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Fasting and Autophagy: Clinical Significance for Longevity

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Abstract

Within this article, autophagy mechanisms in aging receive evaluation. Relevance arises from evidence that impaired autophagic flux accelerates cellular senescence and contributes to age-associated pathologies such as neurodegeneration, cardiomyopathy and metabolic dysfunction. Novel contributions encompass identification of phytochemical-triggered autophagic pathways in tissues. The study describes stages of autophagic processing, examines activation induced by caloric restriction, intermittent fasting, bioactive compounds including resveratrol, spermidine, sulforaphane. Attention directed toward tissue-specific autophagic dynamics in hepatic, cardiac, skeletal muscle and neuronal systems. The work sets objective to elucidate interactions between dietary interventions and autophagic regulation in lifespan extension. To achieve this, literature review combined with comparative and analytical approaches across preclinical models and human trials. Sources from Madeo, Morselli, Linton, Damulewicz, Plafker, Ke, Czaja, Lim, Park, Wang, Li and Palmer underwent analysis. Conclusions describe potential of plant-centric diets integrated with time-restricted feeding to enhance autophagic efficiency. Findings offer resources for researchers developing autophagy-based therapeutic strategies.

Keywords: *Autophagy, Aging, Caloric Restriction, Intermittent Fasting, Phytochemicals, Resveratrol, Sulforaphane, Mitophagy, Lifespan Extension, Tissue Specificity.*

INTRODUCTION

Extensive evidence links autophagic dysfunction with accelerated cellular senescence and emergence of age-related disorders, including neurodegenerative, cardiovascular and metabolic diseases. Strategies to activate autophagy through dietary restriction and phytochemical interventions have demonstrated potential to improve proteostasis and organ function across taxa. Effective translation of these findings to clinical settings requires comprehensive synthesis of molecular mechanisms and intervention outcomes.

1) The present study aims to elucidate interactions between dietary regimens and autophagic regulation in the context of aging. Research objectivesencompass:
2) Characterization of autophagic flux modulation by caloric restriction, intermittent fasting and bioactive compounds.
3) Comparative analysis of tissue-specific autophagic responses in hepatic, cardiac, skeletal muscle and neuronal systems.
4) Evaluation of preclinical and clinical evidence supporting autophagy-mediated lifespan extension through dietary interventions.

Novel contributions include integration of recent findings on phytochemical-induced autophagy pathways and identification of gaps in biomarker development for tissue-selective autophagic assessment. The synthesis provides foundation for targeted design of dietary and pharmacological approaches to promote healthy longevity.

MATERIALS AND METHODS

The article draws on multiple researchers' studies to analyze autophagy's role in aging. F. Madeo [7] established autophagy's significance in lifespan extension across organisms. E. Morselli [8] demonstrated that calorie restriction and resveratrol activate autophagy via SIRT1 pathways. P.-J. Linton [6] explored autophagy mechanisms in cardiomyocytes and their implications in cardiac pathologies. M. Damulewicz [2] investigated ne uron-glia interactions regulated by autophagy. K.S. Plafker [11] illustrated sulforaphane-induced activation of autophagy pathways. P.-Y. Ke [3] and M.J. Czaja [1] studied hepatic autophagic processes in health and disease contexts. S.H.Y. Lim [5] described mechanisms underlying autophagy decline with aging. S.H. Park [10] presented data on dietary influences on aging. C. Wang [13] investigated physical activity's effects on autophagy-related proteins in aging skeletal muscle. P. Li [4] characterized age-associated autophagy alterations in muscle and neurons. S. Verma[12] and J.E. Palmer [9] reviewed neuronal autophagy mechanisms and related pathologies.

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Systematic literature review, comparative, and analytical methods were employed to summarize findings and identify key trends.

RESULTS

The autophagic process occurs through a sequential series of highly regulated stages involving initiation, elongation, maturation, and degradation. An isolation membrane, termed phagophore, emerges beneath specific cellular regions and progressively enlarges to envelop cytoplasmic constituents—for example, malfunctioning organelles and aggregated proteins. Upon completion of its enclosure, the bilayer vesicle adopts an autophagosome identity before merging with lysosomal vesicles to form an autolysosome, where resident hydrolases dismantle the internalized material (Figure 1).

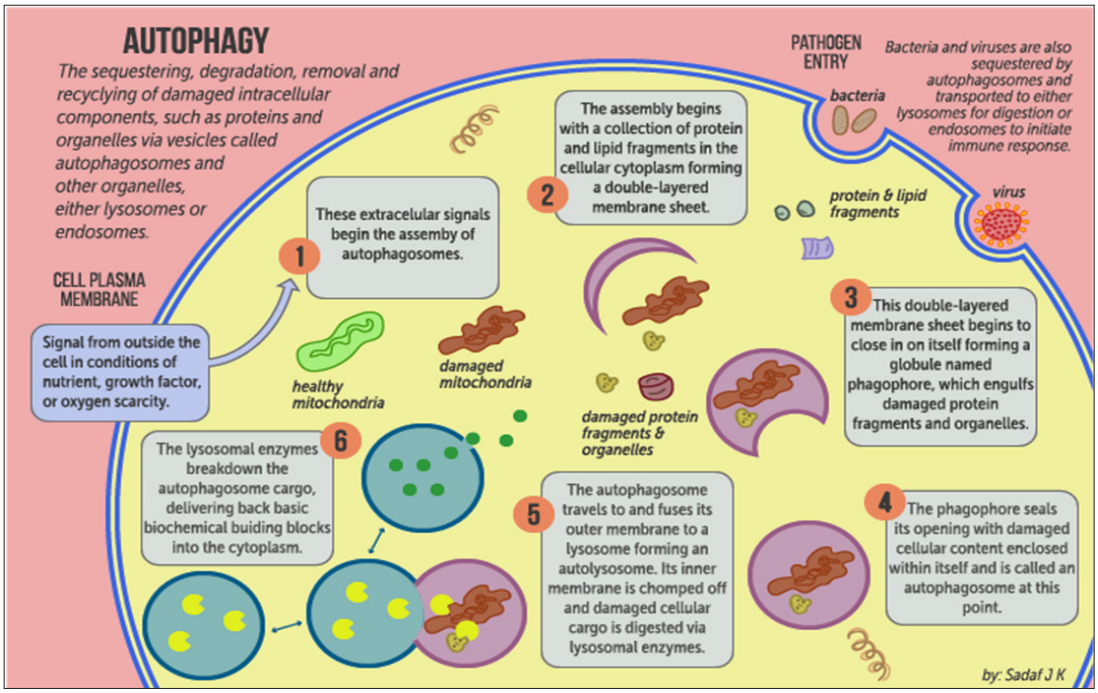

Figure 1. The autophagy process [12]

Seamless progression through each stage preserves intracellular equilibrium; when autophagic throughput falters, cellular aging accelerates and various disorders arise, for example neurodegenerative syndromes, neoplastic growths and metabolic dysfunctions. In-depth examination of molecular pathways governing phagophore nucleation, autophagosome maturation and autolysosomal degradation reveals therapeutic avenues for reinstating or augmenting autophagic capacity.

Autophagy is a fundamental cellular recycling mechanism activated by nutrient deprivation and metabolic stress. By removing damaged macromolecules and organelles, autophagy maintains cellular homeostasis and proteostasis. Experimental models show that reduced autophagy accelerates aging, whereas enhanced autophagy delays aging and extends lifespan in yeast, worms, flies and mice [5]. In mammals, caloric restriction (CR) and intermittent fasting (IF) activate autophagy via inhibition of mTOR and activation of AMPK/SIRT1 pathways, leading to improved cellular stress resistance. Notably, the longevity benefits of CR and of CR-mimetic compounds (e.g. resveratrol) are abolished when key autophagy genes are knocked down, indicating that autophagy is required for fasting-mediated lifespan extension. This suggests that dietary interventions and phytochemicals which induce autophagy may contribute to healthy longevity [8].

Multiple studies confirm that fasting or CR extend lifespan in model organisms by inducing autophagy. For example, in C. elegans and mice, genetic inhibition of autophagy (e.g. by BECN1/Beclin1 knockdown) abolishes lifespan extension normally seen with CR or with SIRT1 activators. Pharmacologically, resveratrol (a SIRT1-activating polyphenol) stimulates autophagy and extends lifespan in yeast and nematodes [7]. Similarly, spermidine (a polyamine) delays aging and increases lifespan in flies and mammals via autophagy induction. These data indicate that autophagy is a necessary component of the pro-longevity effects of dietary restriction. Mechanistically, fasting lowers insulin/IGF1 signaling and activates AMPK/FOXO pathways, which upregulate autophagy genes and mitochondrial turnover [8].

In addition to fasting, certain plant-derived compounds can trigger autophagy pathways. Sulforaphane (from cruciferous vegetables) acts as a calorie-restriction mimetic: it activates NRF2 and AMPK, increases NAD^+, and upregulates autophagy-related proteins, mimicking the nutrient-deprivation state [11]. Curcumin and other polyphenols similarly inhibit mTOR and stimulate AMPK/ULK1, inducing autophagy in various cell types. Resveratrol specifically induces mitophagy via SIRT1-mediated deacetylation of autophagy proteins. Importantly, these phytochemicals often have additive effects with fasting: combined administration of such compounds with CR does

not further extend lifespan in autophagy-deficient models, underscoring a shared mechanism. Thus, a plant-rich diet can deliver bioactive molecules that independently promote autophagy and contribute to healthspan.

Activation of autophagy exhibits tissue-specific patterns driven by distinct metabolic demands and stress signals. In cardiac muscle, high energetic requirements necessitate continuous autophagic turnover to preserve mitochondrial quality and contractile performance. Hepatocytes engage lipophagy and support gluconeogenesis under nutrient scarcity through ULK1-mediated initiation and enhanced lysosomal biogenesis. Skeletal muscle fibers display divergent autophagic flux, with oxidative (type I) fibers relying on elevated mitochondrial turnover via FoxO3/PGC-1α signaling. Neuronal cells require constitutive macroautophagy for proteostasis, while glial autophagy contributes to metabolic coupling and clearance of cellular debris (Table 2).

Table 2. Interorgan specificity of autophagy activation [1-4; 6; 9; 13]

Tissue	AutophagyFunction	Key Mechanisms	PathologicalContext
Cardiac	Removes damaged proteins and organelles to maintain contractile function and mitochondrial integrity	Parkin/p62-mediated mitophagy; mTOR inhibition; AMPK activation	Ischemia–reperfusion injury; age-related hypertrophy and heart failure
Hepatic	Regulates lipid droplet degradation (lipophagy) and gluconeogenesis under nutrient deprivation	ULK1 activation; enhanced lysosomal biogenesis; PPARα–lysosome crosstalk	Nonalcoholic steatohepatitis; hepatic steatosis and inflammation
Skeletalmuscle	Mediates mitochondrial turnover and protein quality control to prevent sarcopenia	FoxO3/PGC-1α signaling; AMPK-ULK1 pathway activation	Aging-related muscle atrophy; impaired metabolic function
Central nervoussystem	Clears aggregate-prone proteins and maintains synaptic vesicle turnover	ATG gene-dependent macroautophagy; LC3-associated phagocytosis in astrocytes	Neurodegeneration; cognitive deficits; neuroinflammatory responses

Recognition of these organ-specific autophagic mechanisms informs targeted therapeutic strategies that modulate autophagy in a tissue-selective manner for the treatment of age-related and metabolic diseases. Further studies must elucidate inter-tissue communication pathways coordinating systemic autophagic responses and develop biomarkers to assess tissue-specific autophagy status in clinical settings.

Plant-based diets tend to be lower in calories and higher in fiber and phytochemicals than typical omnivorous diets. This can create a state of "metabolic fasting" by improving satiety with fewer calories. Moreover, the nutrients in vegan foods (e.g. flavonoids in berries, isothiocyanates in greens) may enhance fasting responses. Intermittent or time-restricted feeding regimens (such as 16:8) further prolong the daily fasting window, intensifying autophagy induction. Epidemiologic studies of long-lived populations (e.g. Blue Zones) often reveal a combination of plant-centered eating and some form of periodic fasting [10]. Figure 3 illustrates how different diets and feeding schedules affect biomarkers of aging in model organisms and humans.

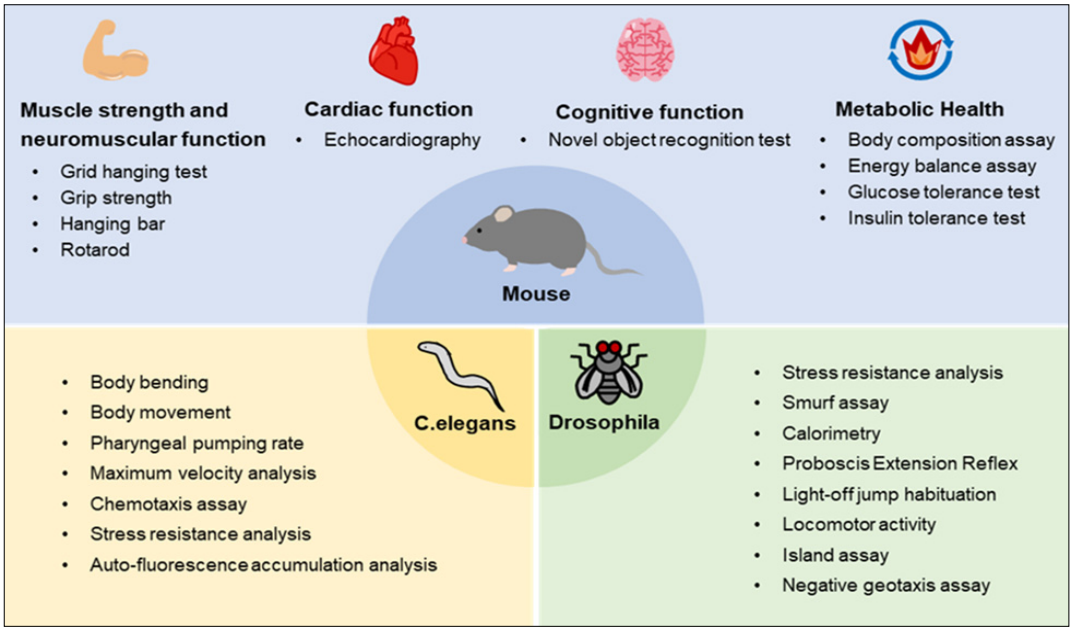

Figure 3. Evaluation of healthspan in aged model organisms. Morselli et al. defined behavioral and physiological tests (e.g. grip strength, glucose tolerance) to assess aging phenotypes in C. elegans, Drosophila, and mice [10]

Indeed, human trials show that even short-term fasting-mimicking diets or combined vegan fasting interventions improve metabolic and inflammatory markers associated with aging (e.g. reduced IGF-1, increased insulin sensitivity), which are linked to longevity.

DISCUSSION

The evidence converges on autophagy as a central mechanism connecting diet to longevity. By clearing cellular debris and supporting mitochondrial quality control, autophagy delays the onset of age-related dysfunction. Plant-based diets naturally supply compounds that activate autophagy regulators (e.g. sirtuins, AMPK) independent of caloric load. For example, sulforaphane and curcumin induce autophagy even without fasting, complementing the effects of nutrient restriction. Combining a vegan dietary pattern with time-restricted feeding may thus amplify cellular cleaning processes. Clinically, this could translate into lower incidence of metabolic, cardiovascular and neurodegenerative diseases. Indeed, CR and fasting have been shown to improve cardiac function, cognitive performance, and immune regulation in animal studies, largely via autophagy pathways.

However, translating these benefits to humans poses challenges. Long-term compliance to fasting is difficult, and complete caloric deprivation has risks. Plant diets must be properly balanced to avoid deficiencies (notably vitamin B_{12} and maybe protein quality). Future studies should focus on the feasibility and efficacy of combined approaches (e.g. a vegan Mediterranean diet with daily time-restricted eating) in improving longevity biomarkers. Optimizing the dose and timing of phytonutrient-rich foods alongside modest fasting regimens could harness maximal autophagic benefit while maintaining nutritional adequacy.

CONCLUSION

Autophagy is a key mediator of the life- and healthspan-extending effects of fasting, CR, and related interventions. Plant-derived compounds such as resveratrol, curcumin and sulforaphane can activate this same pathway, offering fasting-independent boosts to cellular rejuvenation. Integration of a nutrient-rich vegan regimen with intermittent fasting intervals, for instance time-restricted eating, demonstrates considerable promise for extending lifespan. Laboratory experiments and epidemiological investigations converge on diets built around whole-plant items, narrow feeding windows and heightened phytochemical exposure to activate autophagic pathways and slow cellular senescence. Controlled clinical trials remain essential to verify these regimens and to establish precise dietary and fasting parameters that maximize human longevity.

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