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Artículos de revisión

Caloric Restriction Mimetics: A comparative analysis of natural and synthetic agents in autophagy modulation

Miméticos de la Restricción Energética: Un Análisis Comparativo de Agentes Naturales y Sintéticos en la Modulación de la Autofagia

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Resumen

Introducción: La restricción calórica (CR) ha demostrado ser efectiva en prolongar la longevidad y prevenir enfermedades relacionadas con la edad. Sin embargo, su implementación en humanos presenta desafíos como efectos adversos y baja adherencia. Los miméticos de la restricción calórica (CRM) surgen como alternativas prometedoras, replicando los beneficios de la CR mediante la modulación de vías metabólicas clave como AMPK, mTOR y SIRT1.

Método: Se realizó una revisión narrativa basada en estudios desde 2004 hasta octubre de 2024, utilizando términos clave relacionados con la CR y CRM. La selección incluyó estudios en modelos animales y humanos, evaluando agentes naturales como el resveratrol y la espermidina, y sintéticos como la metformina y la rapamicina.

Resultados: Los CRM naturales, como el resveratrol y la espermidina, promueven la autofagia a través de la activación de SIRT1 y la regulación de mTOR, mejorando la homeostasis celular y reduciendo la inflamación crónica. Los agentes sintéticos, como la metformina y la rapamicina, ofrecen una inducción más potente de la autofagia, aunque con riesgos asociados como inmunosupresión. Los estudios en animales muestran mejoras en longevidad y salud metabólica, mientras que en humanos, los beneficios requieren más validación.

Conclusiones: Los CRM representan una opción innovadora para prevenir enfermedades relacionadas con la edad y mejorar la calidad de vida. La combinación de agentes naturales y sintéticos podría optimizar su efectividad, pero son necesarios estudios longitudinales para garantizar su seguridad y aplicación clínica.

Palabras clave: Miméticos de la restricción calórica; autofagia; AMPK; mTOR, SIRT1; longevidad; envejecimiento.

Abstract

Introduction: Caloric restriction (CR) has been proven effective in extending longevity and preventing age-related diseases. However, its implementation in humans faces challenges, such as adverse effects and low adherence. Caloric restriction mimetics (CRMs) are emerging as promising alternatives, replicating the benefits of CR by modulating key metabolic pathways like AMPK, mTOR, and SIRT1.

Method: A narrative review was conducted based on studies from 2004 2004 to October 2024 using key terms related to CR and CRMs. The selection included studies on animal models and humans, evaluating natural agents such as resveratrol and spermidine, and synthetic compounds like metformin and rapamycin.

Results: Natural CRMs, such as resveratrol and spermidine, promote autophagy through SIRT1 activation and mTOR regulation, improving cellular homeostasis and reducing chronic inflammation. Synthetic agents, like metformin and rapamycin, induce more potent autophagy, though with associated risks such as immunosuppression. Animal studies show improvements in longevity and metabolic health, while human benefits require further validation.

Conclusions: CRMs represent an innovative option to prevent age-related diseases and enhance quality of life. Combining natural and synthetic agents could optimize their effectiveness, but longitudinal studies are essential to ensure their safety and clinical applicability.

Keywords: Caloric restriction mimetics; autophagy; AMPK; mTOR; SIRT1; longevity; aging.

Highlights

Caloric restriction is an effective intervention to extend longevity and reduce age-related diseases. However, its adherence is challenging, prompting the development of mimetics that replicate its benefits without reducing caloric intake.

This study compares natural and synthetic agents, analyzing their effectiveness in inducing autophagy and their potential to prevent age-related diseases in human and animal models.

Caloric restriction mimetics could revolutionize the prevention of age-related diseases, enhancing quality of life through personalized and sustainable strategies in anti-aging medicine.

Introduction

Caloric restriction (CR) is one of the most effective interventions to extend lifespan and improve health in animal models[1]. It optimizes metabolic functions, reduces cumulative cellular damage, and preserves homeostasis through reduced energy intake[2,3]. Aging, characterized by the progressive deterioration of cellular function and loss of homeostasis, increases susceptibility to chronic diseases such as type 2 diabetes, cardiovascular diseases, cancer, and neurodegeneration[4,5]. CR delays the onset of these pathologies by modulating metabolic pathways related to cellular stress and inflammation[3,6].

During CR, AMPK activation and mTOR inhibition enhance autophagy, a critical process for the elimination of damaged proteins and organelles[7,8]. This contributes to energy efficiency, reduces oxidative stress, and mitigates chronic inflammation, which are key factors in aging and its associated diseases[6-9]. In animal models, CR has been shown to increase lifespan by 30-50 %, an effect attributed to improvements in mitochondrial efficiency, immune function, and genetic expression related to longevity, such as the activation of sirtuins (SIRT1) and the preservation of telomeres[1,3,8-12].

However, adherence to CR in humans faces significant challenges, such as psychological and social barriers. This has driven the search for alternatives that emulate its benefits without its limitations or adverse effects, such as sarcopenia and reduced bone density in older adults[10,16]. Natural and synthetic caloric restriction mimetics (CRM) have emerged as promising solutions in this regard[13-16].

Mechanisms of anti-aging action: Autophagy

Autophagy is a key process for degrading and recycling dysfunctional cellular components through the lysosomal system[17-19]. This mechanism is essential for maintaining cellular homeostasis, as it removes misfolded proteins and damaged organelles that accumulate over time[20,21]. However, with aging, the efficiency of autophagy declines, contributing to cellular deterioration and the development of chronic diseases such as diabetes, cardiovascular diseases, and neurodegenerative conditions[6,9,13,22].

The induction of autophagy is associated with increased longevity in organisms such as yeast, nematodes, and mammals, improving the clearance of toxic proteins, oxidative stress, and metabolic efficiency[3,16,23]. This process is regulated by AMPK and mTOR, whose complementary roles control autophagy activation in response to cellular energy conditions[7,8]. Additionally, sirtuins, such as SIRT1, also play an important regulatory role[8,11].

Autophagy dysfunction is linked to chronic diseases such as Alzheimer's, where toxic proteins accumulate, and sarcopenia, which affects muscle mass in older adults[22-24]. Promoting autophagy through CR or CRMs has shown significant improvements in cellular function and longevity[5,21]. Natural compounds have demonstrated the ability to induce autophagy, reduce inflammation, and maintain cellular homeostasis[13,25]

Given its central role in aging and related diseases, there is growing interest in developing therapies to optimize autophagic activity in older individuals[3,26,27]. However, modulating autophagy requires caution, as excessive activation can trigger apoptosis in healthy cells[28]. CRMs represent a promising alternative for this purpose, and their analysis will be the focus of this study.

The role of Caloric Restriction Mimetics (CRMs)Caloric Restriction Mimetics (CRMs)

The concept of CRMs has gained relevance due to the demonstrated benefits of CR in longevity and the reduction of age-related diseases[1,3]. Functionally, CRMs aim to replicate the positive effects of CR without reducing energy intake, making them a viable alternative for individuals who struggle to adhere to prolonged CR[3,5]. They represent a promising preventive and therapeutic option with a more accessible clinical application.

CRMs act by modulating key metabolic pathways, such as activating AMPK and inhibiting mTOR, which are fundamental mechanisms underlying CR benefits[8]. AMPK stimulates autophagy, enhances mitochondrial efficiency, and improves insulin sensitivity, while mTOR inhibition reduces protein synthesis and cell growth, promoting longevity and resilience to cellular stress[22].

CRMs also increase NAD+ levels, activating sirtuins that are essential for autophagy regulation and protection against oxidative damage[8,11]. This promotes cellular longevity by maintaining homeostasis and reducing chronic inflammation[3,9].

Challenges and Justification

With these physiological effects known, attempts have been made to clinically apply some of these CRMs, as their activity induces a potential anti-aging effect. There is growing interest in CRM research and development due to the increasing need to address population aging and the associated chronic diseases, which pose a significant burden on healthcare systems[25]. In a context of rising life expectancy, the primary challenge is not only to extend lifespan but also to improve its quality by reducing the incidence of aging-related diseases[3,9].

Although CR has proven effective in delaying aging and chronic diseases, its long-term adherence is challenging, and it may result in undesirable side effects such as muscle loss and decreased bone density[10,16]. Therefore, CRMs offer a more practical and sustainable solution, replicating CR benefits without its drawbacks[3,15] Therefore, they could replace it in clinical practice.

This work analyzes both natural and synthetic agents, providing a comprehensive perspective that identifies effective therapeutic approaches to prevent and treat age-related diseases[27]. It also encourages further research into developing treatments based on the modulation of autophagy and cellular homeostasis[15,22]. In the context of high morbidity and mortality from chronic diseases, CRMs could transform medical approaches toward preventive strategies, reducing the socioeconomic burden of aging[6,9].

The primary objective of this study is to conduct a comparative analysis of CRM effects on autophagy modulation and their impact on molecular pathways involved in cellular aging as an alternative to classic CR. After examining the mechanisms of action of various CRMs, their efficacy in improving cellular longevity, reducing oxidative damage, and mitigating chronic inflammation—key factors in preventing age-related diseases—is evaluated[22].

The study also assesses limitations related to bioavailability and safety in clinical applications[15,25], exploring their therapeutic potential as viable alternatives to CR, with a focus on anti-aging interventions that improve quality of life[3].

Although there is currently extensive knowledge about CRM substances, especially those of natural origin (14), this study has been limited to spermidine and resveratrol as they are the most well-known, abundant in foods, and likely possess the most versatile mechanistic profile, making them ideal candidates for evaluation.

Similarly, metformin and rapamycin were chosen as synthetic CRMs due to the extensive clinical experience with the former and the latter being a model compound for studying this mimetic activity.

The comparison between these two types of CRMs is appropriate since natural compounds are perceived as safe due to their dietary origin, although their bioavailability and clinical efficacy may be limited. On the other hand, synthetic CRMs are designed drugs that often show greater potency, although their use can be associated with side effects or toxicity at certain doses. Evaluating these differences will help identify safer and more effective options.

Additionally, a significant gap exists in the literature regarding how these two types of CRMs could complement each other or be used in combination to maximize clinical benefits. This integrated approach could transform strategies for healthy aging and open new avenues for personalized interventions based on individual metabolic needs.

Methods

This narrative review aims to analyze the molecular mechanisms and therapeutic applications of caloric restriction mimetics (CRMs) in longevity and healthy aging.

The bibliographic search for documents used in this narrative review employed MeSH terms and keywords such as “caloric restriction mimetics,” “spermidine,” “resveratrol,” “autophagy,” and “aging,” combined with Boolean operators (AND, OR) to retrieve the maximum number of relevant articles. The search strategy covered the period from 2004 to October 2024, focusing on studies explaining mechanisms, clinical applications, and effects on longevity. Articles were selected from PubMed/Medline, Scopus, and Google Scholar, including all studies ranging from laboratory and animal models to clinical trials written in English and Spanish. Priority was given to studies published in peer-reviewed journals, particularly those describing mechanisms of action, comparisons between natural and synthetic mimetics, and therapeutic applications in the context of aging.

After removing duplicates, the titles and abstracts of the retrieved studies were reviewed. Articles deemed irrelevant, with weak designs, or unrelated to CRMs, as well as conference abstracts, letters to the editor, viewpoints, and editorials, were excluded. For potentially relevant studies, full texts were reviewed before making the final selection. To describe and explain the similarities and differences between various CRMs, a descriptive comparative approach was used. This involved selecting elements of interest, analyzing similarities, and describing the selected elements in their respective contexts. The selected studies were critically analyzed in terms of methodological design, consistency of results, and recognized limitations.

Results

To understand the rationale for investigating and developing CRMs, it is essential to explore the mechanisms by which CR promotes longevity and improves metabolic health. At the cellular and molecular levels, limited energy availability triggers adaptations that enhance homeostasis and stress resistance, reducing the risk of chronic diseases associated with aging [1,3]. These adaptations are mediated by the regulation of key metabolic pathways, including AMPK activation, mTOR inhibition, and sirtuin modulation[7,8].

AMPK activation, mTOR inhibition

This pathway plays a central role in energy metabolism and cellular aging. AMPK acts as an energy sensor, activated under energy-deprived conditions such as CR, fasting, or intense exercise[1,7]. By detecting low ATP levels, AMPK promotes cellular responses that increase energy production and decrease consumption, supporting cell survival under stress[7,8].

AMPK activation stimulates fatty acid oxidation, enhances glucose uptake, and drives autophagy—a process essential for clearing damaged proteins and dysfunctional organelles[15,22]. This facilitates cellular homeostasis and prevents cumulative damage associated with aging[13,22].

In contrast, mTOR regulates cell growth in response to nutrients and energy availability. Under abundant conditions, mTOR activation stimulates protein synthesis and cell proliferation while suppressing autophagy[8,21]. AMPK activation inhibits mTOR, promoting autophagy, recycling damaged cellular components, and improving cellular function[7,8]. This also reduces low-grade chronic inflammation, a key factor in aging and the progression of chronic diseases[6,9].

Beyond regulating autophagy, AMPK/mTOR modulation enhances cellular adaptation to stress, such as oxidative damage[15,16]. The interaction between these pathways is crucial for maintaining cellular quality and preventing premature aging[13,22].

Sirtuin modulation

Sirtuins, particularly SIRT1, are pivotal for longevity and cellular homeostasis. These NAD^+-dependent enzymes regulate processes including autophagy, stress responses, and inflammation[8,11]. During CR, increased NAD^+ levels activate SIRT1, which deacetylates specific proteins to enhance the formation and function of autophagosomes[13,22].

SIRT1 also deacetylates FOXO3, a transcription factor that upregulates genes involved in antioxidant defense and autophagy[8,11], and modulates p53 activity, reducing cellular senescence and promoting cellular longevity[11,22]. Furthermore, it activates PGC-1α, enhancing mitochondrial biogenesis and the capacity to handle oxidative stress[8,15,16]. Lastly, SIRT1 deacetylates NF-κB, reducing systemic inflammation[6]. These mechanisms collectively contribute to a healthy cellular environment, extending organismal lifespan[9,13].

Additional Processes Modulated by CR

CR influences diverse biological processes beyond mere caloric intake reduction. It triggers molecular and cellular adaptations that enhance metabolic health, reduce oxidative stress, lower inflammation, and optimize mitochondrial metabolism[1,3].

• Oxidative Stress Reduction: One of CR's most significant effects is the reduction of reactive oxygen species (ROS) production, which damages DNA, proteins, and lipids, contributing to cellular decline and chronic diseases[6,16]. CR increases the expression of antioxidant enzymes, such as superoxide dismutase and catalase, which neutralize ROS and protect against oxidative damage[15].

• Nrf2 Pathway Activation: CR activates Nrf2, a master regulator of antioxidant responses, increasing the expression of detoxifying and antioxidant genes. This maintains cellular redox balance and protects against oxidative stress, particularly important in preventing neurodegenerative and cardiovascular diseases[6,13].

• Chronic Inflammation Reduction: CR decreases pro-inflammatory cytokines such as IL-6, TNF-α, and C-Reactive Protein[6,9] and reduces NF-κB activation, a key mediator of chronic inflammation. Additionally, it promotes the clearance of senescent cells, which are a major source of inflammatory mediators[9,12].

• Mitochondrial Function Enhancement: With age, mitochondria deteriorate, reducing energy production capacity and increasing ROS generation. CR stimulates mitochondrial biogenesis, a process regulated by PGC-1α, enhancing ATP production efficiency and enabling mitochondria to better manage oxidative stress[15,16].

• Metabolic Shift: CR promotes a metabolic shift towards greater reliance on fatty acid oxidation and ketogenesis, improving energy efficiency and reducing lipid accumulation. This positively impacts insulin sensitivity and lowers the risk of metabolic diseases like type 2 diabetes[5,8,15]. CR also elevates NAD^+ levels, facilitating DNA repair, autophagy, and mitochondrial biogenesis[8,11].

• The mechanisms activated by CR provide pathways to prevent age-related chronic diseases and offer a promising foundation for developing therapeutic strategies in anti-aging medicine[3,27]. In this context, CRMs, by targeting some or all these biological mechanisms, emerge as potential therapeutic alternatives with practical applicability.

Natural Caloric Restriction Mimetics

Resveratrol

Resveratrol is a natural polyphenol found in foods such as the skin of red grapes, blueberries, blackberries, and peanuts[13,25]. It has drawn researchers' attention due to its antioxidant, anti-inflammatory, and cardioprotective properties[5,13].

It exhibits excellent ability to emulate some benefits of CR, making it an attractive option, particularly because it can stimulate autophagy through the following mechanisms:

• It increases NAD^+ levels, facilitating the activation of SIRT1, promoting the deacetylation of proteins that regulate autophagy[13,25], and inhibiting mTOR[8,15], encouraging cellular maintenance and recycling processes rather than growth. This helps eliminate damaged proteins and dysfunctional organelles, preventing the accumulation of cellular damage associated with aging[8,21].

• It activates the Nrf2 pathway, strengthening the antioxidant response by increasing the expression of enzymes like SOD, catalase, and glutathione peroxidase, reducing oxidative stress and inflammation, and protecting cells from ROS-induced damage[6,15]. This improves cellular health and contributes to better quality of life by reducing factors associated with the development of aging-related diseases.

Studies in animal models have shown that resveratrol improves mitochondrial function, reduces inflammation, and protects against metabolic diseases such as obesity and insulin resistance[8,13]. In mice fed a high-fat diet, it improved insulin sensitivity and reduced liver fat accumulation, demonstrating a protective effect against metabolic syndrome[13,15].

Preliminary clinical studies in humans indicate that it may improve endothelial function, reduce inflammation, and increase insulin sensitivity in patients with type 2 diabetes[5,15]. Although further research is needed to confirm these effects in larger populations over the long term, these findings suggest significant potential as a therapeutic agent to promote healthy aging and prevent associated chronic diseases[3,27].

Spermidine

Spermidine is a natural polyamine present in foods such as wheat germ, soy, mushrooms, and fermented products[5,25]. Polyamines are essential for cell proliferation, DNA stabilization, and the regulation of multiple biological processes, including autophagy and proteostasis[5,15].

Dietary intake of spermidine stimulates its action at the intestinal level; however, endogenous levels decrease with age, which has been associated with increased cellular deterioration and the development of aging-related diseases[13,25].

Its classification as a CRM is based on its actions through the following mechanisms:

• It inhibits acetyltransferases, promoting protein deacetylation, an essential step for autophagy activation, which facilitates the formation of autophagosomes and the degradation of damaged proteins and dysfunctional organelles[15,25].

• It regulates the mTOR pathway, reducing protein synthesis and favoring metabolic efficiency, like other CRMs[5,15].

• It contributes to maintaining protein stability, essential for preventing the accumulation of misfolded proteins associated with aging and neurodegenerative diseases[22,25]. It also improves mitochondrial function by reducing ROS production and promoting the elimination of dysfunctional mitochondria through mitophagy, thereby improving long-term cellular health[15,16].

The latest findings have suggested that spermidine is likely to promote an increase in telomerase activity[14], which strengthens its favorable status as an anti-aging agent.

In animal studies, supplementation has been shown to extend lifespan by inducing autophagy, reducing oxidative stress, and improving cognitive function[15,25].

In humans, higher intake of spermidine-rich foods is associated with lower cardiovascular mortality, better cognitive performance, and lower incidence of aging-related diseases, suggesting a positive impact on longevity and quality of life[5,13,15,25].

In the Table 1, resveratrol and spermidine are compared, considering their characteristics, mechanisms of action, biological effects, and available experimental evidence.

Table 1. Comparing the differences and similarities between resveratrol and spermidine. (Own elaboration).

Characteristic Resveratrol Spermidine
Origin Polyphenol found in grapes, red fruits, and peanuts Natural polyamine found in wheat germ, soy, mushrooms, and fermented foods
Main Mechanism of Action Activation of SIRT1 Inhibition of acetyltransferases
Activated Signaling Pathways Activation of SIRT1 and Nrf2 Inhibition of mTOR, stabilization of proteostasis
Impact on Autophagy Inhibits mTOR through SIRT1 activation, enhances autophagy Induces autophagy by inhibiting acetyltransferases
Antioxidant Effects Increases expression of antioxidant genes via the Nrf2 pathway Promotes antioxidant response and reduces oxidative stress
Reduction of Inflammation Inhibits NF-κB, reducing chronic inflammation Decreases inflammation by enhancing autophagy and removing damaged proteins
Mitochondrial Protection Improves mitochondrial function and reduces ROS production Optimizes mitochondrial function and promotes mitophagy
Evidence in Animal Models Extends lifespan and improves metabolic health in mice Prolongs lifespan in flies, nematodes, and mice; enhances cognitive function
Evidence in Humans Improves endothelial function and insulin sensitivity in type 2 diabetes patients Associated with lower cardiovascular mortality and better cognitive function in older adults
Bioavailability Limited, requires formulations to enhance absorption High bioavailability through dietary intake
Safety and Adverse Effects Well-tolerated in moderate doses, but bioavailability is a challenge Considered safe, associated with positive effects on cognition and cardiovascular health

Synthetic Caloric Restriction Mimetics

Metformin

Metformin is a widely used drug for the treatment of type 2 diabetes due to its ability to improve insulin sensitivity and reduce blood glucose levels[7]. It has pleiotropic effects that may influence aging and longevity[3]. Studies suggest that metformin could reduce the risk of chronic diseases such as cancer, cardiovascular diseases, and neurodegenerative conditions[5,6].

It has a well-established safety profile, making it an attractive option for use in older adults to improve metabolic health and potentially extend longevity[5,27].

Its potential as a CRM lies in its ability to activate AMPK, which leads to mTOR inhibition[7]. This promotes autophagy, reduces oxidative stress, and mitigates metabolic dysfunction—key factors in aging[15,22].

Metformin also activates the SKN-1/Nrf2 pathway, which regulates genes that increase the expression of antioxidant and detoxifying enzymes[6], protecting cells from oxidative damage and reducing chronic inflammation[6,13].

In animal models, metformin prolongs lifespan, improves mitochondrial function, and reduces systemic inflammation[5,22].

In humans, observational studies indicate that diabetic patients treated with metformin have a lower incidence of age-related diseases and greater life expectancy compared to patients treated with other antidiabetic drugs[5,6]. One study found that diabetic patients taking metformin had a longer life expectancy than even non-diabetic individuals not treated with metformin[3,5].

Ongoing clinical trials are investigating its potential to extend lifespan in non-diabetic older adults, exploring its impact on the prevention of aging-related diseases[5,27].

Rapamycin

Also known as sirolimus, rapamycin is a macrolide isolated from a soil bacterium found on Easter Island. Originally developed as an immunosuppressant to prevent organ transplant rejection, it has shown potential as an anti-aging agent due to its ability to extend lifespan in animal models[15,21].

Its potential activity as a CRM focuses on the inhibition of mTORC1, which promotes autophagy independently of sirtuins[5,8]. This process suppresses protein synthesis, redirecting cellular resources toward repair and maintenance, facilitating the clearance of damaged proteins and dysfunctional organelles[5,21].

Additionally, it modulates inflammatory pathways associated with aging and chronic diseases[5,6]. It reduces NF-κB activity, decreasing systemic inflammation[6]. Its capacity to inhibit mTOR also contributes to regulating cellular apoptosis, limiting tissue damage associated with aging[5,8].

Animal studies show that rapamycin extends lifespan, improves insulin sensitivity and metabolic health, and reduces the incidence of tumors and neurodegenerative diseases[15,21].

In humans, preclinical trials suggest similar benefits, although its use requires further investigation to evaluate long-term safety due to its immunosuppressive effects[15,27].

A detailed comparison of the characteristics, mechanisms of action, and experimental evidence between metformin and rapamycin is presented in Table 2.

Table 2. Comparing the differences and similarities between metformin and rapamycin. (Own elaboration)

Characteristics Metformin Rapamycin
Clinical Use Antidiabetic drug used to treat type 2 diabetes Immunosuppressant used to prevent organ transplant rejection
Primary Mechanism of Action Activation of AMPK Inhibition of mTOR
Signaling Pathways Targeted Activation of AMPK, Inhibition of mTOR Direct inhibition of mTORC1
Impact on Autophagy Promotes autophagy by activating AMPK and inhibiting mTOR Strongly induces autophagy by inhibiting mTOR independently of SIRT1
Effects on Inflammation Reduces inflammation by activating Nrf2 and inhibiting NF-κB Reduces chronic inflammation and apoptosis

Characteristics Metformin Rapamycin
Mitochondrial Protection Improves mitochondrial function, reduces ROS Enhances mitophagy, reduces mitochondrial damage
Evidence in Animal Models Extends lifespan, improves metabolic health in mice Prolongs lifespan, reduces tumors, and protects against neurodegeneration
Evidence in Human Studies Associated with reduced incidence of age-related diseases in diabetics Currently under investigation for age-related health benefits
Potential Side Effects Generally safe, but may cause gastrointestinal issues Potential immunosuppressive effects, increased risk of infections

Discussion

The principal CRMs were compared, categorized into natural and synthetic agents, with a focus on their activity as autophagy modulators—considered the primary anti-aging mechanism promoted by CR—and their therapeutic utility for delaying aging and treating associated chronic diseases.

This analysis considered various characteristics to evaluate the different compounds reviewed:

1. Efficacy in Autophagy Modulation

Autophagy, as an essential cellular process for recycling and maintaining homeostasis, is critical in aging and chronic diseases[13,22]. Both natural and synthetic agents effectively induce autophagy, though they differ in mechanisms of action and efficacy.

Natural agents induce autophagy through distinct pathways. Resveratrol activates SIRT1 and Nrf2, enhancing the antioxidant response and reducing inflammation[8,13]. Spermidine inhibits acetyltransferases and modulates mTOR, promoting the clearance of damaged proteins and improving proteostasis[15,25].

Synthetic agents are potent autophagy inducers, acting through more specific and direct routes. Metformin activates AMPK, inhibits mTOR, and improves mitochondrial function[5,7]. Rapamycin directly inhibits mTORC1, triggering a powerful autophagic response to eliminate dysfunctional organelles and damaged proteins[15,21].

In terms of efficacy, synthetic agents are more potent in inducing autophagy due to their direct action on mTOR inhibition[21]. However, natural agents offer the advantage of activating multiple pathways, potentially providing additional benefits such as reducing oxidative stress and improving metabolic health[15,25].

2. Safety and Bioavailability

One of the main challenges in using these compounds, both natural and synthetic, is bioavailability and safety profiles, particularly for long-term application in humans.

Resveratrol, while safe at moderate doses, has low bioavailability due to rapid metabolism and elimination[13,15], limiting its clinical efficacy unless formulations improve absorption. Spermidine has higher bioavailability when ingested through diet and has been shown to be safe even in long-term human studies[12].

Metformin is well-tolerated and has significant usage experience in type 2 diabetes, though it may cause gastrointestinal side effects[3,5]. Rapamycin, despite its effectiveness, has a more complex adverse effect profile, including immunosuppression, which increases the risk of infections[15,21].

Overall, natural agents are safer and better tolerated for prolonged use, although their efficacy is limited by bioavailability challenges[15,13]. Synthetic agents, while more potent, require careful monitoring due to their potential side effects[5,15].

3. Clinical Applications and Therapeutic Potential

The therapeutic potential of CRMs in anti-aging is the focus of extensive research. Their clinical applicability depends on their ability to induce autophagy, safety, impact on longevity, and prevention of aging-related diseases.

Resveratrol and spermidine could be used as safe dietary supplements to enhance metabolic health and delay aging[13,25], potentially serving as a preventive strategy for older adults seeking to improve quality of life without resorting to more aggressive drugs[5,15].

Metformin has demonstrated reduced incidence of chronic diseases such as cancer and cardiovascular conditions in diabetic patients[3,5]. Ongoing trials are evaluating its impact on longevity in non-diabetic individuals.

Rapamycin, still in experimental stages due to its immunosuppressive effects, is less applicable for healthy individuals[5,21] although it has been suggested that this could be improved through an intermittent dosing regimen[14].

Natural compounds could be more easily integrated as dietary supplements due to their safety profile[13,25], while synthetic agents may have more restricted applications, targeting specific populations at high risk of aging-related diseases[5,15]. In the future, one of these substances might be routinely used in anti-aging medicine following clinical research to establish its safety.

Advantages and Limitations of CRMs

CRMs mimic the benefits of CR without its challenges. However, both natural and synthetic agents present advantages and limitations.

Natural Agents:

These stand out for their safety and dietary availability[13,25]. They improve mitochondrial function, reduce inflammation, and activate multiple pathways such as SIRT1 and Nrf2, promoting cellular protection[6,15]. However, they face bioavailability issues[13,15], and further studies are needed to establish optimal doses and long-term effects in humans[25].

Synthetic Agents:

These are highly effective. Metformin is safe but can cause gastrointestinal issues and, in some cases, reduced vitamin B12 absorption[29]. Rapamycin, while effective in promoting autophagy and improving metabolic health, has immunosuppressive effects that increase infection risk[15,21], making it inadvisable for routine use.

Regarding the research conducted, it presents certain limitations that deserve discussion. Firstly, the review predominantly relies on preclinical studies conducted in animals, which poses a challenge for extrapolation to humans. While animal models provide valuable insights into molecular mechanisms, their physiological differences limit the generalizability of the findings. Furthermore, variability in the experimental protocols used in the studies complicates direct comparisons of the results.

Another significant limitation is the lack of longitudinal studies in humans evaluating the long-term impact of CRMs. Most of the reviewed studies are characterized by small sample sizes and limited follow-up periods, which restrict the ability to assess prolonged effects. The available data on potential adverse effects are insufficient to establish a solid safety profile.

Lastly, a lack of integration between experimental and clinical approaches was identified. While preclinical studies emphasize molecular mechanisms, clinical trials rarely measure the same biomarkers, creating a gap in translational interpretation

Challenges and Future Directions in Research

Despite advances in CRM research, significant challenges remain for their clinical implementation as anti-aging interventions. The lack of longitudinal studies in humans confirming their long-term effects on longevity and health is a critical obstacle.

Limited bioavailability of natural agents is another significant challenge[15,25]. Enhancing their absorption and stability through advanced formulations or pharmaceutical delivery technologies is crucial[13,15].

Dosage optimization to maximize benefits without adverse effects is essential, especially for compounds with complex safety profiles. Controlled clinical trials are indispensable for establishing safe and effective long-term parameters with larger population samples that evaluate both the benefits and risks, with a particular focus on key biomarkers, and adopting comparative designs that analyze combinations of natural and synthetic CRMs, assessing possible synergies between them.

CRMs represent an emerging paradigm in anti-aging medicine, allowing intervention in the underlying biological processes driving aging and associated diseases. If optimized, they could significantly impact the prevention of chronic pathologies such as cardiovascular diseases, cancer, and neurodegenerative conditions[6,9], which have a significant incidence in populations over 50, posing a substantial economic burden on healthcare systems.

Metformin could be repurposed as a preventative treatment to reduce the risk of age-related diseases in healthy people. In the case of rapamycin, further studies are required for its safe use, as well as trials to determine whether its intermittent administration could mitigate undesired effects[14], and it could be a valuable option to prevent mitochondrial dysfunction and chronic inflammation that are a driving force behind health problems associated with aging.

The therapeutic combination of natural and synthetic compounds could offer a synergistic approach, maximizing benefits and minimizing risks[13,25]. Personalized strategies based on genetic and metabolic profiles could transform anti-aging medicine into a more effective and individually tailored approach. With adequate research, CRMs have the potential to revolutionize chronic disease prevention, improve health, and extend longevity.

Conclusions

Research on CRMs has shown that both natural and synthetic agents are promising tools for inducing autophagy and promoting longevity. These compounds act by modulating key molecular pathways such as AMPK, mTOR, and SIRT1, improving metabolic parameters, reducing chronic inflammation, preventing aging-related diseases, and potentially extending lifespan.

Aging is one of the primary risk factors for developing chronic metabolic diseases, cardiovascular diseases, cancer, and neurodegenerative conditions. CRMs offer an innovative approach to address these pathologies by targeting the cellular mechanisms driving aging.

By inducing autophagy and reducing cumulative cellular damage, they can slow the aging process and extend healthy life. This implies not only living longer but also with better quality of life, reducing reliance on costly medical treatments and improving overall well-being.

Optimizing bioavailability by improving the absorption and stability of natural compounds and their dosing is essential to expand their clinical effectiveness. Developing new formulations and delivery systems could make these compounds more accessible and effective.

The effective combination of natural and synthetic agents to maximize benefits without increasing the risk of side effects represents a new approach, potentially including personalization based on individual genetic and metabolic profiles.

References

1. Anson RM, Jones B, de Cabo R. The diet-mimetic effect of intermittent fasting on slow-aging processes. Cell Metab. 2005;2(1):25-35. Doi: 10.1016/j.cmet.2005.06.001.

2. Speakman JR, Mitchell SE. Caloric restriction. Mol Aspects Med. 2011;32(3):159-221. doi: 10.1016/j.mam.2011.07.001.

3. López-Otín C, Galluzzi L, Freije JM, Madeo F, Kroemer G. Metabolic control of longevity. Cell. 2016;166(4):802-821. Doi: 10.1016/j.cell.2016.07.031.

4. Fontana L, Partridge L, Longo VD. Extending healthy lifespan—from yeast to humans. Science. 2010;328(5976):321-326. Doi: 10.1126/science.1172539.

5. Martel J, Chang SH, Wu CY, Peng HH, Hwang TL, Ko YF, Young JD, Ojcius DM. Recent advances in the field of caloric restriction mimetics and anti-aging molecules. Ageing Res Rev. 2021;66:101240. Doi: 10.1016/j.arr.2020.101240.

6. Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. Nat Rev Endocrinol. 2018;14(10):576-590. Doi: 10.1038/s41574-018-0059-4.

7. Hardie DG. AMP-activated protein kinase: an energy sensor that regulates all aspects of cell function. Genes Dev. 2011;25(18):1895-1908. Doi: 10.1101/gad.17420111.

8. Madeo F, Zimmermann A, Maiuri MC, Kroemer G. Essential role for autophagy in lifespan extension. J Clin Invest. 2015;125(1):85-93. Doi: 10.1172/JCI73946.

9. Madeo F, Carmona-Gutierrez D, Hofer SJ, Kroemer G. Caloric restriction mimetics against age-associated disease: targets, mechanisms, and therapeutic potential. Cell Metab. 2019;29(3):592-610. Doi: 10.1016/j.cmet.2019.01.001.

10. Speakman JR, Hambly C. Starving for life: what animal studies can and cannot tell us about the use of caloric restriction to prolong human lifespan. J Nutr. 2007;137(4):1078-1086. Doi: 10.1093/jn/137.4.1078.

11. Imai S, Guarente L. NAD+ and sirtuins in aging and disease. Trends Cell Biol. 2014;24(8):464-471. Doi: 10.1016/j.tcb.2014.04.002.

12. Haigis MC, Sinclair DA. Mammalian sirtuins: biological insights and disease relevance. Annu Rev Pathol. 2010;5:253-295. Doi: 10.1146/annurev.pathol.4.110807.092250.

13. Madeo F, Eisenberg T, Pietrocola F, Kroemer G. Spermidine in health and disease. Science. 2018;359(6374). Doi: 10.1126/science.aan2788.

14. Nassar K, El-Mekawey D, Elmasry AE, Refaey MS, El-Sayed Ghoneim M, Elshaier YAMM. The significance of caloric restriction mimetics as anti-aging drugs. Biochem Biophys Res Commun. 2024;692:149354. Doi: 10.1016/j.bbrc.2023.149354

15. Yessenkyzy A, Saliev T, Zhanaliyeva M, Masoud AR, Umbayev B, Sergazy S, Krivykh E, Gulyayev A, Nurgozhin T. Polyphenols as Caloric-Restriction Mimetics and Autophagy Inducers in Aging Research. Nutrients. 2020;12(5):1344. Doi: 10.3390/nu12051344.

16. Longo VD, Panda S. Fasting, circadian rhythms, and time-restricted feeding in healthy lifespan. Cell Metab. 2016;23(6):1048-1059. Doi: 10.1016/j.cmet.2016.06.001.

17. Madeo F, Zimmermann A, Maiuri MC, Kroemer G. Essential role for autophagy in lifespan extension. J Clin Invest. 2015;125(1):85-93. Doi: 10.1172/JCI73946.

18. Pang L, Jiang X, Lian X, Chen J, Song EF, Jin LG, Xia ZY, Ma HC, Cai Y. Caloric restriction-mimetics for the reduction of heart failure risk in aging heart: with consideration of gender-related differences. Mil Med Res. 2022;9(1):33. Doi: 10.1186/s40779-022-00389-w

19. Gabandé-Rodríguez E, Gómez de Las Heras MM, Mittelbrunn M. Control of Inflammation by Calorie Restriction Mimetics: On the Crossroad of Autophagy and Mitochondria. Cells. 2019;9(1):82. Doi: 10.3390/cells9010082.

20. Rubinsztein DC, Marino G, Kroemer G. Autophagy and aging. Cell. 2011;146(5):682-695. Doi: 10.1016/j.cell.2011.07.030.

21. Selman C, Tullet JM, Wieser D, et al. Ribosomal protein S6 kinase 1 signaling regulates mammalian lifespan. Science. 2009;326(5949):140-144. Doi: 10.1126/science.1177221.

22. Sharma, A., & Singh, A. K. Molecular mechanism of caloric restriction mimetics-mediated neuroprotection of age-related neurodegenerative diseases: an emerging therapeutic approach. Biogerontology 2023;24(5): 679–708. Doi:10.1007/S10522-023-10045-Y

23. Cuervo AM, Wong E. Chaperone-mediated autophagy: roles in disease and aging. Cell Res. 2014;24(1):92-104. Doi: 10.1038/cr.2013.153.

24. Sandri M. Protein breakdown in muscle wasting: role of autophagy-lysosome and ubiquitin-proteasome pathways. Nat Rev Mol Cell Biol. 2013;14(6):345-350. Doi: 10.1038/nrm3606.

25. Martin-Montalvo A, Mercken EM, Mitchell SJ, et al. Metformin improves healthspan and lifespan in mice. Nat Commun. 2013;4:2192. doi: 10.1038/ncomms3192.

26. Fontana L, Partridge L, Longo VD. Extending healthy life span—from yeast to humans. Science. 2010;328(5976):321-326. Doi: 10.1126/science.1172539.

27. Levine B, Kroemer G. Autophagy in the pathogenesis of disease. Cell. 2008;132(1):27-42. Doi: 10.1016/j.cell.2007.12.018.

28. Maiuri MC, Zalckvar E, Kimchi A, Kroemer G. Self-eating and self-killing: crosstalk between autophagy and apoptosis. Nat Rev Mol Cell Biol. 2007;8(9):741-752. Doi: 10.1038/nrm2239.

29. Sánchez H, Masferrer D, Lera L, Arancibia E, Ángel B, Albala C. Vitamin B12 deficiency associated with high doses of metformin in diabetic older adults. Nutr Hosp. 2014;29(6):1394-400. Doi: 10.3305/nh.2014.29.6.7405.