



**INTERNATIONAL JOURNAL OF
PHARMACEUTICAL SCIENCES**
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: <https://www.ijpsjournal.com>



Review Article

Impaired Autophagic Clearance in Aging: Mechanisms and Therapeutic Perspectives on Age-Related Diseases

Gayatri Gaikwad^{1*}, Priya Daingade², Tushar Shelke³

¹ Final Year B.Pharmacy Student, Department of Pharmacy, Genba Sopanrao Moze College of Pharmacy, Wagholi, India.

² Professor, Department of Pharmaceutics, Genba Sopanrao Moze College of Pharmacy, Wagholi, India.

³ Principal, Department of Pharmacology, Genba Sopanrao Moze College of Pharmacy, Wagholi, India.

ARTICLE INFO

Published: 25 Oct 2026

Keywords:

Autophagy, Autophagic clearance, Aging, Age-related diseases, Lysosomal dysfunction, Mitophagy, mTORC1, Cellular senescence

DOI:

10.5281/zenodo.23640715

ABSTRACT

As we age, the cells inside the body start to dysfunction, resulting in damaged parts of cells such as damaged proteins. Autophagy is a vital cellular process that recycles the damaged parts to keep the cell healthy. Autophagic clearance rate drops with age, which might be caused by autophagosome dysfunction, impaired lysosomal activity, etc. As a result, damaged organelles build up, causing stress, inflammation, deterioration of cells, and mitochondrial dysfunction. The surge and worsening of age-related diseases such as Parkinson's disease, Alzheimer's disease, and Sarcopenia is related to impaired autophagic clearance. To create therapies and treatments, one must understand how this vitiation takes place. There are many ways such as regular exercise, a calorie deficit diet, and drugs regulating autophagy and targeting lysosomal and mitochondrial functions. Altogether, rebuilding autophagic clearance can support cell functioning and lessen the damage caused by age-related diseases and slow down the development of such diseases.

INTRODUCTION

A common occurrence like aging causes a moderate decrease in how aptly the body's cells work. Autophagy is an essential cellular procedure for the breakdown of cytosolic constituents, including the construction of autophagosomes, their fusion with

lysosomes, and the disintegration of the substance inside them [1]. This procedure keeps the cells pristine, and support internal balance, and it is appraised as one of the major contributors to a person's life span and healthy aging [2].

Efficiency of this clearance process decreases with aging. Diminution of Lysosomal function, of the

***Corresponding Author:** Gayatri Gaikwad

Address: Final Year B.Pharmacy Student, Department of Pharmacy, Genba Sopanrao Moze College of Pharmacy, Wagholi, India.

Email ✉: gayatrigaikwad2004@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



overall autophagic flux, and of the formation of autophagosome with increasing age is a process still largely to be clarified at a molecular level [3]. This decline is not directly a side effect of aging, it is progressively identified as one of the key procedures operating age-related cellular damage [4]. A large amount of evidence points to autophagy as a major contributor in deciding health and lifespan, since including autophagy has revealed quantifiable developments in organismal longevity over numerous investigational models [5].

The diseases that are more common in the elderly, are closely linked to the decline in autophagy. Impaired autophagy is now acknowledged as a split, fundamental proposition linking some age-related diseases and cancer, with regulatory procedures that vary by tissue but coincide on akin results [6]. Autophagy plays a role in supporting cardiac function, and its deterioration with age is related to vascular remodelling and disease [7]. Sarcopenia, which is a disease of the skeletal muscle, is caused by autophagic dysfunctions resulting in muscle loss and weakness, albeit the precise techniques are still being resolved [8], and reinstating autophagy through particular regulators has been shown to hinder loss of muscle and encourage healthier aging in both animal and human studies [9]. The “metabolic clash” seen in Type 2 Diabetes Mellitus in which autophagic dysfunction disturbs normal glucose regulation is another metabolic disease affected by impaired autophagic clearance [10].

Because of these strong relations, there is growing engrossment in therapies that can reimpose or support autophagy in the elderly, as part of an extensive pro-longevity approach to supervising age-related diseases [2]. New methods to halt or treat several age-related diseases can be found by understanding how autophagy declines with age, and ways to reinstate it, in order to support healthier aging.

Molecular Mechanisms of Autophagy Decline in Aging

Autophagy involves the deterioration and recycling of the cytosolic constituents, including the concerted activity of core autophagy-related (Atg) proteins, including ULK1, Atg9-WIP1, and the Vps34-beclin1

complex [1]. This procedure is composed of continual membrane formation, autophagosome-lysosome fusion, and cargo degradation, and is crucial not only for cellular cleanup but also for immune protection and stress response.

As cells age, this procedure turns out to be less competent. Changes happen at almost every step of the pathway, comprising autophagosome formation, lysosomal function, and overall autophagic flux, though the exact molecular drivers of this decline continue to be an operative region of the research [3]. This decline is progressively identified as a main benefactor to cellular aging rather than a dormant outcome of it [4]. Because autophagy also promptly supports cell survival and metabolic function, its disability has wide downstream impacts on cellular health [11].

Apart from the traditional macroautophagy pathway, non-canonical structures of autophagy have also been revealed to adapt with age, adding further complication to how autophagy dysfunction donates to aging phenotypes. Mitochondrial quality control through mitophagy is affected closely, with age-related decline in mitophagy connected to the amassing of dysfunctional mitochondria across numerous tissues. At the lysosomal level, failure of lysosomal acidification has been displayed to immediately damage autophagic flux under cellular stress conditions, such as glucose destitution, elucidating how lysosomal dysfunction alone can restrict the whole pathway. These molecular alterations have also caused engrossment in autophagy-related proteins as possible biomarkers for discovering and chasing aging-related disease succession [12].

Why Autophagy Declines with Age

Various, interconnecting mechanisms navigate the age-associated impairment:

- **Transcriptional and epigenetic downregulation of Atg genes-** Many tissues show a decreased expression of autophagy-related genes (ATG5, ATG7, BECN1, LC3B, ULK1). Epigenetic changes, including altered acetylation of histone and DNA methylation donate to this suppression [3].
- **Chronic mTORC1 hyperactivation-** Tenacious nutrient sensing and growth-factor signalling keep



mTORC1 working repeatedly to suppress ULK1. Insulin/IGF-1 signalling itself is modified with age, fortifies this hindrance.

- **Lysosomal dysfunction-** Accumulation of lipofuscin, damaged membrane and minimized v-ATPase activity lead to failure in lysosomal acidification. Therefore, when autophagosome formation takes place, fusion and breakdown are ineffective in building the characteristic accumulation of autophagic vacuoles detected in aged cells [13,14].
- **Oxidative stress and Redox imbalance-** Oxidative species can inactivate key autophagy proteins and even go on to lacerate the lysosomal membrane. Stress kinases activated by redox can stimulate and then later still also inhibit autophagy [15].
- **Senescent cell burden and SASP-** Senescent cells show autophagy and pro-inflammatory parts that further subdue autophagy in adjacent cells [16,17].
- **Impaired selective autophagy-** Aging evacuates NAD⁺ and nutrient signals, interrupting cells from identifying damaged mitochondria and lipid waste. This produces chronic oxidative stress that jams the lysosome recycling centers with undegradable metabolic debris [18,19].

Disease-specific patterns (as cited in the literature):

- Neurodegenerative diseases- Autophagy-lysosomal clearance of amyloid- β and tau is impaired in Alzheimer's disease and is central [20,21]. Mitophagy defects are found in Parkinson's disease [22].
- Cardiovascular disease and vascular senescence- Autophagy conserves the role of endothelial cells

and cardiomyocytes; its degeneration operates vascular stiffness, atherosclerosis and heart failure [7,23–25].

- Sarcopenia and musculoskeletal aging- Muscle-specific autophagy is required to retain strong and healthy muscle fibres. When autophagy does not work properly, muscle fibres start to grow smaller and become fragile. This breakdown occurs because the cells cannot take out parts successfully. Over time, this leads to a loss of muscle strength and function [8,9,26].
- Metabolic disease- Autophagy helps control how the body responds to insulin supports the function of beta cells, in the pancreas and manages metabolism. When autophagy slows down it can lead to type 2 diabetes and diabetic nephropathy [10,27].
- Ocular aging- Autophagy dysfunction is implicated in age-related degeneration pathogenesis and autophagy dysfunction is a central element, in the development of age-related macular degeneration [28,29].

Reciprocal Relationship with Aging Hallmarks

- Impaired autophagy speeds up signs of aging: genomic instability (not being able to remove damaged DNA repair proteins or cell parts) losing control of proteins in the body problems with mitochondria, cells stopping working properly and changes in how cells talk to each other. On the other hand, things that bring back autophagy (cutting down on food taking rapamycin exercising) slow down many of these signs at the same time [2,5].

Autophagy Dysfunction Across Age Groups and Disease Context

Table 1: Comparative Autophagic Status by Age Groups

Variables	Young Adults (20-39 yr)	Middle Aged (40-64 yr)	Older Adults (≥ 65 yr)
Basal Autophagic flux	High	Mildly reduced	Reduced
Inducible response	Vigorous	Partially preserved	Blunted or absent
Lysosomal acidification	Efficient	Emerging defects	Prominent failure
Key Atg gene expression	High	Progressive decline	Low
Mitophagy efficiency	High	Reduced	Severely impaired
mTORC1 activity	Balanced	Mildly elevated	Chronically elevated



Variables	Young Adults (20-39 yr)	Middle Aged (40-64 yr)	Older Adults (≥ 65 yr)
Clinical correlates	Efficient proteostasis	Early metabolic inflexibility	Protein aggregates, Sarcopenia

Table 1 shows the continuous autophagic failure: young cells exhibit speedy LC3- II yield and cargo clearance; middle-aged cells gather early autophagosomes; aged cells have substantial undegraded autolysosomes and cytosolic aggregates.

Autophagy Dysfunction in Age-Related Diseases

Autophagic dysfunction is now acknowledged as a split mechanism underlying a broad scale of age-related diseases and cancer, with tissue-specific regulatory contrasts that eventually coincide on similar patterns of cellular damage[6]. Its impact expands beyond the four main systems explored below, with emerging proof also involving autophagy decline in chronic kidney disease [30,31] and age-related macular degeneration [28,32].

1. Neurodegenerative Diseases

The nervous system is mostly sensitive to the effects of declining autophagy mainly because neurons do not divide. These cells cannot spread out the build-up of damaged proteins by splitting like cells can. Because of this, even a tiny drop in autophagy can let damaging proteins pile up over time. This can lead to the type of cell damage that is seen in diseases that impact the brain and nerves.

In Parkinson's disease, poor autophagy is a reason why the disease gets worse. When the way cells clear out their debris is splintered, misfolded and aggregated proteins, alpha-synuclein collect inside the nerve cells. This leads to difficulties with how the nerve cells work, causing eventual cell death. Scientists have been examining closely at where in the process, this breakdown takes place. They are also working on methods to bring back autophagy in the nerve cells that are affected [22].

A similar situation happens in Alzheimer's disease build-up of amyloid-beta plaques and tangles made of tau protein, are two signs of the disease. Since autophagy clears these types of damaged proteins when it doesn't work well, the brain loses one of its ways to fight the build-up. This has made fixing autophagic

clearance more and more important for treating Alzheimer's [20].

Alzheimer's disease also worsens due to stress from oxygen and old cells that no longer work well. Both these things work closely with the decline in autophagy. As the nerve cells get older, the balance of oxygen-related activities in the cell becomes worse. This seems to speed up the aging of the cells making them more likely to fail. Since autophagy usually helps tackle oxygen damage by cleaning out parts of the cell, the problems with autophagy and oxygen balance seem to make each other worse. This produces a cycle that makes nerve cells more stressed and not work well [15].

In various brain diseases, the cause of nerve cell death has been found to be autophagy and part of cell that break things down. There could be many reasons as to why the cell doesn't perform autophagy effectively such as, inability of the cell to make correct structures of proteins, or mishap in carrying enzymes. Due to this, nerve cells lose their path to clean out damaged parts. This can kick off the procedure that causes nerve cell death. This indicates that the autophagic decline and the breakdown part is the reason behind various brain diseases, not just in one [21].

State of health of the energy parts of the cell called mitochondria, is also extremely significant in brain diseases. This is related to a type of autophagy called "mitophagy". This activity clears out damaged energy parts. With aging, this procedure becomes less efficient. Damaged energy parts gather in nerve cells, this leads to oxygen stress and reduced energy for the cell. Both these things are inefficient for the nerve cells that require a lot of energy in order to regulate effectively. This has led to a significant area of research to make mitophagy better. Scientists have been searching for ways to aid this process work better in nerve cells at risk [33].

All these discoveries show that even though brain diseases have various symptoms, they all have something in common. They all depend on autophagy and mitophagy to stop misfolded proteins and parts from



building up. This typical issue suggests that treatments that assist, work better in general and not just for misfolded proteins.

2. Cardiovascular Diseases

Ageing is one of the major risk factor for many diseases worldwide, impacting the heart and blood vessels. Cardiovascular disease remains one of the causes of death among the elderly. Autophagy is not a simple garbage disposal in the system, it is a careful balancing act. In normal heart cells and blood vessels, autophagy helps to degrade proteins and old organelles, allowing these cells to function efficiently for long periods of time. As we get older, autophagy itself begins to decline and this protective effect wears off. The consequence of this is that the heart and blood vessels are more vulnerable to damage and disease.

Scientists have discovered spots in the autophagy pathway that could be of service as targets for therapy helping to slow down cardiovascular aging. These spots are often called “checkpoints” meaning there are specific steps in autophagy where a drug or other involvement could realistically step in and reinstate normal function before serious damage builds up [23]. This change is crucial for how we approach ways to halt heart disease. Before cell damage becomes visible, we can concentrate on reinforcing the cell’s own cleanup systems before the problem arises.

The issue is getting more intense as cardiovascular disease is already common in people. Reviews that emphasis on adults in India show just how widespread heart disease in this group is [34]. In a sense, studies of how aging alters the cardiovascular system disclose that aging touches almost every aspect of heart and blood vessel function. It influences how well the heart pumps blood and how pliable blood vessels remain over time [25].

A positive line of research is ongoing about non-coding RNAs, these molecules do not code for proteins, yet manage to influence how genes are turned on or off. Scientists are starting to inspecting whether these molecules can fine-tune autophagy in patients with cardiovascular disease. This approach would accommodate the body’s cleanup procedure rather than adding an entirely new drug and could target autophagy where it is most required [7]. Even though it remains a

newer approach, it provides a more precise way to support the cells’ autophagic activity.

Vascular senescence; the aging and the loss of function of cells that line blood vessels, has also become a target. When these vascular cells become senescent, they stop proliferating and start releasing inflammatory signals that can injure adjacent healthy tissue adding to cardiovascular disease. Due to the interconnection between autophagy and cellular senescence, researchers propose that directly targeting senescence could be another effectual way to shelter the aging cardiovascular system [24].

Consequently, these studies reveal that cardiovascular aging is mainly driven by autophagic decline. This decline ends up affecting both the heart muscle and the blood vessels that feed it. Recent research suggests that preserving or restoring autophagy can help individuals experiencing cardiovascular problems as they get older.

3. Sarcopenia

The loss of muscle mass and strength that takes place as we grow older is called Sarcopenia. It is easy to misunderstand the symptoms of this disease. For years, scientists thought that because autophagy breaks down parts of cells, halting it might help keep muscle tissue from being damaged. Newer studies have proven that the opposite is actually true. The drop in activity as we age leads to muscle decline which ultimately causes muscle loss. To fix this issue, studies are being conducted worldwide [8].

Some of the proof is drawn from genetic research. A protein called TP53INP2 helps keep autophagy functioning in muscle cells. When scientists turned on TP53INP2 in muscles, it was proven to help prevent sarcopenia. This worked in animal and human muscle samples. So these results provide evidence that improving autophagy rather than blocking it can protect aging muscles [9].

Our diet also plays an important role here. Nutrition is significant for keeping muscles strong as we age. Some diets, ways of protein intake and certain supplements have been studied for their capacity to help adults suffering severe muscle loss. These approaches seem to



work, at least in part by encouraging associated processes in the body [35].

Sarcopenia often goes hand in hand with osteoporosis, which is the loss of bone strength and density with age. These two conditions share various problems in how tissues break down [36]. Because of this, some researchers view muscle and bone aging as interconnected, not separate. Often weakness in one shows up with weakness in the other [26].

Recent studies have made it easier for doctors to detect sarcopenia and track how it progresses. There is also knowledge of the metabolic alterations that take place with aging. These insights are aiding to design treatment options.

The mTOR-autophagy pathway has become a focus for treating osteoporosis due to the connection between muscle and bone. This pathway controls cell growth as well as autophagy. By adjusting it, there is hope to substantiate both muscle and bone health at the time. This displays how interlinked muscle and bone aging really are at the molecular level [37].

All of this suggests a shift, in our view of autophagy in ageing muscles. We don't see this as something to be hindered anymore. We see it, rather, as a procedure of ageing. We need to turn this around, so that older adults can keep their strength up and stay mobile. This can be done either by genetics, diet or medicine. The aim is to keep the cells working well as we get older.

4. Metabolic Disorders

Metabolic health depends on how the body manages glucose. It needs to reserve energy, release it when required and keep things balanced across important organs like the liver, pancreas, muscle and fat tissue. One procedure that supports all of this, is autophagy. It is an internal cleanup system but it often gets disregarded. As we age, autophagy becomes less active. This decline exhausts the body's potential to regulate metabolic functions. The outcomes become most obvious to conditions like Type 2 Diabetes Mellitus, this disease is one of the most common and rapidly growing metabolic issues connected to aging.

The connection between autophagy and type 2 diabetes has been described as a type of dispute inside the cell, calling it a "metabolic clash". The body requires blood

sugar levels to regulate correctly, and when autophagy stops working properly, cells lose a crucial tool for handling stress, clearing damaged parts and adjusting to changes in nutrients. This mismatch reveals that demands on the metabolic system begin to exceed what a weakened autophagy system can handle. Poor blood sugar control, which is a hallmark of type 2 diabetes, is the cause for a fragile metabolic system [10]. This problem doesn't just take place at a specific site. It indicates a breakdown in communication between metabolically active tissues. When autophagy declines with age, these tissues struggle to harmonize and supervise each other effectively.

It is not only related to blood sugar. Controlled diabetes over time results in serious complexities. One of these is nephropathy; a slow, harmful state that damages the kidneys. High blood sugar levels impair the filtering units inside the kidneys over many years. Autophagy aids to defend kidney cells by removing waste, just like it does in other parts of the body. So when autophagy declines, the kidneys become more vulnerable to long-term harm from blood sugar. This is the reason researchers are now paying close attention to autophagy as a treatment target. Enhancing autophagy could help manage blood sugar and also preserve the kidneys in people who are diabetic [27]. Reinstating activity might slow or even prohibit kidney damage that often develops after years of uncontrolled blood sugar. A solitary approach focused on autophagy could help fight the disease as well as one of its harmful side effects.

Research shows that autophagic failure with age influences more than just blood sugar. It affects a range of metabolic disorders that surge as we get older. This indicates that the effects of declining autophagy aren't bound to one disease. Rather, they point to a systemic issue. As the body's cellular maintenance systems weaken, various metabolic pathways start to fail at once. Because this dysfunction affects systems concurrently, scientists see various possible entry points where reinstating autophagy could make a difference than treating one disease at a time, focusing on autophagy provides a way to address the main cause behind many of them [38]. This wider view switches attention from treatments to tackling a shared



underlying problem; the breakdown in cellular cleanup with aging.

Diseases which become prominent with age are formed by the body's decreasing capacity to perform autophagy as we age. Autophagy has been investigated to be effective treatment whether an individual is suffering through a metabolic disease, cardiovascular disease or a neurodegenerative disease. There may be a way to merge treatments for age-related conditions. The overall health can be improved by supporting the body's cleanup procedure.

Therapeutic Perspectives on Age-Related Diseases

A. Pharmacological Modulation of Core Autophagy Machinery

mTORC1 inhibitors are the most studied class. mTORC1 inhibitors, including rapalogs, can promote autophagy by relieving mTORC1-mediated inhibition of the ULK1 complex. In models, they assist heart function, decrease protein disease and lead to a healthier life for longer. They are not easy to use in people as they suppress the immune system a lot, and have bad effects on metabolism when given in large quantities. Researchers are researching ways to use them often or in smaller amounts [5,38].

Metformin, AICAR and other new AMPK activators help the body clean up damaged parts by boosting autophagy. They do this by altering the function of ULK1 and inhibiting mTORC1. Part of the effect of metformin on ageing is due to autophagy, which helps slow ageing. Metformin works the way it does because autophagy is important. Metformin's role in protecting against ageing involves autophagy. In some ways, metformin works by the process of autophagy.

Beclin-1 agonists and peptides disrupting the interaction between Bcl-2 and Beclin-1 can specifically enhance nucleation. This approach prevents mTOR suppression. It allows for accurate regulation of autophagy. The aim is to improve the process without disturbing cellular functions too much. This could be useful in diseases where autophagy needs to be switched on. It offers a controlled way to control the pathway.

Lysosomal acidification enhancers and v-ATPase modulators are engineered to restore terminal

degradation capacity, a barrier that pure initiation inducers cannot pass [13,14].

B. Selective Autophagy Enhancement

Mitophagy inducers (urolithin A, NAD⁺ precursors, PINK1-Parkin pathway activators) are promising therapies for neurodegenerative and muscle diseases [18,33]. Drugs that enhance aggregatephagy by increasing p62 or other adaptor expression or by promoting recognition of specific aggregates are in early development for Alzheimer's and Parkinson's disease.

C. Natural Products and Dietary Approaches

Plant-derived autophagy inducers are resveratrol (SIRT1-AMPK axis), spermidine (epigenetic induction of Atg genes), curcumin, trehalose (mTOR-independent) and several polyphenols [39,40]. Caloric restriction and intermittent fasting are physiological inducers, and their benefits are largely autophagy-dependent. Nutritional approaches for sarcopenia are protein timing and micronutrients supporting lysosomal function [35].

D. Senolytics, Senomorphics, and Combination Strategies

Senescent cells display and transmit autophagy defects. Senolytic agents (dasatinib + quercetin, navitoclax, fisetin) clear senescent cells and secondarily recover tissue autophagy capacity. Senomorphics that inhibit the SASP without killing cells may have similar benefits with less toxicity [16,17]. It is theoretically attractive to combine senolytics with inducers. Now, senolytics and inducers of autophagy are being tested.

E. Gene Therapy, RNA-Based, and Emerging Modalities

The overexpression of ATG5, ATG7 and TFEB in tissues gives good results, in mouse models of neurodegeneration and sarcopenia. Another layer of control is provided by modulation of non-coding RNA [7]. CRISPR-based methods or AAV-delivered strategies are still in the research stages, but have the potential to make a big difference in the future.

Drug delivery technologies that can more easily target tissues and avoid harming other areas are very important to use autophagy modulators. This is especially true when the target is the brain or the aged heart [41].



F. Disease-Specific Therapeutic Considerations

- I. Neurodegeneration: Dual strategies inducing autophagy and improving function are preferred (trehalose + TFEB activators). Timing is everything. Excessive autophagy induction in late-stage disease, when lysosomes are already weak could do more harm, than good.
- II. Cardiovascular: Intermittent rapamycin or AMPK activators for protection against cardiac ageing and senescence with minimal metabolic side effects. This method might help to slow down ageing of the heart and blood vessels. It could have long-term benefits without impacting metabolism [23,24].
- III. Sarcopenia: Exercise is still the way to get the body to work its best. Scientists are looking into medicine that act like exercise and help the body clean out parts. This includes things that change the TP53INP2 pathway.
- IV. Metabolic Disease: Metformin and other AMPK activators in clinical use give a solid starting point; drugs that specifically boost autophagy may add extra benefit, for diabetic kidney disease.
- V. Ocular and Renal: Local delivery routes, like renal-targeted methods could help reduce exposure, to the whole body. This approach may lower side effects by focusing the treatment where it is needed most.

Challenges, Biomarkers, and Future Directions

Crucial challenges are: (i) to differentiate the profitable from the immoderate or unfinished autophagy (the later can be destructive); (ii) to develop dependable, non-invasive biomarkers of autophagic flux in humans [12]; (iii) tissue and disease stage specificity are contemplated; and (iv) the binary role of autophagy in cancer is balanced.

Future investigational concerns include multi-omics mapping and age-related autophagy decline in human tissues, evolution of flux-sensitive PET or circulating markers, and well-designed clinical trials of irregular or combination regimens that reinstate physiological autophagy in the absence of chronic hyperactivation.

CONCLUSION

Impaired autophagic clearance is one mechanism associated with aging and several age-related diseases. The autophagic pathway halts its processes over time. This happens due to alterations in how Atg genes are turned on, constant activation of mTORC1, issues with the lysosomes, too much oxidative stress and increasing senescent cells. All of these problems lead to protein toxicity issues with mitochondria and the breakdown of tissues. These issues straight away cause brain diseases, heart problems, loss of muscle strength and other problems that might take place later in life.

Reinstating flux using MTOR/AMPK modulators, selective mitophagy inducers, naturally occurring compounds, caloric restriction, senolytics or targeted delivery strategies grants a solitary approach that could hinder several age-related conditions at once. We still require human biomarkers to quantify autophagic flux. To ensure that the induction of dose is done right, we need to control it. Well-designed clinical trials must be conducted to test irregular dosing and combination therapies. In the elderly, resolving these issues will reveal how well-established treatments can expand health span and reduce the time spent in poor health during later life.

Eventually, the increasing body of evidence places autophagy not solely as a cellular housekeeping act, but also as a core component that decides how well an organism can undergo stress. By occurring at this shared junction, future therapies may move the focus from treating every age-related disease separately to conserve function across organ systems. Autophagy has become a central focus of this emerging approach. This shift provides a more coherent path toward healthier aging and it may revolutionize the way we think about resilience in the body.

REFERENCES

1. Tanida I. Autophagy basics. *Microbiol Immunol*. 2011;55 (1):1–11. doi:10.1111/j.1348-0421.2010.00271.x
2. Chmielewski PP, Data K, Strzelec B, Farzaneh M, Anbiyaiee A, Zaheer U, et al. Human Aging and Age-Related Diseases: From Underlying Mechanisms to Pro-Longevity Interventions. *Aging Dis*. 2024 Jun 2;16 (4):1853–77. doi:10.14336/



- AD.2024.0280 PubMed PMID: 38913049; PubMed Central PMCID: PMC12221391.
3. Lim SHY, Hansen M, Kumsta C. Molecular Mechanisms of Autophagy Decline during Aging. *Cells*. 2024 Aug;13 (16):1364. doi:10.3390/cells13161364
4. Picca A, Marzetti E, Leeuwenburgh C. Autophagy Meets Aging: An Overview. *Cells*. 2023 Feb 2;12 (3):489. doi:10.3390/cells12030489 PubMed PMID: 36766829; PubMed Central PMCID: PMC9914474.
5. Danics L, Abbas AA, Kis B, Pircs K. Fountain of youth—Targeting autophagy in aging. *Front Aging Neurosci*. 2023 Mar 29;15. doi:10.3389/fnagi.2023.1125739
6. Wu N, Zheng W, Zhou Y, Tian Y, Tang M, Feng X, et al. Autophagy in aging-related diseases and cancer: Principles, regulatory mechanisms and therapeutic potential. *Ageing Res Rev*. 2024 Sep 1;100:102428. doi:10.1016/j.arr.2024.102428
7. Scalabrin S, Cagnin S. Cardiovascular diseases in the elderly: possibilities for modulating autophagy using non-coding RNAs. *Front Cell Dev Biol*. 2025 Jul 31;13. doi:10.3389/fcell.2025.1520850
8. Xie G, Jin H, Mikhail H, Pavel V, Yang G, Ji B, et al. Autophagy in sarcopenia: Possible mechanisms and novel therapies. *Biomed Pharmacother*. 2023 Sep 1;165:115147. doi:10.1016/j.biopha.2023.115147
9. Sebastián D, Beltrà M, Irazoki A, Sala D, Aparicio P, Aris C, et al. TP53INP2-dependent activation of muscle autophagy ameliorates sarcopenia and promotes healthy aging. *Autophagy*. 2024 Aug 2;20 (8):1815–24. doi:10.1080/15548627.2024.2333717 PubMed PMID: 38545813.
10. Alanazi YA, Al-kuraishy HM, Al-Gareeb AI, Alexiou A, Papadakis M, Bahaa MM, et al. Role of Autophagy in Type 2 Diabetes Mellitus: The Metabolic Clash. *J Cell Mol Med*. 2024;28 (23):e70240. doi:10.1111/jcmm.70240
11. Sedlackova L, Kataura T, Sarkar S, Korolchuk VI. Metabolic function of autophagy is essential for cell survival. *Autophagy*. 2023 Aug 3;19 (8):2395–7. doi:10.1080/15548627.2023.2165753 PubMed PMID: 36727253.
12. Miceli C, Leri M, Stefani M, Bucciantini M. Autophagy-related proteins: Potential diagnostic and prognostic biomarkers of aging-related diseases. *Ageing Res Rev*. 2023 Aug 1;89:101967. doi:10.1016/j.arr.2023.101967
13. Hwang ES, Song SB. Impaired Autophagic Flux in Glucose-Deprived Cells: An Outcome of Lysosomal Acidification Failure Exacerbated by Mitophagy Dysfunction. *Mol Cells*. 2023 Nov 1;46 (11):655–63. doi:10.14348/molcells.2023.0121
14. He Y, Fan Y, Ahmadpoor X, Wang Y, Li ZA, Zhu W, et al. Targeting lysosomal quality control as a therapeutic strategy against aging and diseases. *Med Res Rev*. 2024;44 (6):2472–509. doi:10.1002/med.22047
15. Yu N, Pasha M, Chua JJE. Redox changes and cellular senescence in Alzheimer's disease. *Redox Biol*. 2024 Jan 17;70:103048. doi:10.1016/j.redox.2024.103048 PubMed PMID: 38277964; PubMed Central PMCID: PMC10840360.
16. Zheng L, He S, Wang H, Li J, Liu Y, Liu S. Targeting Cellular Senescence in Aging and Age-Related Diseases: Challenges, Considerations, and the Emerging Role of Senolytic and Senomorphic Therapies. *Aging Dis*. 2024 Feb 27;15 (6):2554–94. doi:10.14336/AD.2024.0206 PubMed PMID: 38421832; PubMed Central PMCID: PMC11567261.
17. Saliev T, Singh PB. Targeting Senescence: A Review of Senolytics and Senomorphics in Anti-Aging Interventions. *Biomolecules*. 2025 Jun 13;15 (6):860. doi:10.3390/biom15060860 PubMed PMID: 40563501; PubMed Central PMCID: PMC12190739.
18. Picca A, Faitg J, Auwerx J, Ferrucci L, D'Amico D. Mitophagy in human health, ageing and disease. *Nat Metab*. 2023 Dec;5 (12):2047–61. doi:10.1038/s42255-023-00930-8 PubMed PMID: 38036770; PubMed Central PMCID: PMC12159423.



19. Kumar AV, Mills J. Non-canonical autophagy in aging and age-related diseases. *Front Cell Dev Biol.* 2023 Feb 23;11. doi:10.3389/fcell.2023.1137870
20. Angst G, Jia N, Esqueda LET, Fan Y, Cai Q, Wang C. Autophagy in alzheimer disease pathogenesis and its therapeutic values. *Autophagy Rep.* 4 (1):2471677. doi:10.1080/27694127.2025.2471677 PubMed PMID: 40395993; PubMed Central PMCID: PMC12064067.
21. Nixon RA. Autophagy–lysosomal-associated neuronal death in neurodegenerative disease. *Acta Neuropathol (Berl).* 2024 Sep 11;148 (1):42. doi:10.1007/s00401-024-02799-7 PubMed PMID: 39259382; PubMed Central PMCID: PMC11418399.
22. Zhang X, Zhang H, Dong J, Cai H, Le W. Advances in autophagy for Parkinson's disease pathogenesis and treatment. *Ageing Neurodegener Dis.* 2025;5 (1):6. doi:10.20517/and.2024.33 PubMed PMID: 41536634; PubMed Central PMCID: PMC12797875.
23. Abdellatif M, Montégut L, Kroemer G. Actionable autophagy checkpoints in cardiovascular ageing. *Eur Heart J.* 2023 Dec 7;44 (46):4819–21. doi:10.1093/eurheartj/ehad661
24. Hall SA, Lesniewski LA. Targeting vascular senescence in cardiovascular disease with aging. *J Cardiovasc Aging.* 2024 Apr;4 (2):16. doi:10.20517/jca.2023.45 PubMed PMID: 39119148; PubMed Central PMCID: PMC11309369.
25. Zhao D, Wang Y, Wong ND, Wang J. Impact of Aging on Cardiovascular Diseases. *JACC Asia.* 2024 Apr 8;4 (5):345–58. doi:10.1016/j.jacasi.2024.02.002 PubMed PMID: 38765662; PubMed Central PMCID: PMC11099824.
26. Ali SR, Nkembo AT, Tipparaju SM, Ashraf M, Xuan W. Sarcopenia: recent advances for detection, progression, and metabolic alterations along with therapeutic targets. *Can J Physiol Pharmacol.* 2024 Dec 1;102 (12):697–708. doi:10.1139/cjpp-2024-0201 PubMed PMID: 39186818; PubMed Central PMCID: PMC11663012.
27. Li QR, Xu HY, Ma RT, Ma YY, Chen MJ. Targeting Autophagy: A Promising Therapeutic Strategy for Diabetes Mellitus and Diabetic Nephropathy. *Diabetes Ther.* 2024 Oct;15 (10):2153–82. doi:10.1007/s13300-024-01641-3 PubMed PMID: 39167303; PubMed Central PMCID: PMC11410753.
28. Jiang F, Ma J, Lei C, Zhang Y, Zhang M. Age-Related Macular Degeneration: Cellular and Molecular Signaling Mechanisms. *Int J Mol Sci.* 2025 Jun 26;26 (13):6174. doi:10.3390/ijms26136174 PubMed PMID: 40649951; PubMed Central PMCID: PMC12249930.
29. Yorston D. Age-related macular degeneration (AMD): an introduction. *Community Eye Health.* 2025;37 (125):7–8. PubMed PMID: 40151374; PubMed Central PMCID: PMC11938193.
30. Merchant AA, Ling E. An approach to treating older adults with chronic kidney disease. *CMAJ Can Med Assoc J.* 2023 May 1;195 (17):E612–8. doi:10.1503/cmaj.221427 PubMed PMID: 37127307; PubMed Central PMCID: PMC10151089.
31. Shankland SJ, Rule AD, Kutz JN, Pippin JW, Wessely O. Podocyte Senescence and Aging. *Kidney360.* 2023 Oct 31;4 (12):1784–93. doi:10.34067/KID.0000000000000284 PubMed PMID: 37950369; PubMed Central PMCID: PMC10758523.
32. Babaker R, Alzimami L, Al Ameer A, Almutairi M, Alam Aldeen R, Alshatti H, et al. Risk factors for age-related macular degeneration: Updated systematic review and meta-analysis. *Medicine (Baltimore).* 2025 Feb 21;104 (8):e41599. doi:10.1097/MD.00000000000041599 PubMed PMID: 39993131; PubMed Central PMCID: PMC11856985.
33. Mishra E, Thakur MK. Mitophagy: A promising therapeutic target for neuroprotection during ageing and age-related diseases. *Br J Pharmacol.* 2023;180 (12):1542–61. doi:10.1111/bph.16062
34. Jan B, Dar MI, Choudhary B, Basist P, Khan R, Alhalmi A. Cardiovascular Diseases Among Indian Older Adults: A Comprehensive Review. *Cardiovasc Ther.* 2024 Jun 25;2024:6894693.



doi:10.1155/2024/6894693 PubMed PMID: 39742010; PubMed Central PMCID: PMC11323990.

ijms25168693 PubMed PMID: 39201377; PubMed Central PMCID: PMC11354581.

35. Goes-Santos BR, Carson BP, da Fonseca GWP, von Haehling S. Nutritional strategies for improving sarcopenia outcomes in older adults: A narrative review. *Pharmacol Res Perspect*. 2024 Oct 14;12 (5):e70019. doi:10.1002/prp2.70019 PubMed PMID: 39400516; PubMed Central PMCID: PMC11472304.
36. Das C, Das PP, Kambhampati SBS. Sarcopenia and Osteoporosis. *Indian J Orthop*. 2023 Nov 19;57 (Suppl 1):33–41. doi:10.1007/s43465-023-01022-1 PubMed PMID: 38107805; PubMed Central PMCID: PMC10721746.
37. Chen R, Yang C, Yang F, Yang A, Xiao H, Peng B, et al. Targeting the mTOR-Autophagy Axis: Unveiling Therapeutic Potentials in Osteoporosis. *Biomolecules*. 2024 Nov 15;14 (11):1452. doi:10.3390/biom14111452 PubMed PMID: 39595628; PubMed Central PMCID: PMC11591800.
38. Autophagic failure with age: influence on metabolic disorders and prospects for therapeutic targeting. *Expert Opin Ther Targets* [Internet]. [cited 2026 Sep 28]. Available from: <https://www.tandfonline.com/doi/abs/10.1080/14728222.2025.2584012>
39. Mundo Rivera VM, Tlacuahuac Juárez JR, Murillo Melo NM, Leyva Garcia N, Magaña JJ, Cordero Martínez J, et al. Natural Autophagy Activators to Fight Age-Related Diseases. *Cells*. 2024 Sep 26;13 (19):1611. doi:10.3390/cells13191611 PubMed PMID: 39404375; PubMed Central PMCID: PMC11476028.
40. Xu T ting, Deng Y yi, Yu X yong, Li M, Fu Y yuan. Natural autophagy modulators in non-communicable diseases: from autophagy mechanisms to therapeutic potential. *Acta Pharmacol Sin*. 2025 Jan;46 (1):8–32. doi:10.1038/s41401-024-01356-y PubMed PMID: 39090393; PubMed Central PMCID: PMC11697321.
41. Yoshihara K, Horiguchi M. Drug Delivery Strategies for Age-Related Diseases. *Int J Mol Sci*. 2024 Aug 9;25 (16):8693. doi:10.3390/

HOW TO CITE: Gayatri Gaikwad, Priya Daingade, Tushar Shelke, Impaired Autophagic Clearance in Aging: Mechanisms and Therapeutic Perspectives on Age-Related Diseases, *Int. J. of Pharm. Sci.*, 2026, Vol 4, Issue 10, 3758-3768. <https://doi.org/10.5281/zenodo.23640715>

