

Proteostasis; autophagy; spermidine; berberine; longevity; anti-aging.

ABBREVIATIONS

AMPK - AMP: activated protein kinase.

CR: Caloric Restriction (Restricción Calórica).

eIF5A: Eukaryotic Initiation Factor 5A.

FOXO: Forkhead Box O.

IL-6: Interleukin 6.

mTORC1: Mechanistic Target of Rapamycin Complex 1.

NAD+: Nicotinamide Adenine Dinucleotide.

NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells.

PGC-1α: Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha.

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ROS: Reactive Oxygen Species.

SIRT1: Sirtuin 1.

TFEB: Transcription Factor EB.

TNF-α: Tumor Necrosis Factor Alpha.

ULK1: Unc-51 Like Autophagy Activating Kinase 1.

INTRODUCTION

Aging is a global challenge with profound implications for public health, the economy, and society. This complex biological process is characterized by the progressive decline of cellular functions, increasing organismal vulnerability and contributing to the development of chronic diseases such as cardiovascular diseases, type 2 diabetes, and neurodegenerative disorders[1]. With an aging population on the rise, the search for effective strategies to promote healthy aging has become a scientific priority[2].

Among the cellular mechanisms affected by aging are the loss of proteostasis, accumulation of oxidative damage, and mitochondrial dysfunction. These processes lead to the buildup of misfolded proteins, damaged organelles, and reactive oxygen species (ROS), which are key factors in the functional decline associated with aging[3,4]. In this context, the regulation of autophagy and mitochondrial function has emerged as a promising therapeutic target to slow aging and prevent associated pathologies[5,6].

Caloric restriction (CR) is one of the most studied interventions for extending lifespan and improving health in experimental models. However, its implementation in humans faces practical barriers such as low adherence and potential adverse effects[7,8]. This has spurred interest in CR mimetics, compounds that emulate the beneficial effects of CR without requiring reduced caloric intake[9]. Among these, spermidine and berberine stand out as natural molecules with complementary effects on autophagy regulation, mitochondrial biogenesis, and cellular homeostasis[10,11].

Spermidine, a polyamine found in foods such as wheat germ, stimulates essential processes such as autophagy and proteostasis regulation, contributing to cellular longevity[12]. Berberine, an alkaloid derived from plants of the Berberis genus, promotes mitochondrial biogenesis and energy balance, with significant impacts on the prevention of metabolic diseases[13,14]. These complementary mechanisms position both compounds as key candidates in anti-aging strategies.

This study aims to narratively review the specific molecular mechanisms through which spermidine and berberine contribute to healthy aging. Additionally, their effects are compared, and their potential synergies in combined therapies are explored, discussing current limitations and opportunities for clinical application[15]. This review seeks to provide a solid scientific foundation to advance the development of more effective and personalized anti-aging interventions.

METHODS

A bibliographic search was conducted for documents used in this narrative review using MeSH terms and keywords in the PubMed, Scopus, Web of Science, and Cochrane Library databases to identify relevant articles on caloric restriction mimetics, with a particular focus on spermidine and berberine. The literature search covered the period from 2004 to 2024, as research in this field has primarily developed over the past two decades[16].

To maximize the comprehensiveness of the search and minimize bias, advanced search strategies were applied using Boolean operators and specific keyword combinations related to caloric restriction, autophagy, mitochondrial biogenesis, and the effects of spermidine and berberine in preclinical and clinical models. Additionally, the reference lists of selected articles were manually reviewed to identify additional relevant publications.

Studies were selected based on the following inclusion criteria:

- Original publications, systematic and non-systematic reviews, randomized controlled trials (RCTs), and observational studies.
- Articles analyzing the molecular mechanisms, therapeutic applications, and practical limitations of spermidine and berberine in preclinical and human models.
- Studies in English or Spanish with full-text access.

Studies were excluded if they:

- Focused on compounds other than spermidine and berberine.
- Were not available in English or Spanish.
- Lacked full-text access.
- Did not present appropriate methodologies or relevant data for the review.

To minimize bias in study selection, some elements of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) methodology were applied in the identification, screening, eligibility, and inclusion of articles, despite this being a narrative review. The process began with retrieving documents from the mentioned databases. After removing duplicates, the titles and abstracts of all retrieved studies were reviewed. Studies that were not related, as well as conference proceedings, letters to the editor, viewpoints, and editorials, were excluded. For potentially relevant studies, full texts were reviewed before making the final selection.

The co-authors discussed and agreed on the final list of reference texts, totaling 15 (see Figure 1). Each article was

critically evaluated for methodological quality and scientific relevance, prioritizing those with the greatest impact and rigor. Studies with replicability and statistical validity were considered to ensure the reliability of the conclusions drawn.

To describe and explain the similarities and differences between the various analyzed elements, the study employed a descriptive comparative approach. This involved selecting elements of interest, analyzing the similarities, and describing the selected elements within their respective contexts.

RESULTS

Aging is a complex biological process that affects all multicellular organisms, involving structural and functional changes that increase vulnerability and reduce the organism's adaptive capacity[1]. One key factor contributing to functional decline is the loss of proteostasis, a critical process for cellular homeostasis and healthy longevity[2,3].

During aging, the ability to maintain protein stability and functionality decreases, leading to the accumulation of misfolded

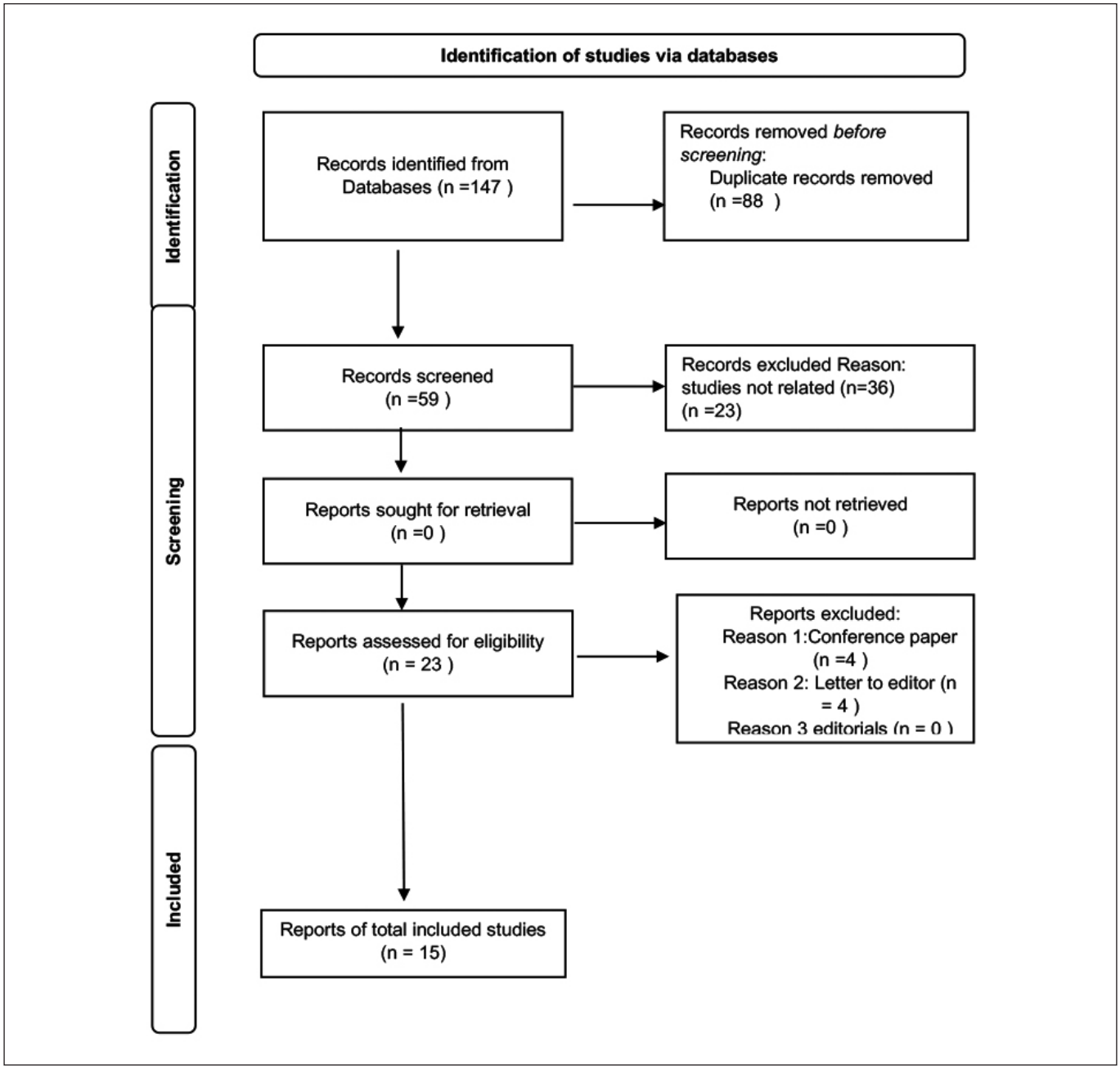

Figure 1. Flowchart to illustrate the process of selecting and filtering articles in this narrative review (PRISMA Model Realignment)

Table 1. Summary table with the works located that deal with the topics studied

Title	Authors	Journal
Meta-analysis of the effect and safety of berberine in the treatment of type 2 diabetes mellitus, hyperlipemia and hypertension	Lan, J., Zhao, Y., Dong F., Yan, Z., Zheng, W., Fan, J., Sun, G.	J. Ethnopharmacol.
Calorie restriction mimetics: can you have your cake and eat it, too?	Ingram DK, Roth GS.	Ageing Res Rev
Higher spermidine intake is linked to lower mortality: a prospective population-based study	Kiechl, S. et al.	Am. J. Clin. Nutr.
The effect of spermidine on memory performance in older adults at risk for dementia: a randomized controlled trial	Wirth, M. et al.	Cortex
Caloric restriction mimetics against age-associated disease: targets, mechanisms, and therapeutic potential	Madeo F., Carmona-Gutierrez D., Hofer S. J., Kroemer G.	Cell Metab.
Polyamines control eIF5A hypusination, TFEB translation, and autophagy to reverse B cell senescence	Zhang, H. et al.	Mol. Cell
Effects of spermidine supplementation on cognition and biomarkers in older adults with subjective cognitive decline (SmartAge)-study protocol for a randomized controlled trial	Wirth, M. et al.	Alzheimers Res Ther.
Berberine in Cardiovascular and Metabolic Diseases: From Mechanisms to Therapeutics	Feng, X., Sureda, A., Jafari, S., Memariani, Z., Tewari, D., Annunziata, G., et al.	Theranostics
Spermidine alleviates cardiac aging by improving mitochondrial biogenesis and function	Wang, J. et al.	Aging
Identification of longevity compounds with minimized probabilities of side effects	Janssens, G. E. & Houtkooper, R. H.	Biogerontology
The quest to slow ageing through drug discovery	Partridge, L., Fuentealba, M. & Kennedy, B. K.	Nat. Rev. Drug Discov.
Spermidine-induced hypusination preserves mitochondrial and cognitive function during aging	Hofer, S. J. et al.	Autophagy
eIF5A hypusination, boosted by dietary spermidine, protects from premature brain aging and mitochondrial dysfunction	Liang, Y. et al.	Cell Rep.
Effects of Berberine on the Gastrointestinal Microbiota	Zhang, L., Wu, X., Yang, R., Chen, F., Liao, Y., Zhu, Z., et al.	Front. Cel. Infect. Microbiol.
Mechanisms of spermidine-induced autophagy and geroprotection	Hofer, S. J. et al.	Nat. Aging

proteins and toxic aggregates characteristic of age-related diseases such as Alzheimer's and Parkinson's disease[1,2]. This progressive deterioration arises from mitochondrial homeostasis disruption, caused by external factors and intracellular triggers such as advanced glycation end products, highly toxic protein aggregates, or excessive ROS production due to abnormal mitochondrial respiration[5,6].

Cells deploy mechanisms to counteract these damages, with proteostasis being one of the most effective. Proteostasis encompasses processes that ensure the proper folding, quality control, and degradation of proteins, including the ubiquitin-proteasome system and autophagy, both of which facilitate the elimination of damaged or unnecessary proteins.

In elderly individuals, these protective systems are also impaired, diminishing cellular defenses, increasing vulnerability, and contributing to pathological effects typical of advanced age[6,7]. Reduced system efficiency leads to the accumulation of defective proteins and generalized cellular deterioration[1,2]. Additionally, macroautophagy, responsible for eliminating dysfunctional organelles and proteins, declines with age, exacerbating proteostatic collapse and accelerating organismal decline[8].

Properly stimulated, macroautophagy can renew proteostasis, making it an excellent target for anti-aging interventions. Research suggests that improving mitochondrial function and proteostasis simultaneously could yield synergistic benefits[9,10,11], necessitating interventions that maximize efficacy.

From a therapeutic perspective, maintaining autophagy is essential for cellular function, with several intervention strategies emerging:

Targeting signaling pathways such as IGF-1/insulin and the AMP/ATP ratio. Autophagy is stimulated by nutrient scarcity or a high AMP/ATP ratio but is inhibited by nutritional abundance. This correlates with energy restriction-based interventions[12]. Additionally, the IGF-1/insulin pathway and FOXO/DAF-16 transcription factors promote autophagy, as does SIRT1 activation via polyphenols, NAD+, or caloric restriction (CR).

Modulating autophagy-related proteins. Autophagy activation depends on the ULK1 kinase, regulated by AMPK and the mTORC1 complex, which stimulates Beclin 1, a key autophagy-promoting protein. Studies on mimicking Beclin 1 activity show promising potential[13].

Enhancing autophagosome activity and lysosomal function. Dietary interventions such as energy restriction show high efficacy in modulating these processes by interacting with key signaling pathways.

Several therapeutic interventions have been proposed to delay aging and associated diseases[14,15], focusing on mechanisms that sustain cellular survival and proteome stability (proteostasis). This is crucial in preventing chronic and degenerative age-related diseases[16].

Proteostasis dysfunction is linked to various pathologies, particularly in tissues with low cellular turnover (nervous system, myocardium), which are especially susceptible to cumulative damage. Disruptions in proteostasis contribute to the development of neurodegenerative diseases like Alzheimer's and Parkinson's, which are prevalent among older populations[1]. Maintaining the cellular proteome is vital not only for health and longevity but also for reducing degenerative disease incidence and achieving healthy aging[2,16].

Dietary interventions involving energy restriction[17] have shown promise but face challenges such as low adherence and adverse effects like sarcopenia risk[18]. Alternatives include compounds capable of mimicking CR benefits while limiting its adverse effects, known as CR mimetics[12,13,19].

Natural compounds such as spermidine and berberine have been identified as active promoters of proteostasis. These two agents, with well-documented anti-aging properties, stand out for their potential roles in maintaining cellular health and longevity.

SPERMIDINE

Spermidine is a naturally occurring substance found in various foods and endogenously in the human metabolism. Recent studies have highlighted its ability to stimulate autophagy[20-22]. It acts by inhibiting acetyltransferases and activating key signaling pathways such as AMPK, SIRT1, and FOXO3a, in addition to modulating autophagic factors related to lysosomal biogenesis, thereby contributing to cellular longevity and maintaining proteostasis[1,23].

Chemically, spermidine is a natural polyamine that plays a crucial role in cellular metabolism, particularly in the context of aging. It is synthesized endogenously and can also be obtained from dietary sources, including wheat germ, soybeans, nuts, and fermented vegetables, as well as whole-grain-derived products. Its anti-aging properties and effects on essential cellular processes, such as autophagy, cellular repair, and metabolic regulation, have gradually been revealed[1,2].

Polyamines, such as spermidine, are organic compounds containing multiple amino groups, enabling them to interact with nucleic acids and proteins. This molecular interaction makes spermidine vital for maintaining cellular homeostasis and modulating metabolic pathways, which are particularly vulnerable during aging[2,4]. Spermidine, along with other polyamines, stabilizes nucleic acid and protein structures, key factors in preserving cellular integrity. Moreover, it regulates gene expression and protects against oxidative stress, which are crucial in preventing age-related diseases and promoting longevity[2-4].

Molecular Mechanisms

One of spermidine's primary mechanisms of action in aging is its induction of autophagy, a catabolic process that enables cells to degrade and recycle damaged or unnecessary components. Autophagy is essential for removing misfolded proteins and dysfunctional organelles, processes that decline with age and contribute to the accumulation of toxic cellular waste.

Spermidine promotes autophagy by inhibiting acetyltransferases, enzymes that acetylate certain proteins, thereby suppressing autophagy. By inhibiting these enzymes, spermidine maintains the activity of key autophagic proteins, facilitating the removal of damaged components and supporting proteostasis and cellular protection throughout aging[2,4].

Autophagy regulation by spermidine is well-documented and central to its therapeutic potential in anti-aging. Experimental models have demonstrated its ability to improve protein quality and reduce the burden of toxic aggregates in critical organs such as the nervous system and liver, which are particularly affected by aging-related waste accumulation[3,4].

Another significant mechanism is spermidine's activation of AMPK and regulation of mTORC1 activity, two key players in

longevity signaling and cellular metabolism. AMPK acts as a metabolic sensor under low-energy conditions, regulating anabolic and catabolic pathways to preserve cellular energy. By activating AMPK, spermidine enhances autophagy and mitochondrial biogenesis, critical processes for maintaining cellular efficiency and reducing oxidative damage[1,4].

mTORC1, which regulates cell growth and proliferation in response to nutrient levels, is overactivated during aging, leading to autophagy inhibition and increased accumulation of misfolded proteins. Spermidine inhibits mTORC1 activity, facilitating autophagy activation and reducing protein damage and cellular inflammation. These effects on AMPK and mTORC1 pathways not only enhance cellular quality but are also associated with increased longevity and improved function in animal models[2,4].

Telomere length is a key indicator of cellular aging, as telomeres shorten with each cell division until the cell loses its ability to divide. Spermidine may contribute to telomere protection by activating telomerase, helping to maintain their length and preventing premature shortening, particularly in highly proliferative tissues such as the immune and epithelial systems, where this protection is essential for proper functioning[2,5]. This positions spermidine as a potential anti-aging compound, as it may delay cellular aging and reduce aging-related diseases in these tissues[5].

A key mechanism related to proteostasis is the post-translational hypusination of eIF5A, a protein essential for protein translation that is activated through this highly conserved process[21,24-26]. Hypusination occurs in two steps: DHS (deoxyhypusine synthase) transfers a 4-aminobutyl group from spermidine to a lysine residue on eIF5A, requiring NAD+. Subsequently, DOHH (deoxyhypusine hydroxylase) converts deoxyhypusine into hypusine by adding an OH group, enabling eIF5A activation 21.

eIF5A activation regulates protein synthesis during initiation, elongation, and termination phases, overcoming ribosomal stalling[27]. It also facilitates the translation of mitochondrial proteins, improving mitochondrial functionality and stimulating autophagy[28-31]. This process further activates TFEB, a transcription factor that regulates lysosomal biogenesis and autophagy by inducing pro-autophagic genes. TFEB is inhibited by mTORC1, which has anti-autophagic activity[30,31].

Spermidine plays a crucial role in autophagy stimulation through the activation of eIF5A and TFEB. Reduced spermidine levels may impair the functionality of mitochondria-dependent cells, such as immune cells[21,29]. TFEB activation via eIF5A could also enhance mitophagy, optimizing energy production and mitochondrial biogenesis[20,32].

These mechanisms are particularly significant in the context of neurodegenerative diseases such as Alzheimer's and Parkinson's, where the accumulation of defective proteins has devastating effects. By promoting eIF5A and TFEB activation, spermidine offers therapeutic potential to improve protein quality and cellular homeostasis, reducing the impact of these disorders[8,16].

Evidence in Animal and Human Models

Experimental evidence supporting spermidine's effects on health and longevity is robust in both animal models and observational human studies. In murine models, spermidine supplementation extended lifespan and improved cardiac health, memory, and immune function. These benefits are attributed to its ability to activate autophagy, enhance mitochondrial function, and reduce defective protein accumulation in critical tissues essential for survival and quality of life[8,16].

Preclinical studies have demonstrated its potential to delay aging and improve health in animal models. Given its low likelihood of adverse effects[33], spermidine is considered a promising candidate for clinical trials in humans[34].

In humans, controlled clinical trials are needed to confirm its effects suggested by animal research. Current findings support its use as an anti-aging agent that could be integrated into dietary and therapeutic strategies to enhance health during aging. Epidemiological studies suggest that regular consumption of spermidine-rich foods correlates with a lower incidence of cardiovascular diseases and increased healthy longevity. A high-spermidine diet has been linked to improved longevity, reduced mortality, and a lower prevalence of age-associated diseases such as cardiovascular diseases and cancer. Furthermore, it has shown potential to mitigate cognitive decline, correlating with greater hippocampal volume and cortical thickness, both associated with preserved cognitive function in older individuals[20,35-37].

Limited clinical studies with spermidine have reported positive effects in aging-related contexts. For example, a study using wheat germ extract, rich in spermidine, evaluated cognitive aspects in individuals over 60. An initial three-month phase observed slight memory improvement[38]. However, an extended 12-month follow-up showed no significant improvement except in high-adherence subgroups, where evident benefits emerged[39].

While spermidine appears safe[33], caution is advised with high doses in individuals with neoplastic conditions, as polyamines have been linked to cancer development. Nevertheless, spermidine's potential to reduce cancer risk through autophagy stimulation and immune surveillance offers a counterpoint, making it a promising candidate for further investigation.

BERBERINE

Berberine is a plant-derived compound with numerous beneficial properties. It has been shown to activate the AMPK pathway, which supports mitochondrial biogenesis and cellu-

lar energy metabolism, improving ATP production in striated muscle. These activities are essential for preserving mitochondrial function and protein balance, both of which are key in preventing metabolic and neurodegenerative diseases associated with aging[1,19].

Berberine is an isoquinoline alkaloid extracted from various plants in the Rutaceae, Ranunculaceae, and Berberidaceae families. In the latter, the Berberis genus is particularly notable, with species such as B. vulgaris (barberry) and B. aristata. This compound has a long history in traditional Chinese medicine and other ancient medical practices for its antimicrobial, anti-inflammatory, antidiabetic, anticancer, and cardiovascular therapeutic properties[40-42].

Despite its low bioavailability, berberine has garnered significant scientific interest due to its ability to improve glycemic control and lipid metabolism, making it a promising option for managing metabolic diseases[43]. Advances in formulations to enhance its bioavailability have further positioned berberine as an anti-aging agent.

With its unique chemical structure, berberine exhibits high affinity for key enzymes and molecular pathways critical in metabolic regulation. It influences processes related to inflammation, mitochondrial dysfunction, and oxidative stress, providing therapeutic benefits not only in managing chronic diseases like diabetes and dyslipidemia but also in improving quality of life and longevity in aging populations[44].

Molecular Mechanisms

Berberine regulates two crucial proteins involved in cellular energy control and metabolic homeostasis: SIRT1 (sirtuin 1) and AMPK. SIRT1 activation is critical for mitochondrial biogenesis, allowing cells to replace dysfunctional mitochondria. This process reduces aging-associated cellular damage and enhances energy production efficiency[43,45].

AMPK activation, on the other hand, stimulates autophagy and regulates lipid and glucose metabolism. It plays a key role in maintaining ATP levels and clearing damaged proteins and organelles through autophagy. These effects improve mitochondrial function and eliminate dysfunctional components, preserving cellular integrity and functionality during aging[43,45].

Mitochondrial dysfunction, a hallmark of cellular aging, is characterized by inefficient energy production and increased ROS generation, which damage proteins, lipids, and DNA. Berberine mitigates mitochondrial dysfunction by activating AMPK and SIRT1, promoting mitochondrial biogenesis and ATP production in energy-demanding tissues like skeletal muscle. This function is especially relevant in aging, as it helps preserve muscle mass and functional capacity[44,45].

Berberine also reduces oxidative stress by lowering ROS levels, protecting cells from damage and improving metabolic efficiency. This mechanism is vital for combating aging-associated diseases such as cardiovascular and neuromuscular pathologies[45].

Furthermore, berberine exhibits anti-inflammatory and antioxidant properties, essential for its anti-aging potential. It modulates the expression of pro-inflammatory and antioxidant genes, targeting signaling pathways involving NF-κB and PGC-1α. NF-κB inhibition reduces pro-inflammatory cytokines such as IL-6 and TNF-α, key contributors to chronic low-grade inflammation that accelerates aging and age-related diseases like diabetes and cardiovascular disorders[46].

Berberine also enhances PGC-1α activity, a regulator of mitochondrial biogenesis and antioxidant mechanisms, which protects cells from oxidative damage. This activity is particularly beneficial for metabolic health and cognitive function, mitigating the impact of inflammatory and oxidative processes that intensify with aging[46].

Evidence in Animal and Human Models

Berberine has demonstrated positive effects in several animal models and human clinical studies, supporting its potential as an anti-aging agent. In aged rodents, berberine administration improved cognitive and muscular function, reduced mitochondrial dysfunction, and decreased oxidative stress in muscle tissue. These effects are attributed to the activation of the AMPK/SIRT1/PGC-1α pathway, which regulates mitochondrial function and cellular turnover, reversing certain aspects of functional decline associated with aging[45,46].

Preliminary human clinical trials have shown benefits in glucose and lipid control, suggesting its potential to improve metabolic health in middle-aged and older individuals. Additionally, berberine consumption has been associated with reduced inflammatory markers in patients with metabolic diseases, indicating its role in preventing age-related conditions like diabetes and cardiovascular diseases[43,44].

DISCUSSION

Spermidine and berberine share fundamental mechanisms in their anti-aging effects, particularly AMPK activation and autophagy regulation. This activation improves cellular metabolism, mitochondrial function, and the removal of waste products, directly contributing to cellular longevity and metabolic health during aging[12,43].

Both compounds stimulate autophagy through specific mechanisms. Spermidine inhibits acetyltransferases, promoting the deacetylation of key proteins involved in autophagy. Berberine, via AMPK activation, similarly stimulates cellular recycling, maintaining homeostasis and reducing oxidative stress caused by damaged proteins[1,2,45]. These shared effects are critical in protecting against neurodegenerative and metabolic diseases, such as cardiovascular conditions, that are common in aging[46].

Despite these similarities, spermidine and berberine exhibit key differences in their mechanisms of action, suggesting complementary benefits when combined in anti-aging therapies. Spermidine uniquely modulates signaling pathways that directly impact protein quality, such as its interaction with transcription factors like FOXO3a and its ability to activate eIF5A. This supports lysosomal biogenesis and proteostasis, enhancing cellular function and reducing toxic protein aggregates associated with aging-related diseases[2,16].

In contrast, berberine's additional effects on lipid and glucose metabolism, mediated through SIRT1 activation and mitochondrial biogenesis, make it especially effective in mitigating mitochondrial dysfunction and protecting against metabolic diseases like type 2 diabetes and cardiovascular disorders[43,44].

The combination of these effects offers a multifactorial approach, optimizing various aspects of cellular aging, from the removal of damaged proteins to supporting healthy mitochondrial function[46]. A combined intervention could yield synergistic effects, enhancing the efficacy of anti-aging therapies by addressing both proteostasis and bioenergetics, two critical factors in aging.

Current Limitations in Research

Despite the growing interest in spermidine and berberine as anti-aging compounds, their practical implementation faces significant limitations. One of the most notable barriers is their low bioavailability. Spermidine has limited bioavailability, reducing its effectiveness in human contexts. Similarly, berberine demonstrates poor bioavailability due to its low intestinal absorption and rapid hepatic elimination. These factors limit the concentration of these compounds in target tissues, impacting their clinical efficacy[43,44].

In addition to pharmacokinetic limitations, there are few longitudinal human studies evaluating their long-term effects. Although animal models have shown positive results in lifespan extension and improvements in metabolic and cognitive function, extrapolating these findings to humans remains challenging. Anti-aging interventions require extended follow-up periods to adequately evaluate their benefits and risks, but current studies are limited in observation time, complicating the understanding of cumulative effects and the long-term safety of these compounds[45,46].

Future Potential in Anti-Aging Therapies

To enhance the efficacy of spermidine and berberine, research focusing on improving their bioavailability is essential. One possibility is the development of advanced formulations to improve absorption, such as nanoparticle delivery systems or liposomal encapsulation, strategies that have been shown to increase the availability of other bioactive compounds.

Another approach could involve designing structural analogs of spermidine and berberine specifically engineered to resist metabolic degradation and improve absorption in the digestive system[43].

Table 2. Comparative summary of similarities and differences in the mechanisms of action of spermidine and berberine in anti-aging interventions targeting proteostasis

Characteristic	Spermidine	Berberine	Similarities
AMPK Activation	Indirectly activates AMPK, improving energy balance.	Directly activates AMPK, supporting autophagy and mitochondrial function.	Both activate AMPK, promoting cellular longevity.
Autophagy Stimulation	Inhibits acetyltransferases, facilitating autophagy.	Stimulates autophagy via AMPK, reducing oxidative stress.	Both eliminate damaged proteins and organelles.
Mitochondrial Function	Indirectly improves mitochondrial function.	Directly facilitates mitochondrial biogenesis via SIRT1.	Both support mitochondrial health.
Proteostasis	Maintains protein quality and reduces harmful aggregates.	Does not directly affect proteostasis but reduces oxidative damage.	Spermidine focuses on protein quality, while berberine reduces oxidative damage.
Additional Effects	Protects against neurodegenerative diseases.	Assists in metabolic diseases (type 2 diabetes, cardiovascular issues).	Both protect against aging-related diseases.
Combined Applications	Optimizes cellular quality when used with berberine.	Enhances mitochondrial function when combined with spermidine.	Potential combination for a comprehensive anti-aging therapy.
Precautions	High doses may alter protein balance.	Excess AMPK or SIRT1 may disrupt cellular signaling.	Both require dose control to avoid side effects.

Additionally, it is crucial to determine the optimal dosage and potential side effects of these compounds when administered over long periods. The interaction of spermidine and berberine with various molecular pathways could have unintended effects in certain contexts, potentially disrupting cellular balance in healthy individuals. Future clinical trials should focus on defining safe and effective doses of these compounds and understanding their combined effects with other anti-aging agents, such as metformin and resveratrol, paving the way for more personalized and effective therapies[44,46].

Clinical Implications

The integration of spermidine and berberine into clinical practice holds significant potential for preventing and treating aging-related diseases. By promoting proteostasis and enhancing autophagy, spermidine emerges as a promising option for managing neurodegenerative diseases where the accumulation of misfolded proteins plays a key pathogenic role. Preclinical studies suggest that it can improve neuronal health and protect against cognitive decline, although more human research is needed to confirm its effectiveness in these specific contexts[43,45].

On the other hand, berberine, with its ability to improve glucose and lipid metabolism alongside its positive effects on mitochondrial biogenesis, offers potential applications in treating metabolic diseases such as type 2 diabetes and dyslipidemia, as well as improving cardiovascular function in aging populations. The regulation of SIRT1 and AMPK by berberine supports mitochondrial health and energy homeostasis, key factors in preventing metabolic and cardiovascular diseases. As a complementary therapy, berberine could help manage metabolic risk factors and enhance the quality of life in older adults[43,45].

The combination of these two substances in personalized medicine strategies represents an innovative approach to addressing aging and its associated diseases. These molecules could be incorporated into individualized protocols based on patients' genetic, metabolic, and lifestyle characteristics. For example, genetic profiling to identify variations in genes related to autophagy, such as ATG5 and FOXO3, or mitochondrial function, such as PGC-1α, could guide the dosing and formulation of combined therapies. Additionally, the use of specific biomarkers, such as ROS or proteostasis indicators, could further optimize their clinical application.

In practice, these molecules could be administered as supplements within dietary regimens tailored to individual needs or integrated into combination treatments with other geroprotective agents. Advanced technologies, such as wearable devices that measure oxidative stress or metabolic activity, could enable real-time intervention adjustments, maximizing therapeutic responses. This approach could not only enhance healthy longevity but also prevent the progression of chronic diseases, paving the way for more effective and targeted therapies in anti-aging medicine.

CONCLUSIONS

Spermidine and berberine demonstrate significant potential in modulating key cellular processes related to longevity, such as autophagy and mitochondrial biogenesis. Their complementary action could offer a promising therapeutic approach to prevent aging-related diseases.

Despite the demonstrated benefits, their clinical application remains limited due to poor bioavailability and the need for long-term clinical trials.

Future research should focus on developing advanced formulations that optimize the absorption and stability of these compounds, as well as determining optimal dosages and interactions with other anti-aging agents. Long-term clinical trials will be essential to confirm the safety and efficacy of these therapies in aging human populations.

Exploring synergistic combinations of spermidine and berberine, aimed at improving proteostasis and mitochondrial function, could address multiple aspects of cellular aging, thereby promoting healthy and high-quality longevity.

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