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AVTOFAGIJA: SKUPNI MEHANIZEM UČINKOV POSTA IN FITOKANABINOIDOV

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Avtofagija je evolucijsko ohranjen mehanizem celične obnove, ki ima ključno vlogo pri vzdrževanju presnovnega ravnovesja in odzivanju na fiziološki stres. Sodobni prehranski vzorci, za katere je značilno pogosto in pretirano vnašanje hrane, lahko porušijo te prilagoditvene mehanizme ter prispevajo k razvoju presnovnih motenj. Človek pa se je razvijal v razmerah občasnega pomanjkanja hrane, v katerih se je aktivirala avtofagija, kar je predstavljalo pomembno evolucijsko prednost. Post povzroči blag presnovni stres (hormeza), ki aktivira citoprotektivne poti in poveča celično odpornost. Podobno so študije pokazale tudi za več rastlinskih spojin, vključno s fitokanabinoidi, da vplivajo na uravnavanje avtofagije v zdravih in tumorskih celicah. Čedalje več dokazov kaže, da kanabinoidi večinoma aktivirajo avtofagijo in zato veljajo za potencialne modulatoje celične homeostaze. Razumevanje skupnih mehanizmov, preko katerih tako post kot fitokanabinoidi inducirajo avtofagijo, lahko prispeva k razvoju terapevtskih pristopov, usmerjenih v presnovno neravnovesje, vnetne procese in potek določenih bolezni. Koordinirana in časovno pravilno odmerjena aktivacija avtofagije bi lahko predstavljala obetavno možnost za optimizacijo zdravja.

Znanstvena veda:
Biotehnika

Ključne besede:
avtofagija,
fitokanabinoidi,
post,
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Autophagy: The Shared Mechanism Between Fasting and Phytocannabinoids

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Autophagy is a conserved cellular self-renewal process essential for maintaining metabolic balance and responding to physiological stress. Modern dietary patterns, characterized by frequent and excessive food intake, often disrupt these adaptive mechanisms and contribute to metabolic disorders. In contrast, humans evolved under conditions of intermittent food scarcity, during which fasting-induced autophagy provided a survival advantage. Fasting generates mild metabolic stress (hormesis) that activates cytoprotective pathways and enhances cellular resilience. Similarly, several plant-derived compounds, including phytocannabinoids, have been shown to modulate autophagy in both healthy and tumour cells. Emerging evidence indicates that cannabinoids predominantly promote autophagic activity, positioning them as potential modulators of cellular homeostasis. Understanding the shared mechanisms through which fasting and phytocannabinoids induce autophagy may help inform therapeutic strategies targeting metabolic dysregulation, inflammation, and disease progression. Coordinated, well-timed activation of autophagy may therefore offer promising avenues for health optimisation.

Science:
Biotechnology

Keywords:
Autophagy,
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Fasting,
Cellular homeostasis,
Hormesis.

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1 Introduction

Modern dietary patterns in Western societies are characterized by frequent food intake and chronic caloric excess, conditions that contrast sharply with the environment in which humans evolved. For most of human history, intermittent periods of food scarcity shaped metabolic adaptations that supported survival during fasting. One of the most important of these adaptive mechanisms is autophagy, an evolutionarily conserved intracellular recycling process that maintains cellular integrity and homeostasis during nutrient deprivation. Autophagy enables cells to degrade damaged organelles, misfolded proteins, and other cytoplasmic material within autophagosomes that subsequently fuse with lysosomes for degradation and reuse of components. These fundamental mechanisms were clarified through major discoveries recognized by Nobel Prizes awarded to Christian de Duve (de Duve 1963) in 1974 and Yoshinori Ohsumi in 2016 (Takeshige et al., 1992; Ohsumi 2014).

Fasting is one of the strongest non genetic inducers of autophagy. During nutrient restriction, the body initiates a hormetic stress response that activates cytoprotective pathways, enhances metabolic efficiency, reduces inflammation, and promotes cellular renewal. A wide range of fasting regimens, including intermittent fasting, periodic fasting, and therapeutic fasting, have demonstrated benefits for metabolic homeostasis, immune modulation, neuroprotection, and markers of healthy ageing in preclinical and clinical studies (Longo and Mattson 2014; Mattson et al. 2018).

Research also shows that fasting improves glucose regulation, lipid metabolism, oxidative stress markers, and brain function across diverse models including humans, rodents, and invertebrates (Dai et al. 2022; Cho et al. 2019; Meng et al., 2020; Seidler and Barrow 2022). Evidence further demonstrates that phytocannabinoids, particularly tetrahydrocannabinol (THC) and cannabidiol (CBD), can modulate autophagy. THC induces autophagy mediated cell death in glioma cells through endoplasmic reticulum stress and inhibition of the Akt mTORC1 pathway (Salazar et al. 2009). CBD enhances autophagy in breast cancer and intestinal epithelial cells (Shrivastava et al. 2011). Cannabinoid induced autophagy has been associated with anticancer effects, reduced angiogenesis, and decreased metastatic potential (Abrams 2018; Machado Rocha et al. 2014).

Phytocannabinoids are among several plant derived compounds known to activate autophagy, along with citrus bergamot, green tea, resveratrol, and cinnamon. Although fasting and phytocannabinoids arise from different biological contexts, both influence cellular homeostasis through the activation of autophagy. Understanding the shared mechanisms through which these stimuli promote cellular renewal provides an important foundation for developing therapeutic approaches that address metabolic dysregulation, inflammation, and disease progression. Their coordinated and appropriately timed application may offer promising opportunities for enhancing cellular resilience and supporting long term health.

2 Methods

This review was based on a structured examination of scientific literature describing the effects of fasting and phytocannabinoids on autophagy, metabolic regulation, and physiological homeostasis. The search was performed on Science Direct, PubMed, Scopus, Google scholar, and Google using keywords: *autophagy*, *fasting*, *intermittent fasting*, *starvation*, *phytocannabinoids*. Sources included clinical studies, animal studies, in-vitro experiments, and systematic reviews. Relevant publications were identified from the compiled tables in the original manuscript and from additional peer-reviewed articles cited therein. Studies were grouped by type of fasting or cannabinoid exposure and summarised according to their reported effects on autophagy and related cellular mechanisms. No formal meta-analysis was performed; findings were synthesized qualitatively.

3 Results

The reviewed literature shows that different types of fasting and phytocannabinoids exert significant effects on metabolic balance autophagy, and overall physiological homeostasis across human, animal, and in-vitro studies.

Table 1: Studies Reporting Autophagy-Related or Homeostatic Effects of Fasting and Phytocannabinoids

Type of publication	Fasting	Phytocannabinoids	Total Studies
Human studies	12	2	14
Animal studies	10	4	14
In-vitro / cell studies	3	5	8
Mixed or multi-model studies	4	1	5
Total number of studies identified	**29**	**12**	**41**

3.1 Effects of fasting on homeostasis

The influence of fasting on various forms of homeostasis is consistently documented across multiple study designs. Long-term fasting improves muscle function and contributes to physiological homeostasis. Shorter fasting periods, including ten-day complete fasting, enhance glucose metabolism, while Ramadan fasting improves glucose control in both healthy individuals and those with metabolic conditions. Intermittent fasting positively affects cholesterol metabolism, supports metabolic homeostasis, and induces broad pleiotropic benefits across biochemical, physiological, and metabolic domains. Starvation studies highlight adaptive responses to stress, shifts in oxidative balance, and changes in liver function during complete food deprivation.

Table 2: Influence of fasting on homeostasis

Homeostasis	Fasting	Literature
the effect of long-term fasting on muscle function	long-term fasting	Laurens et al., 2021
physiological homeostasis	10-day complete fasting	Dai et al., 2022
glucose homeostasis	Ramadan fasting	Gnanou et al., 2015
glucose homeostasis	Ramadan fasting	Varady, 2016
the effect of intermittent fasting on cholesterol metabolism	intermittent fasting	Cho et al., 2019
pleiotropic effect on homeostasis	intermittent fasting	Longo and Panda, 2016

metabolic homeostasis	intermittent fasting	Kim et al., 2017
attention is paid to eating disorders; unexplored effects on homeostasis	fasting as starvation in adolescence	Davis & Smith 2018
metabolic homeostasis	starvation	Rozental et al., 1967

3.2 Intermittent and periodic fasting

Intermittent fasting, characterized by fasting intervals lasting from 16 to 48 hours, consistently improves lipid metabolism, glucose regulation, insulin sensitivity, and markers of inflammation. Numerous studies report improved cognitive performance, enhanced neurogenesis, and better sensory and motor function in animal models. Time-restricted eating and 5:2 fasting schedules lead to modest but clinically meaningful weight loss and reductions in blood pressure, along with improvements in oxidative stress markers. Alternate-day fasting improves physiological and molecular markers of ageing, including reduced body fat, improved cardiovascular parameters, and elevated beta-hydroxybutyrate levels. Long-term intermittent fasting promotes longevity, strengthens the intestinal barrier, enhances intestinal flora health, and increases resistance to stress.

3.3 Cultural and religious fasting practices

Cultural and religious fasting regimens, such as Ramadan fasting, the Christian Great Lent, and the Baha'i fast, exert measurable physiological and psychological effects. Ramadan fasting improves glucose homeostasis, lowers lipid levels, enhances mood, and strengthens quality of life indicators. Christian and Orthodox fasting traditions, which involve structured reductions in caloric intake and specific dietary restrictions, contribute to improved metabolic health and spiritual well-being. Baha'i dry fasting increases mindfulness, inner resilience, and adaptive stress coping.

3.4 Therapeutic and prolonged fasting

Therapeutic fasting methods, such as the Buchinger method (Buchinger 1932; Buchinger 2020), combine reduced caloric intake with movement, outdoor activity, and relaxation practices. These protocols produce wide-ranging benefits, including improved immunity, reduced inflammation, better neuroendocrine balance, and a strengthened sense of well-being. Prolonged water-only fasting has been shown to normalize blood pressure safely under clinical supervision and significantly influence the gut microbiome, resulting in increased microbial homogeneity and lasting improvements in digestive tract balance. Extended fasting contributes to reductions in oxidative stress, promotes tissue regeneration, and supports recovery from chronic inflammatory diseases such as rheumatoid arthritis (Müller et al., 2021). Prolonged starvation in animal models increases antioxidant defence, alters metabolic pathways, and modulates oxidative stress responses.

3.5 Overview of therapeutic fasting outcomes

A broad review of therapeutic fasting literature confirms positive outcomes across a wide range of conditions. Fasting longer than ten days is associated with improved symptoms in numerous chronic illnesses. Literature reviews covering therapeutic, intermittent, and daily fasting indicate benefits for cognitive disorders, cardiovascular disease, type 2 diabetes, and weight management. Animal studies demonstrate enhanced antioxidant capacity, improved survival under stress, and overall strengthened resilience.

Table 3: Therapeutic effects of fasting

Fasting Type	Typical Health Benefits	Key References
Intermittent fasting (including time-restricted eating)	Better metabolic homeostasis; modest weight loss; reduced blood pressure; improved cognitive and motor function; healthy ageing benefits	Varady 2016; Lowe et al. 2020; Dai et al. 2022; Cho et al. 2019; Longo and Mattson 2014; Mattson et al. 2017; Fallows & McKenzie 2021; Mohr et al., 2021
Alternate-day fasting / 5:2 fasting	Reduced body fat; improved cardiovascular markers; enhanced metabolic flexibility	Seidler and Barrow 2022; Longo and Mattson 2014; Mattson et al. 2017; Stekovic et al. 2019
Prolonged fasting (water-only fasting, 10+ days)	Blood pressure normalization; improved gut microbiome; reduced inflammation; greater resilience to metabolic stress	Ezpeleta et al., 2024; Wilhelmi de Toledo et al. 2013; Zhao et al. 2022; He et al., 2019
Therapeutic fasting protocols	Improved immune function; reduced inflammation; beneficial in chronic	Wilhelmi de Toledo et al. 2013; Ku et al., 2017;

	metabolic and inflammatory diseases	Goldhamer et al., 2001; Michalsen et al., 2005
Religious/cultural fasting (Ramadan, Lent, Baha'i, dry fasting)	Improved glucose control; reduced lipid levels; better mood, well-being, mindfulness, and stress adaptation	Azizi 2010; Farooq et al. 2020; Videnšek 2020
Starvation models (animal studies)	Insight into adaptation to nutrient deprivation, oxidative regulation, and survival	Rozental et al. 1967

3.6 Phytocannabinoids and autophagy

Phytocannabinoids, especially THC and CBD, play a clear role in inducing autophagy. THC promotes autophagy-mediated cell death in glioma cells, tumour xenografts, and human tumour samples, demonstrating the capacity to selectively target malignant cells while sparing healthy tissue. CBD increases autophagy in breast cancer models and in intestinal epithelial cells, offering mechanistic explanations for its therapeutic effects in breast cancer and inflammatory bowel disease. Synthetic cannabinoids induce autophagy in pancreatic adenocarcinoma cells primarily by influencing energy metabolism and the early production of reactive oxygen species. Cannabinoids also demonstrate anti-angiogenic effects and reduce metastasis through inhibition of matrix metalloproteinases. Combined THC/CBD formulations reduce tau protein levels and amyloid accumulation in neuronal tissue, suggesting strong neuroprotective potential associated with autophagy activation.

Table 4: Cannabinoids and Autophagy

Cannabinoid	Model / Cell Type	Observed Effect on Autophagy	Key References
THC (Δ9-tetrahydrocannabinol)	Human glioma cells; tumour xenografts; human glioma biopsies	Strong induction of autophagy leading to selective cancer cell death	Salazar et al. 2009
CBD (cannabidiol)	Breast cancer cells; intestinal epithelial cells	Increases autophagic flux in healthy and malignant cells	Shrivastava et al. 2011
Synthetic cannabinoids	Breast cancer cells	Autophagy induction with	Qamri, et al. 2009

		reduced cancer cell viability	
Combined THC + CBD formulations	Neuronal models; neurodegenerative disease models	Enhanced autophagy associated with reduced tau and amyloid accumulation	Lee et al., 2021; Costa et al., 2016; Vrechi et al., 2025; Aso & Ferer 2014
Phytochemical autophagy inducers (bergamot polyphenols, EGCG from green tea, resveratrol, cinnamon extract)	Various cell lines and animal models	Activation of autophagy through anti-oxidant and metabolic signalling pathways	General review sources in manuscript

3.7 Comparison of mechanisms between fasting and phytocannabinoids

Across studies, fasting and phytocannabinoids consistently activate autophagy and contribute to improved cellular homeostasis. Both stimuli trigger a hormetic response that enhances resilience to stress, stimulates the recycling of damaged cellular components, and promotes metabolic flexibility. Fasting does so by shifting the body into a nutrient-deprived state that upregulates autophagic pathways, while phytocannabinoids activate autophagy through receptor-mediated signalling and intracellular stress pathways. Together, these findings indicate that both approaches share a fundamental mechanism of action centred on autophagy induction and cellular renewal.

Table 5: Comparison of Autophagy-Related Effects of Fasting and Phytocannabinoids

Aspect	Fasting	Phytocannabinoids	Key References
Primary trigger of autophagy	Nutrient deprivation and metabolic stress activate cellular recycling pathways	Receptor-mediated signalling and intracellular stress responses initiate autophagy	Longo & Mattson 2014; Mattson et al. 2017; Salazar et al. 2009; Shrivastava et al. 2011
Core autophagy pathway activated	AMPK activation and mTOR inhibition promote autophagosome formation	Inhibition of Akt/mTORC1 and induction of ER stress stimulate autophagy	Dai et al. 2022; Cho et al. 2019; Salazar et al. 2009

Outcome in healthy cells	Enhanced cellular repair, improved mitochondrial efficiency, improved resilience to oxidative stress	Modulation of inflammatory and metabolic pathways; increased autophagy in epithelial cells	Seidler & Barrow 2022; Shrivastava et al. 2011
Outcome in tumour cells	Can slow tumour growth indirectly through metabolic effects	Strong induction of autophagy-mediated cancer cell death, particularly in glioma and breast cancer models	Salazar et al. 2009; Shrivastava et al. 2011
Associated cellular stress response	Hormetic response leading to increased antioxidant defence and resistance to metabolic stress	Increased ROS production in synthetic cannabinoid models; ER-stress–mediated tumour cell death	Rozental et al. 1967; Ventura, et al., 2025; Sanz-Pérez et al., 2025
Neuroprotective autophagy effects	Increased neurogenesis and improved brain function in fasting models	Reduced tau and amyloid accumulation through enhanced autophagic clearance	Cho et al. 2019; Lee et al., 2021; Costa et al., 2016; Vrechi et al., 2025; 2020; Aso & Ferer 2014
Overall effect on autophagy	Consistent physiological inducer of autophagy across models	Potent pharmacological inducer of autophagy in cancer and selected healthy cells	Summary of references above

4 Discussion

Fasting and phytocannabinoids have an intricate connection in the way they influence cellular homeostasis through their shared ability to activate autophagy and associated stress-response pathways. Although they arise from different biological contexts, both stimuli converge on mechanisms of intracellular recycling, metabolic regulation, and enhancement of cellular resilience. This convergence suggests a shared mechanistic foundation with broad therapeutic relevance.

Fasting is one of the most potent physiological inducers of autophagy. Across diverse fasting models—including intermittent fasting, time-restricted eating, alternate-day fasting, prolonged water-only fasting, and religious fasts such as Ramadan—studies consistently demonstrate improvements in metabolic health. These benefits include enhanced glucose and lipid regulation (Dai et al., 2022;

Gnanou et al., 2015; Lowe et al., 2020), increased insulin sensitivity (Kim et al., 2017), reductions in inflammation (Michalsen & Li, 2013), and favourable effects on blood pressure and body weight (Goldhamer et al., 2001). Many of these outcomes reflect the hormetic stress response induced by nutrient restriction, which activates cytoprotective pathways, improves mitochondrial function, and supports more efficient oxidative stress management (Longo & Mattson, 2014; Zhao et al., 2022). Neuroprotective effects—including enhanced neurogenesis, improved cognition, and increased neuroplasticity, have also been documented (Cao et al., 2022; Mattson et al., 2018; Seidler & Barrow, 2022), further indicating that fasting-induced autophagy contributes to both systemic and cellular resilience.

Phytocannabinoids, particularly Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), also influence autophagic pathways, though in a more context-specific manner. THC induces autophagy-mediated cell death in glioma cells via endoplasmic reticulum stress and inhibition of Akt/mTORC1 signalling (Salazar et al., 2009), while CBD enhances autophagic flux in breast cancer cells and intestinal epithelial models (Shrivastava et al., 2011). Synthetic cannabinoids show similar effects, inducing shifts in energy metabolism and early reactive oxygen species signalling that lead to autophagic activation (Qamri et al., 2009; Lee et al., 2021). Combined THC/CBD preparations exhibit additional neuroprotective properties, including reductions in tau and amyloid pathology, suggesting that cannabinoid-induced autophagy may contribute to delaying or mitigating neurodegenerative processes (Aso & Ferrer, 2014; Machado Rocha et al., 2014). These findings align with broader evidence that phytocannabinoids can modulate key intracellular pathways involved in survival, apoptosis, and metabolic balance (Costa et al., 2016; Vrechi et al., 2025). Although fasting generally promotes adaptive stress responses that support cell survival, whereas phytocannabinoids may induce autophagic cell death in malignant cells, both approaches share the capacity to enhance metabolic flexibility and regulate intracellular recycling. The overlapping mechanisms—autophagy induction, modulation of mTOR activity, activation of endoplasmic reticulum and oxidative stress signalling, and targeted removal of damaged cellular components—support the view of autophagy as a central integrative process linking these two interventions (De Duve, 1963; Ohsumi, 2014; Takeshige et al., 1992; Wang & Levine, 2010).

The therapeutic implications of this convergence are substantial. Structured fasting protocols offer a non-pharmacological method for activating autophagy and improving metabolic and neurological health across a wide range of populations

(Mattson et al., 2017; Ezpeleta et al., 2024). By contrast, Phytocannabinoids provide targeted pharmacological modulation of autophagy, particularly relevant for oncology and neurodegenerative diseases (Abrams, 2018; Ventura et al., 2025).

Together, these findings raise the possibility that combining metabolic interventions such as fasting with phytocannabinoid-based therapies could enhance or fine-tune autophagic activity. However, careful attention to timing, dosage, individual physiological status, and the risk of autophagy overactivation is essential, as excessive or dysregulated autophagy may lead to adverse outcomes (Costa et al., 2016; Sanz-Pérez et al., 2025). This fascinating convergence suggests a promising area for further research and highlights autophagy as a key biological process that links lifestyle interventions and plant-derived compounds for health and longevity.

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