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1 Review

The Role of Autophagy in Maintaining Human Health and Disease Prevention

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Abstract Autophagy, a highly conserved catabolic process, plays a fundamental role in maintaining cellular homeostasis by degrading and recycling unnecessary or dysfunctional cellular components through lysosomal pathways. It serves as a vital mechanism for clearing damaged proteins, organelles, and other cytoplasmic constituents, ensuring the cell's functional integrity, especially under stress conditions such as nutrient deprivation. Various forms of autophagy macro-autophagy, micro-autophagy, and chaperone-mediated autophagy are involved in distinct regulatory pathways that respond to different physiological and pathological stimuli. Recent research continues to uncover the molecular underpinnings and biological significance of these pathways, emphasizing their critical contributions to human health and disease.

Keywords Autophagosome, Lysosome, mTOR Pathway, Phagophore, Protein Degradation

1. Introduction

Autophagy is derived from the Greek terms auto, which means "self," and Phay, which means “eating” [1]. Christian de Duve discovered that lysosomes are cellular organelles in the 1950s when he reported the existence of several hydrolases thanks to the advancement of electron microscopy. Autophagy was defined by de Duve in 1963 as the process by which cells fuse vesicles holding proteins with lysosomes, resulting in the breakdown of cellular protein [2,3]. Both humans and yeast go through autophagy, which involves transferring cytoplasmic items to the lysosome for elimination and recycling [4].

Autophagy is the broad term for the breakdown of cytoplasmic components within lysosomes.[5]. Autophagy may also perform additional tasks and is vital for cellular housekeeping since it can eliminate tired, superfluous, or undesirable components [6]. CMA is a selective type of autophagy that only targets proteins for lysosomal breakdown [2]. Cytoplasmic chaperons belonging to the Hsp70–Hsp90 family and membrane receptors that can identify protein complexes are required for this process to function with chaperons [7]. Only in stressful circumstances

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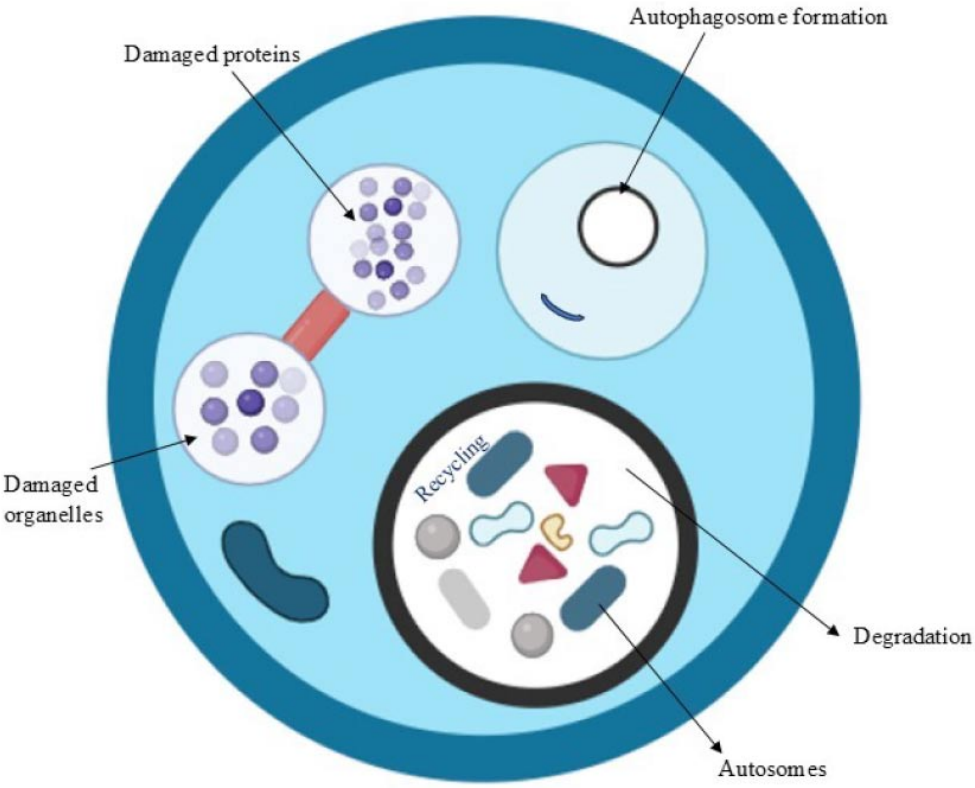


Graphical Abstract

and in mammalian cells has this type of autophagy been found [7,8]. Autophagy is relatively low in cells under normal circumstances, however when hunger and certain signalling molecules are present, it increases several times [7,9]. The fact that skeletal muscle cells' levels of mitophagy diminish with age, which lowers the muscles energy supply, may help to explain this [10]. By eliminating cancerous cells and breaking down endogenous or external carcinogens, autophagy the body's main cleansing process may prevent or treat cancer. Additionally, it can promote the growth of healthy cells. [1]. It resists harmful, degenerative, carcinogenic, and pathogenic substances to keep the body's systems in balance and regulate everyday activities; hence, its dysregulation is known to result in a variety of human illnesses [1].

Recent studies have revealed that autophagy has a wider range of physiological and pathological functions than previously believed, including development, anti-aging, tumour suppression, antigen presentation, microorganism elimination, cell death, starvation adaptation, and intracellular protein and organelle clearance [5]. The three stages of autophagy are amino acid/peptide synthesis, breakdown, and sequestration. Although the inflammatory reaction brought on by bacterial pneumonia can be lethal, inflammation is necessary for the antibacterial response. Therefore, it could be challenging to establish clear connections between autophagy and higher-order processes [5].

In this contribution, we investigate the functions of autophagy activators and inhibitors in the preservation of cellular equilibrium and elaborate on their dysregulation in glaucoma. Our analysis is situated within the broader landscape of disease, in which autophagy is being recognized as a critical therapeutic axis.

2. Process and Types of Autophagy

The autophagic process is divided into four steps:

(1) commencement and nucleation of phagophores.

(2) expansion and closure of phagophores to create a complete autophagosome.

(3) Joining the lysosome.

(4) Autophagic cargo breakdown and release/ recycling. Each of these processes requires a different autophagy-related (ATG) protein. Process of autophagy is details in Figure 1.

2.1. Types of Autophagy

2.1.1 Micro autophagy

After the yeast Saccharomyces cerevisiae demonstrated macro autophagy and the majority of the core autophagy related (ATG) genes were discovered in

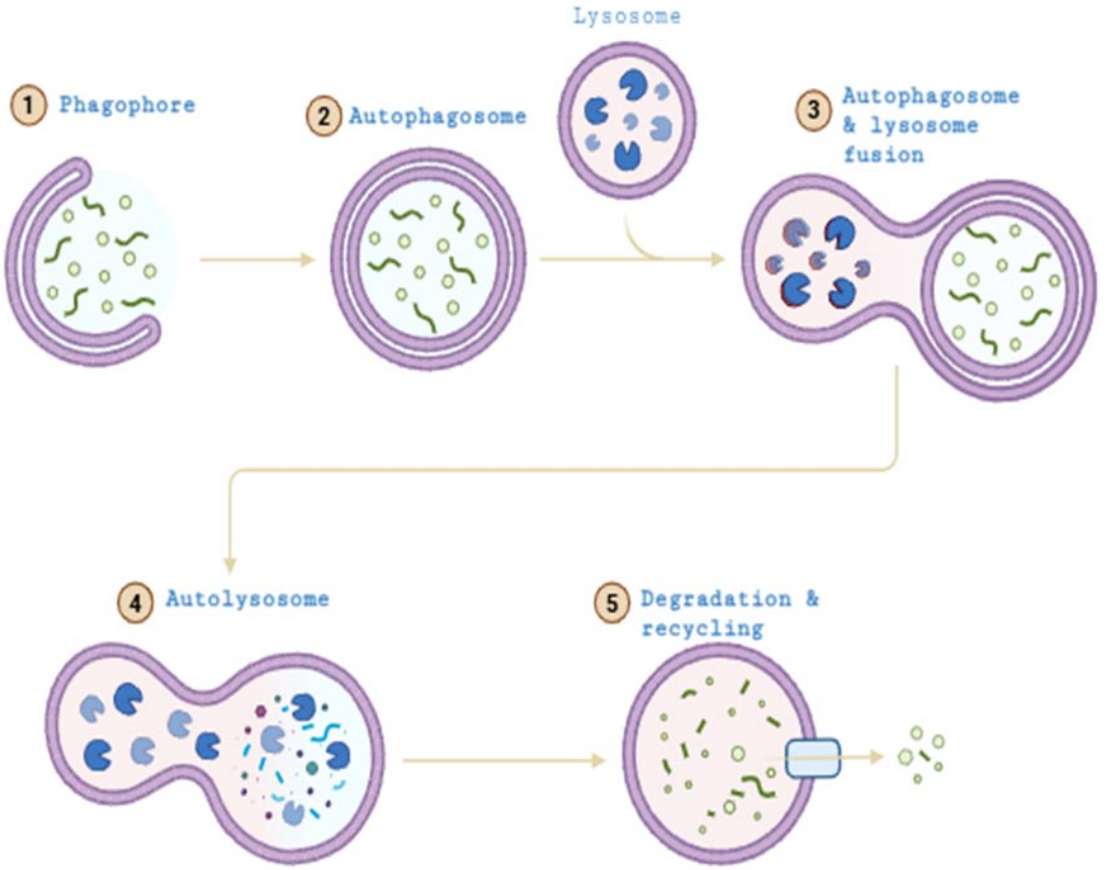


Figure 1: Process of autophagy, shows the main stages of macroautophagy, which include the production of phagophores, the maturation of autophagosomes, and their fusion with lysosomes, which results in the breakdown and recycling of cellular material.

1993, studies on the molecular mechanisms behind macro autophagy commenced in 1992 [11,12]. Research on macro autophagy soon spread from yeast to plants and mammals, revealing its importance in a range of biological processes and human illnesses which brought the area a lot of attention [12,13]. For breakdown during macroautophagic, a double membrane structure isolates random cell material, including organelles, soluble cytosolic proteins, and protein clumps [6]. This structure is known as the autophagosome. The double-membraned, cup-shaped phagophore is the first morphologically identifiable structure in macro autophagy; its edges extend and combine to form an autophagosome [14]. Several proteins have been identified as playing a function in macro autophagy [6]. Known as ATG genes, most of these were found while screening of yeast mutants lacking autophagy or the related CVT pathway itself [15,16]. The phosphatidylinositol 3-kinase (PI 3K) complex is another key protein complex in macro autophagy because it facilitates the nucleation of vesicles [17]. Three highly conserved proteins the phosphatidylinositol 3-kinase Vps34 [24], the protein kinase Vps15, and Atg6 are part of this complex. However, higher eukaryotes have not yet been shown to have Atg17 homologues [18]. The molecular elements of macro autophagy were first identified in yeast, where genetic screens found over 40 ATG (autophagy-related) proteins that control macro autophagy at various phases, the majority of which have mammalian orthologs [14].

A highly conserved cellular system called macro autophagy, or autophagy, enables cells to degrade and recycle their internal constituents (Figure 2). It is necessary for maintaining cellular homeostasis and responding to a variety of stressful events, such as malnutrition, infection, and hypoxia. The mechanics, physiological applications, and pathological abnormalities linked to macro autophagy are examined in this review [19].

2.1.1.1 Mechanism of macro-autophagy

The following sequential stages are part of the dynamic, multi-step process of macro autophagy:

Induction: The activation of the Unc-51-like kinase 1 (ULK1) complex, which is made up of ULK1,

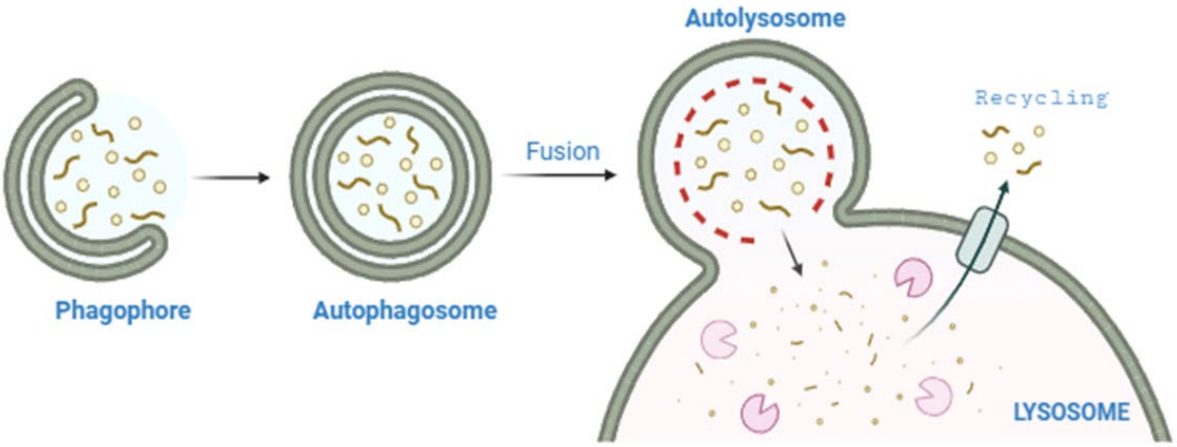


Figure 2: Working of macro-autophagy, shows how a phagophore develops into an autophagosome, which then merges with a lysosome to produce an autolysosome, enabling the breakdown and recycling of cellular material.

ATG13, ATG101, and FIP200, marks the start of macro autophagy. Mammalian target of rapamycin (mTOR), a nutrient-sensing kinase that tightly controls autophagy, inhibits it in nutrient-rich environments [20]. When cellular stress or food deprivation inhibits mTOR, the ULK1 complex can phosphorylate downstream targets and trigger autophagy [20]. In turn, this causes the phagophore assembly site (PAS) to attract autophagy machinery[21].

Nucleation: During this stage, a first membrane called the phagophore is formed. The forerunner to the autophagosome is this membrane [22]. This phase is crucial for the class III phosphatidylinositol 3-kinase (PI3K) complex. Beclin-1, VPS34, VPS15, and ATG14L form the complex, which produces phosphatidylinositol 3-phosphate (PI3P) at the PAS. By attracting autophagy-specific proteins that encourage phagophore growth, PI3P serves as a Signalling molecule [23].

Elongation and Cargo Sequestration: As the phagophore membrane lengthens, it absorbs cytoplasmic substances such as intracellular pathogens, protein aggregates, and damaged organelles [24]. Two conjugation systems like ubiquitin mediate this phase. Light chain 3 (LC3) of microtubule-associated protein 1 lapidates, and the ATG12–ATG5–ATG16L1 complex develops on the expanding phagophore membrane [25]. Following ATG4's breakdown of LC3 to create LC3-I, LC3 is conjugated to phosphatidylethanolamine (PE) to create LC3-II.

Finalization and Development: Finally, the autophagosome, a double-membraned vesicle, forms when the expanding phagophore encloses the targeted cytoplasmic material. This mechanism is necessary for the development of autophagosomes and the identification of cargo [12]. During growth, the autophagosome also recruits proteins and anchoring factors for subsequent fusion with lysosomes [25].

Fusion of lysosomes: An autophagosome is fused with a lysosome to form an autolysosome. This crucial step is mediated by proteins including SNAREs, Rab GTPases, and tethering factors, ensuring precise docking and membrane fusion [26]. Hydrolytic enzymes are regulated by the acidic environment of the lysosome

Degradation and Recycling: The material that is captured by the autolysosome is then broken down into its constituent parts by the lysosomal hydrolases that are present in the organelle as well as other hydrolases that are imported into the organelle [27]. These include sugars, fatty acids and amino acids which are then transported back into the cytoplasm for use in anabolic and energy producing processes thus aiding in the maintenance of homeostasis [28].

2.1.1.2. Physiological Roles of Macro autophagy

Macro autophagy has several crucial roles in the physiology of cells and organisms, including:

Nutritional Recycling: Macro autophagy is the process whereby cells digest their own components and produce the necessary ingredients when there is no enough food intake [21]. This ensures the formation of energy and construction of macromolecules that are necessary for living [29].

Organizational Quality Control: Autophagy is a process that identifies and focuses on those organelles which are damaged or unrequired such as ER-phage, pexophagy for peroxisomes and mitophagy for mitochondria. This helps in maintaining the health of the cells as it avoids accumulation of dysfunctional organelles [30,31].

Immune Defence: Autophagy assists the immune

system in the process of antigen presentation and getting rid of intracellular pathogens (xerophagy). It also neutralizes cytokines and inflammasomes, which are proteins that mediate inflammation by disassembling them [32].

Development and Differentiation: In the processes of cell differentiation, tissue remodelling and embryogenesis, autophagy is involved [16]. It is also involved in disposal of the cellular components that are required for these processes. Tumour Suppression: Autophagy inhibits removal of carcinogenic materials the damaged proteins and organelles. It also decreases the cellular stress which might lead to carcinogenesis [23,33].

2.1.1.3. Macro autophagy Defects and Associated disorders:

The various illnesses which have been associated with the dysfunction of autophagy have made clear its role in the maintenance of cell and organismal homeostasis [20]. Huntington's, Parkinson's and Alzheimer's diseases are the result of inadequate levels of autophagy which leads to deposition of proteins aggregates and damaged organelles [18]. Parkinson's disease and Alzheimer's disease, for instance, are linked to decreased clearance of α-synuclein and amyloid-β protein clumps, respectively [22].

Autophagy has two functions concerning cancer. On the one hand, autophagy serves to prevent the development of cancers by maintaining the normal state of cells[34]. However, pre-existing tumours can exploit autophagy for their survival in hostile conditions such as lack of food and oxygen. Autophagy inhibitors are being studied as potential agents in cancer therapy [25]. In infectious Diseases, some pathogens avoid autophagy-induced damage by either avoiding autophagosome-lysosome fusion or by fleeing the autophagic compartments. For example, this type of survivorship is used by Salmonella and Mycobacterium TB within their hosts [35,36]. Obesity, Type two diabetes and Non-alcoholic fat liver are examples of metabolic disorders forming a cluster of metabolic spectrum disorders that result from the dysregulation of autophagy [15]. Some of these conditions involve defective mitochondrial function or defective lipophagy, which is the autophagic degradation of lipid droplets [16]. Autophagy helps shield the heart from ischemia reperfusion injury by reducing oxidative stress and eliminating damaged mitochondria [14]. On the contrary, lack of strict regulation of autophagy enhances heart failure [11]. Crohn's disease and systemic lupus erythematous (SLE) both are chronic inflammatory and auto autophagy disoeders [26]. It also modulates cytokines and alters antigen presenting cells and responses.

2.1.1.4. Implications for Therapeutics

Lysosomal fusion parallax and the more common depression of chloroquine & hydroxychloroquine is the focus for some of the researches especially in terms of targeting cancer [4]. A basic mechanism essential to cellular development, homeostasis, and stress response is macro autophagy [37]. Its complex regulation fortified various pathological states, portraying its several physiological functions as well [38]. The recent advances in the understanding of how molecular machinery controls autophagy presented new avenues to approaches to diseases [39]. More research is required to improve various strategies and tackle the tasks set by the modulation of autophagy [28].

2.1.2. Micro-autophagy

In the early 1980s, electron microscopic investigations of animal cells also revealed micro autophagy is a procedure whereby cytosolic proteins enter lysosomes through the lysosomal membranes [12]. When multi-vesicular bodies (MVBs) are formed, soluble proteins are transported to the late endosomes [40]. Therefore, both endocytic and autophagic components are involved in micro autophagy [1]. The two kinds are invagination and protrusion. The best-characterized protrusion-type micro autophagy route is micropexophagy, which occurs in the yeast Komagata Ella phaffii. It is known to incorporate membrane deformation dependent on the ATG8/ ATG12 conjugation systems as well as de novo membrane synthesis covering the membrane closure point. [12]. These processes are most likely mediated by macro autophagy machinery like core ATG proteins and SNARE proteins. Micro-autophagy is also known to preferentially break down lysosomal membranes (macrolipophagy), lipid droplets (macrolipophagy), photodamaged chloroplasts (microchlorophagy), and subdomains of the nucleus (microencephaly) [41]. Cellular components are broken down by lysosomes through membrane invasions in Endo lysosomal system compartments during micro autophagy [14]. Although only micro-ER-phage has been discovered in human systems to date, micro-autophagy can also break down proteins and other organelles in yeast, including mitochondria, lipid droplets, ER, peroxisomes, and even nuclear fragments [42]. In LE/ MVBs, the breakdown of cytosolic proteins is referred to as endosomal micro autophagy (Emi), which can be further divided into subcategories according to the molecular machinery and cargo selectivity

[14]. The majority of cargo degradation takes place during LE/MVB-lysosome fusion, however it can also happen in the LE/MVB compartment itself [43].The degradation of several macro autophagy receptors by this route may control the transition between in bulk and selective macro autophagy. In Drosophila, oxidative and genotoxic stressors as well as food deprivation cause an upregulation [12,41]. Both TOR and the EGO complex are regulatory complexes that govern micro autophagy. The GTPase Gtr2 and the proteins Ego1 and Ego3 make up this complex [44]. In vitro, micro autophagy could be inhibited at different stages using a variety of chemical inhibitors. However, because at mutants involve the vacuole's uptake of bigger particles, they appear to be partially impaired in specific selective micro autophagic processes (such as mitophagy or macropexophagy) [6]. We don't know much about micro autophagy, particularly how it's regulated and its potential effects on human health and illness, because there aren't many methods accessible for its investigation [45]. The process of micro autophagy is detail din Figure 3.

The method by which micro autophagy begins is rather selective and involves the recognition of certain cytoplasmic substrates. Proteins that are designated for degradation typically have a unique sequence known as the KFERQ motif; it functions as a sort of identification tag [46]. This motif aids in identifying the proteins that are ready for autophagic degradation. Things start to become interesting at this point because of the heat shock cognate protein 70, or HSC70 for short [47,48]. The KFERQ-containing proteins are identified as the ones that must be escorted off for lysosomal destruction, much like a bouncer at a club. In fact, HSC70 binds to these proteins to ensure they are prepared for their exit [46]. Because it indicates that only specific proteins are involved, this identification process is extremely significant.

2.1.2.1. Stage 1: Recognition

Micro autophagy starts with the recognition of cytoplasmic substrates. Specific proteins meant to be degraded often contain a conserved pentapeptide motif, the KFERQ motif [49]. Recognition signals indicate which proteins should be destroyed through autophagic degradation [7]. This step is based on the function of HSC70, a molecular chaperone [48]. HSC70 binds to proteins containing the KFERQ pentapeptide, treating them as substrates for lysosomal degradation [48,50]. This selective targeting guarantees that only select proteins, including damaged or misfolded proteins, are broken down so that proteostasis can survive in the cell [42].

Stage 2: Binding

During this subsequent stage, or Binding, a fascinating phenomenon occurs [51]. Once a substrate has been detected, the HSC70 complex will interact with certain receptors on the lysosomal membrane, now bound to the substrate [52]. One important component of this interaction is LAMP2A. It plays a vital role in binding and pushing things along in the micro autophagic pathway [53].

Stage 3: Internalization

The internalization stage is described as the

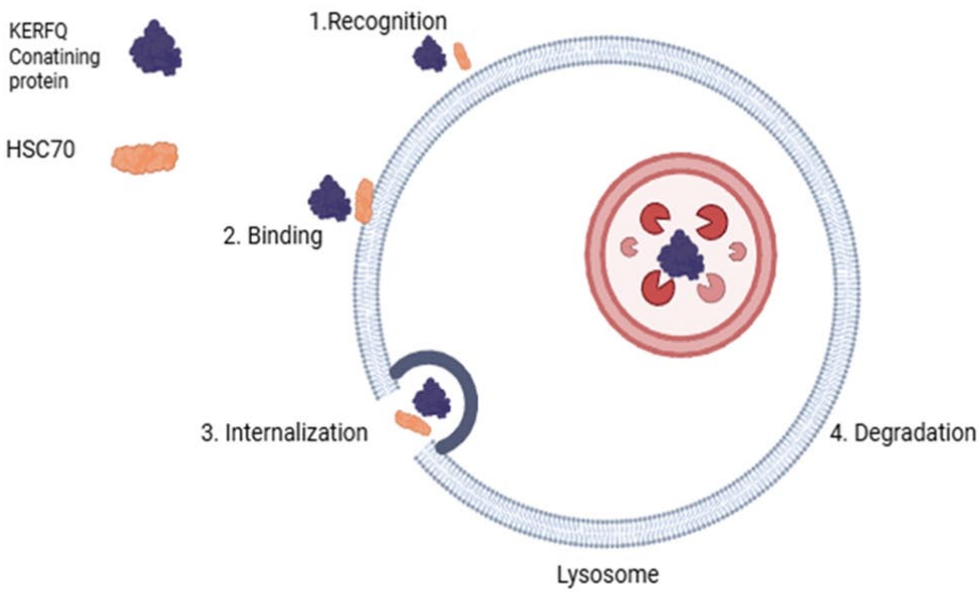


Figure 3: Process of Micro-autophagy, shows the key stages of chaperone-mediated autophagy, wherein HSC70 locates, binds to, internalizes, and moves KERFQ-containing proteins into the lysosome for elimination.

phase in which the substrate is covered by a lysosomal membrane. Internalization takes place either by invagination, protrusion, or septation of the lysosomal membrane, depending on what type of micro autophagic event is taking place [54]. This is the process by which the substrate-bound-membrane-later becomes engaged as a series of invaginations or intraluminal vesicles (ILVs) formed by the invagination of the lysosomal membrane around regions of substrate and ultimately secludes it inside the lysosome [38,40]. Sometimes, non-selective engulfment of lysosomal material might even occur and is responsible for exporting bulk cytoplasmic material for degradation by the lysosome under nutrient-starvation conditions [55]. Internalization is a very dynamic process influenced by numerous cellular parameters, including nutrient levels and stress signals [7,56]. The ingested substrate would be affected by the lysosome's enzymes [57]. The food consumed is broken down by these hydrolytic enzymes, which include lipases, proteases, Lysosomal enzymes accelerate the breakdown of numerous compounds and perform a number of other crucial tasks in addition to contributing to the autophagy and phagocytosis of cellular components[58].

Once the basis units have decayed, the cytoplasm will recycle them back into use for metabolic processes [42,59]. Although damaged or superfluous cellular components are eliminated through breakdown, nutrients are released for cellular activity through metabolic stress [45,60]. Thus, effective breakdown is essential for maintaining cellular energy balance and preventing dangerous aggregates [1,20].

2.1.2.2. Autophagy regulation

Micro autophagy is modulated by a dynamic interaction between various signalling pathways and multiple cellular components [61]. A few important regulatory pathways include:, the mammalian target of rapamycin (mTOR), an important regulator of autophagy. mTOR activation inhibits micro autophagy and other related autophagic pathways under nutrient-rich conditions [7,62]. However, inhibition of mTOR during starvation conditions leads to an increased level of autophagy [20], Low-energy-dependent kinase that inhibits mTOR and directly activates autophagy-related proteins [63,64]. The lysosomal dynamics are critical for the proper functioning of lysosomal membrane receptors, such as LAMP2A, which is key for substrate binding and internalization [65]. Post-translational modifications, Phosphorylation, acetylation, and ubiquitination of autophagic proteins control their functions and associations, thus affecting the process of micro autophagy [6].

2.1.3. Chaperone-mediated autophagy [CMA]

Highly selective, CMA shares a pentapeptide targeting motif that is biochemically linked to KFERQ with all of its substrates [45]. It is believed that approximately 30% of cytosolic proteins have such a sequence based on immunoprecipitation tests and sequence analysis[52]. Proteins involved in vesicular trafficking, calcium and lipid binding proteins, transcription factors and their inhibitors, proteasome components, and several glycolytic enzymes are among the many substrate proteins that CMA breaks down [45,48]. The only time these proteins degrade is when CMA is triggered [6]. CMA only occurs in proteins that have a C-terminal pentapeptide KFERQ motif; cytosolic proteins with this sequence are recognized by the HSC70 cochaperone and transported to the lysosome [1]. The mechanism of CMA is shown in Figure 4.

The first stage of CMA, which is known as target protein recognition. The KFERQ-like motif is a unique pentapeptide motif, which is essentially a tag, found in proteins that are destined to degrade [38] [48]. The initial sequence of the protein may have this motif, or it may appear after the protein is produced [12]. A cytosolic chaperone complex, mostly composed of Hsc70 (not to be confused with heat shock cognate protein 70) and its friends, intervenes to identify it once it is exposed [66]. Hsc70 is important in this situation; it functions similarly to a club bouncer, only allowing the appropriate proteins to enter by attaching to the KFERQ motif [67]. Because it ensures that CMA is selective and doesn't randomly break down proteins, this step is crucial.

When LAMP-2A actually binds to the substrate, there is a kind of morphological transformation into a larger structure, which is really helpful in all subsequent steps of the process in Chaperone-Mediated Autophagy [68]. Interestingly, how much of LAMP-2A is present on a lysosomal membrane can vary [48]. Such variations can actually greatly affect how efficient CMA will become [38]. Things such as the condition of the cell, oxidative stress, and even nutritional levels can have huge implications on how LAMP-2A works [12]. Alright, so let's dig a little deeper into just exactly how these substrate proteins are getting inside the lysosome [69]. It's pretty cool, actually. When the substrate runs into LAMP-2A, it starts to unroll, meaning that it can fit inside the narrow channels formed by the oligomers of LAMP-2A[66]. Hsc70 and its buddies are part of what helps to do this unfolding once the substrate is inside the lysosome [48]. Lys-Hsc70 steps in then to make sure

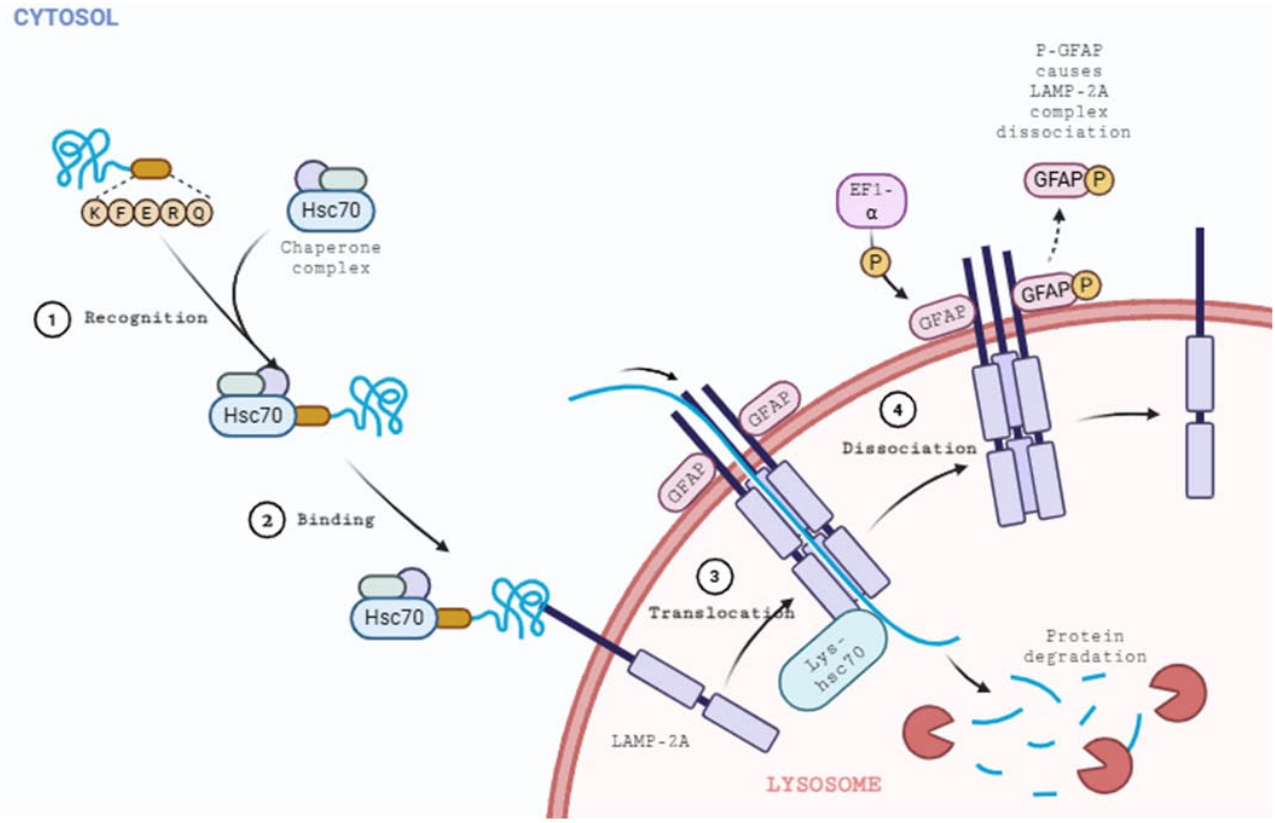


Figure 4: Mechanism of CMA, depicts the mechanism of chaperone-mediated autophagy, showing how Hsc70 recognizes and transports substrate proteins to the lysosomal membrane for translocation and subsequent degradation.

it folds right and assists in further internalization of its substrate [68]. It's a rather complicated dance, really. All this movement implies fantastic team work by the chaperones inside the cytosol followed by the lysosome just showing how well everything works within the process [70]. After passing through with decline and dissociation, the substrate protein is discharged into the lysosome lumen [52,60]. It comes into contact with a number of hydrolytic enzymes, such as proteases, which degrade it into smaller peptides and amino acids [71]. Such degradative breakdown is quite useful because of the property of this cell to use parts for various purposes again [66]. Then, at this stage of cleavage, it breaks the CMA cycle by releasing a substrate where the LAMP-2A oligomer collapses [67]. It is supported and co-ordinately performed with some ancillary proteins of which is EF1α and also glial fibrillary acidic protein [5].

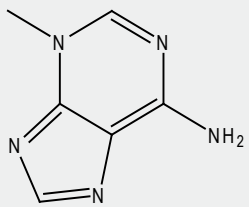
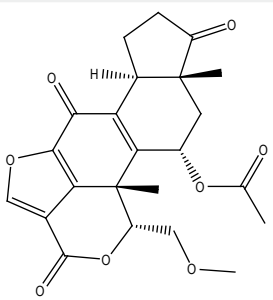
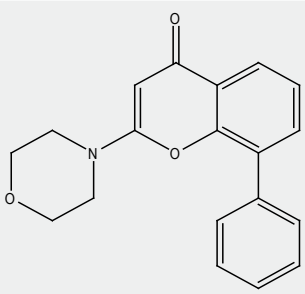
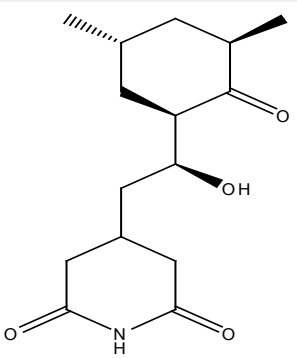
CMA's physiological activities support the process of stress adaption and are essential for maintaining cell homeostasis [67]. By dissolving damaged or wrongly folded proteins, CMA prevents toxic aggregates from increasing, thereby preventing neurodegenerative diseases [70]. It also hugely impacts the adaptation of our body to metabolic shifts [71]. As soon as nutrients become inadequate, CMA comes in to supply amino acids for energy [72]. This adaptive response is what the energy balance relies on [5,20]. Next comes the oxidative stress response. CMA keeps everything in check by clearing out oxidized proteins and protects our cells from damage [37]. CMA enhances our immune system's capacity to combat infections by degrading compromised immunological components [73]. Lastly, there is a link to tumour suppression [67]. This action of CMA is essential in controlling the pathways responsible for cancer, and very relevant for the prevention of cancer. This process is controlled by numerous factors which include the Nutrient status: LAMP-2A increased during fasting and starvation with high activity of CMA; Hormonal Signals: through the control of and links to our metabolic pathways such as hormones with insulin and glucagon CMA [48,68,71]. Reduction in oxidative stress as brought upon by activation by reactive oxygen species, an ROS-mediated effect on LAMP2A activity of which, naturally declines as people age in their years, causing diminished CMA activities [74]. This is usually accompanied by low levels of LAMP-2A and lysosomal activity [48]. CMA mediates the degradation of protein substrates, thereby regulating a host of physiological processes [57]. Normal functioning of these physiological processes is therefore ensured by the integrity of the

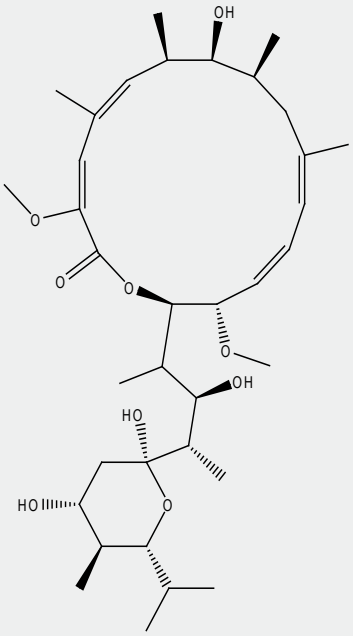
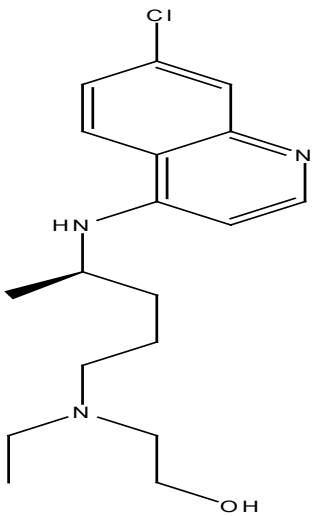
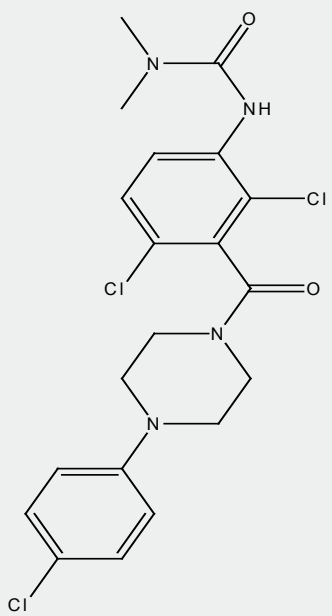
CMA function, while deficiency in CMA would disrupt this balance [75].

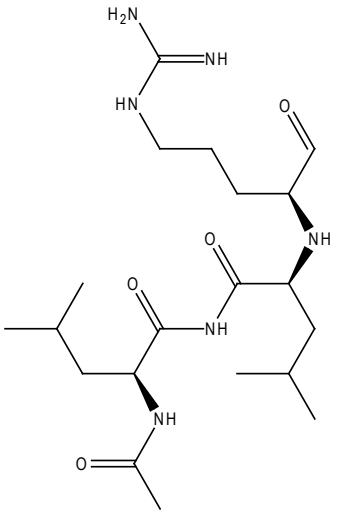
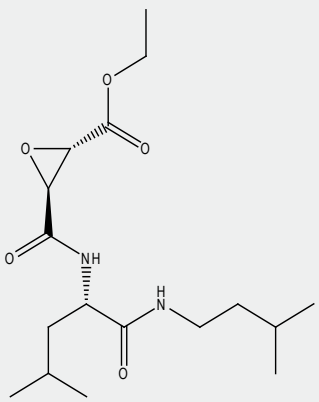
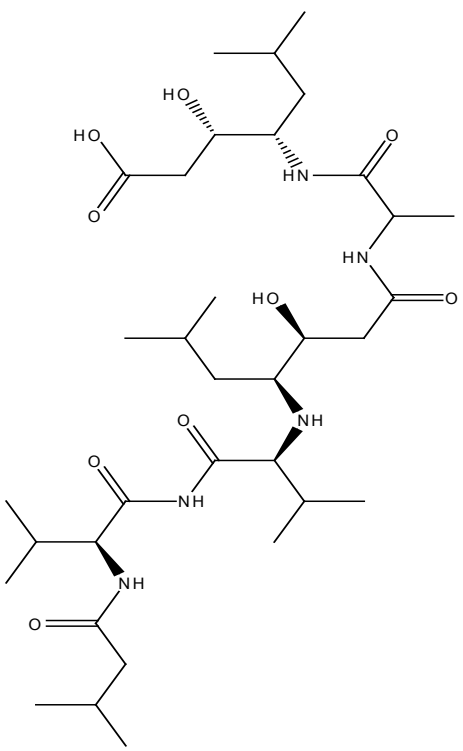
3. Autophagy inhibitors and activators

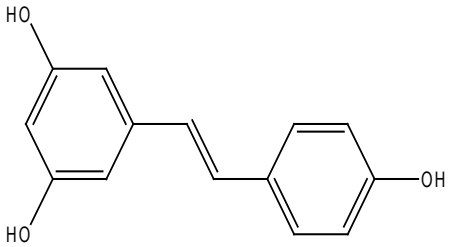
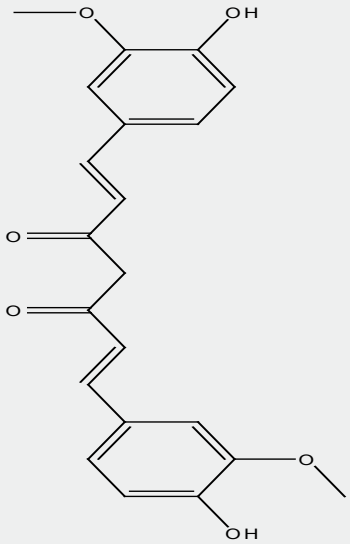
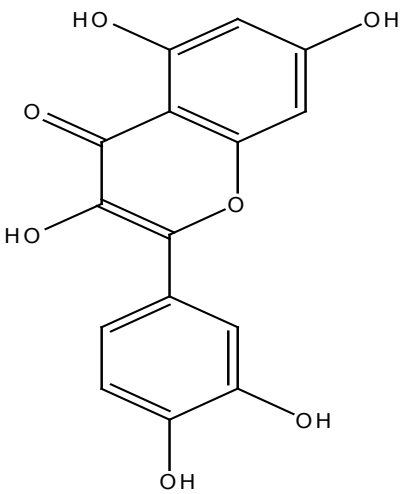
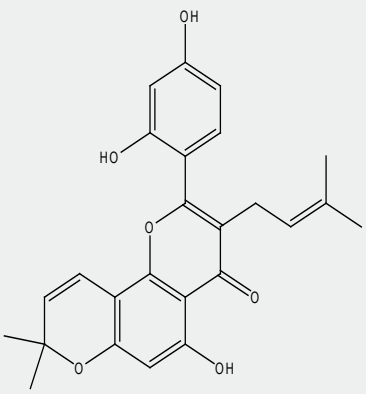
In a certain membrane domain, a population of PI3Ks may be activated, which could lead to autophagosome formation [73]. Three forms of PI3Ks have been identified in mammalian cells [73]. Autophagy inhibition is a function of class I PI3K[28]. Autophagic control is believed to be unrelated to class II PI3K activity [76]. The early stages of autophagosome formation in human cells depend on class IIIPI3K, an autophagy activator and functional homologue of yeast Vps34 [73].activators of autophagy Numerous recent articles discuss how upregulating autophagy may be therapeutically beneficial for a variety of illnesses [7]. The potential therapeutic benefit of autophagy activators has made new study on them a popular issue [1]. A developing list of autophagy activators and inhibitors is provided below.

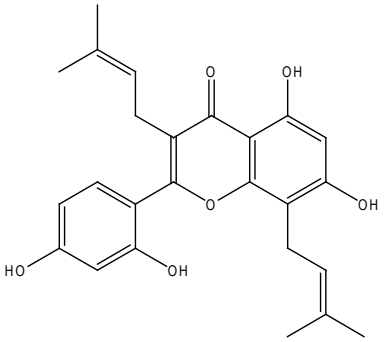
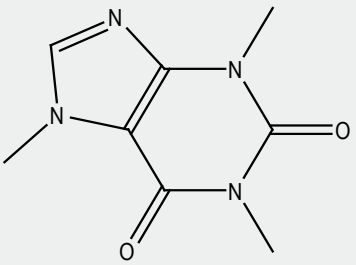
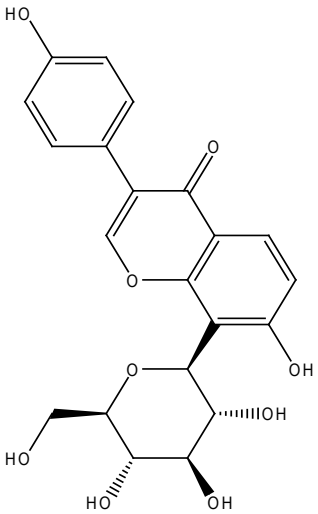
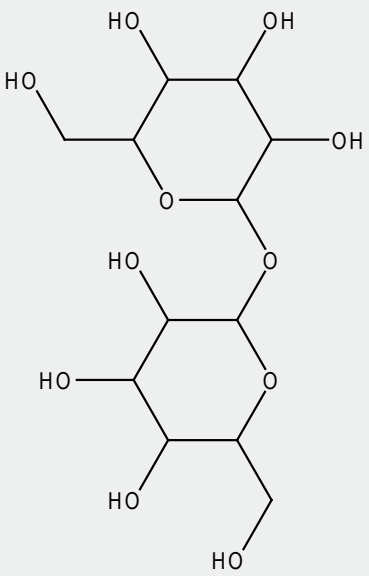
Table 1: Various inhibitors and activators of autophagy

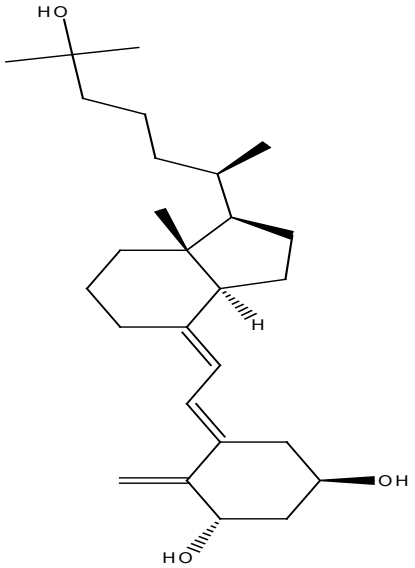
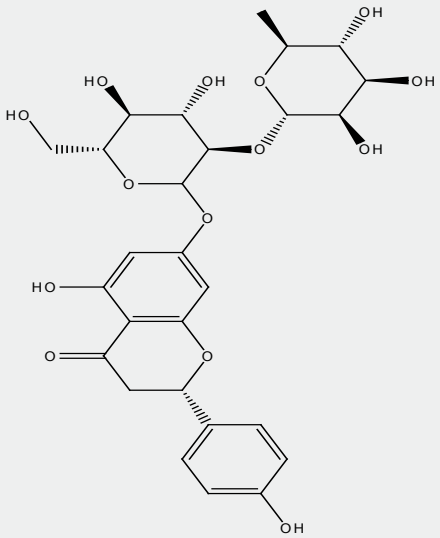
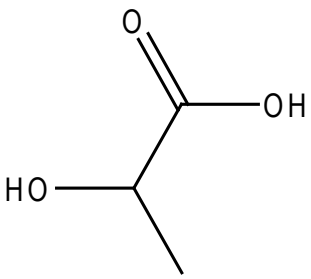
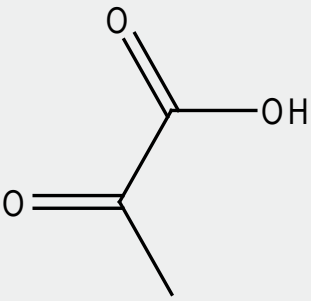
Sr.no.	Name and molecular formula	Structure	Mechanism	References
		INHIBITORS		
1.	3-Methyladenine - C6H7N5		inhibitor of PI 3-kinase	[77]
2.	Wortmannin - C23H24O8		inhibitor of PI 3-kinase	[78,79]
3.	LY294002 - C19H17NO3		inhibitor of PI 3-kinase	[78,79]
4.	Cycloheximide- C15H23NO4		inhibitor of protein synthesis	[80]

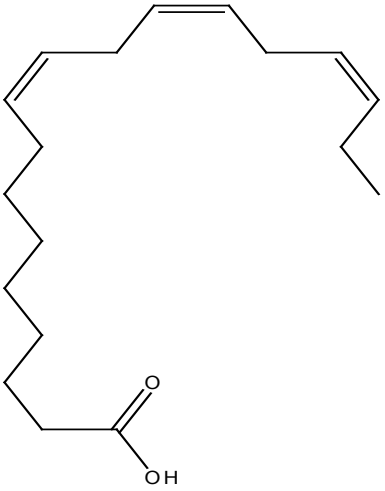
5.	Bafilomycin A1- C35H58O9		ATPase inhibitor of the vacuole type	[81]
6.	Hydroxychloroquine- C18H26ClN30		Lumen alkalizer in the lysosomes	[73,82]
7.	Lys05- C23H24C13N5		- Lumen alkalizer in the lysosomes	[83]

8.	Leupeptin - $C_{20}H_{38}N_6O_4$		An inhibitor of acid protease	[84]
9.	E64d - C17H30N2O5		An inhibitor of acid protease	[73,85]
10.	Pep statin - $C_{34}H_{63}N_5O_9$		An inhibitor of acid protease	[73,85]
		ACTIVATORS		

11.	resveratrol-$C_{14}H_{12}O_3$		disturbance of the BECN1 –Bcl-2 complex, AMPK activation, and the PI3K/ Akt/mTOR pathway	[7,86]
12.	curcumin- $C_{21}H_{20}O_6$		inhibition of the PI3K/Akt/ mTOR system	[87]
13.	quercetin- $C_{15}H_{10}O_7$		suppression of the Akt/mTOR pathway and its impact on HIF-1α-mediated signal transduction; activation AMPK and SIRT1	[88]
14.	morusin- C25H24O6		restricting p70S6K phosphorylation, which impacts the mTOR-Sch9/ p70S6K pathway	[89]

15.	mulberrin- $C_{25}H_{26}O_6$		restricting p70S6K phosphorylation, which impacts the mTOR-Sch9/ p70S6K pathway	[7,89]
16.	caffeine- $C_8H_{10}N_4O_2$		blocker of the mTOR signalling pathway	[90]
17.	Puerarin- $C_{21}H_{20}O_9$		control over sirtuin-1 (SIRT1) and proteasome subunit beta 5 (prosbeta5)	[91]
18.	trehalose- $C_{12}H_{22}O_{11}$		suppression of the glucose transporters	[92]

19.	calcitriol- $C_{27}H_{44}O_3$		inhibition of the transporters of glucose	[7]
20.	naringin- $C_{27}H_{32}O_{14}$		SIRT1 and AMPK activation, regulation-based promotion of mitochondrial biogenesis of signals from LKB1/ AMPK/PGC-1α	[93]
21.	lactate- $C_3H_6O_3$		The precise process has not been determined however it is likely autophagy activation through ubiquitin-independent mechanisms.	[94]
22.	pyruvate- $C_3H_4O_3$		The precise process has not been determined however it is likely autophagy activation through ubiquitin-independent mechanisms	[7,94]

23.	linolenic acid- $C_{18}H_{30}O_2$		elevated expression of the pink-1 gene	[95]

4. Autophagy related disorders

Autophagy is like a cellular recycling system that helps remove waste and broken parts, keeping cells healthy. When it doesn't work properly, it can lead to various diseases, such as Alzheimer's, Parkinson's, and Huntington's due to protein buildup in the brain. Autophagy also plays a complex role in cancer, potentially preventing or promoting it. Some germs can even manipulate autophagy to evade the immune system. Additionally, autophagy problems are linked to metabolic issues like obesity, diabetes, and fatty liver disease. Researchers are studying autophagy to develop new treatments for these conditions[96]. Figure_5 represents various disorders associated with autophagy. A detailed overview of glaucoma is accessible further, taking into account latest updates on the condition.

Recent updates on autophagy in glaucoma: Autophagy in human glaucoma has just recently been investigated in vitro. Reduced levels of SQSTM1 and LC3-II proteins were observed in TM cell primary cultures isolated from glaucomatous eyes [97]. In order to determine if the data in this investigation represented elevated flux or hindered autophagy, autophagy flux was not measured. The upregulation and phosphorylation of the downstream MTOR signaling substrate RPS6KB in glaucomatous cells suggests constitutive activation of MTOR signaling [97,98]. Furthermore, when exposed to a hyperoxic environment, glaucomatous TM cells were unable to initiate autophagy reports autophagy, and lysosomal proteolysis was found to be reduced [97]. These findings provide credence to the theory that the outflow pathway exhibits a biphasic autophagy response, as has been shown in other illnesses (e.g., cancer, Alzheimer disease) [99]. Autophagy may be triggered early in an illness as a stress-reduction strategy (such as oxidative damage or mechanical stress), but later on, this mechanism may be disrupted, resulting in a reduction in autophagic function [45,52]. Additionally, patients with a subtype of lysosomal storage disorders frequently exhibit glaucoma and ocular hypertension as clinical symptoms [60].

The second most prevalent cause of permanent blindness in the world, glaucoma, is known to be associated with age. Retinal ganglion cells gradually degenerate as a result of this visual neuropathy [100]. Increases in ROS can cause trabecular-meshwork (TM) cells to decline throughout the normal aging process [39]. The development of glaucoma is significantly influenced by oxidative stress, which damages Intraocular pressure (IOP) and aqueous humour outflow are controlled by the trabecular meshwork (TM) cells. [98,101]. As a result, oxidative damage builds up with age, which leads to apoptosis and glaucoma [101]. In order to preserve intracellular homeostasis and defend against ongoing oxidative stress, TM cells trigger autophagy to get rid of damaged proteins and organelles [24,101]. For instance, it can trigger mTOR-independent autophagy, which may help TM cope with mechanical pressures and preserve cellular homeostasis [100]. used pig eyes in an in vitro experiment where they gave some eyes (control eyes) a normal physiological pressure of 8 mmHg and other eyes a high pressure of 30 mmHg [101]. Eyes under high pressure had higher levels of LC3-II (light chain 3-type II, microtubule-associated protein-1) compared to controls. The LC3-I (Type I) membrane component is substituted in order to initiate the manufacturing and elongation process of autophagosomes [97,98]. Moreover, TM

cells in the eyes exposed to high pressure contained autophagosomes and autolysosomes according to ultrastructural investigation [39].

Since optic nerve axotomy causes the death of RGCs, which is a hallmark of glaucoma, it can be used as a model to study the progression of the condition. Autophagy was found to increase within five days after mouse optic nerve axotomy. Both the overexpression of the autophagy regulator Atg5 and the formation of autophagosomes were blamed for this. Following axotomy, autophagy was demonstrated to increase RGC survival [102]. RGCs were shown to have mitochondria inside autophagosomes in this investigation. Using aged autophagy-deficient transgenic mice, an identical optic nerve axotomy experiment revealed that older people were more susceptible to injury than younger ones. These elderly animals displayed changes in the mitochondrial structure and oxidative stress response, which led to more axonal damage in RGCs [103]. In a different study, autophagy was found to initiate in the dendrites of RGCs instead of the cytoplasm of the cell in a rat model of glaucoma. Furthermore, it was discovered that the autophagosomes in the dendrites included organelles, indicating that dendritic activity may be active [104]. This suggests that cytoprotective stress may initially trigger autophagy, but that apoptosis may be triggered if the stress reaches a threshold. In a different study, however, autophagosomes were observed in RGC axons 1 hour following optic nerve axotomy in rats. Moreover, damage-induced axonal degeneration was accelerated when the autophagy process was suppressed [105]. Human TM cell cultures from glaucomatous eyes with high intraocular pressure (IOP) did not exhibit autophagy pathways when exposed to high oxygen concentrations(40 % O2) [106]. This structural protein was not altered in glaucomatous eye cells, while control TM cells from healthy eyes responded to hyperoxia by autophagizing because their levels of LC3-II increased. Moreover, LC3-II accumulation and increased LC3 immunoreactivity in the RGC layer were seen 6–24 hours after the short surge in a rat experimental paradigm in IOP [107]. In the same experimental setting, it was also shown that calpain-mediated cleavage of b2eclin-1 impairs the autophagy process [108]. Additionally, a model of transgenic mice that expressed the autophagosome LC3 and had chronic hypertension DBA/2J: GFP-LC3 and decreased autophagic flux demonstrated exacerbated axonal damage, elevated IOP values, and extra RGC loss when compared to the DBA/2J mouse model of spontaneous ocular hypertension [109]. Each of these trials shows that at the beginning of the illness, autophagy is quickly triggered in response to increased IOP. But if these ailments persisted over time, autophagic activity would reach saturation and cease to function as intended [77,105]. Thus, the pathophysiology and development of glaucoma may be influenced by the alteration of autophagic flow [98].

5. Summary

Autophagy, Is an primary faveolate mechanics that breaks down and recycles faveolate parts to confirm honeycombed homeostasis, Is a topic that Is reviewed In detail. Among the topics mentioned. The paper discusses several forms of autophagy, including as macro-autophagy, micro-autophagy, and chaperon-mediated autophagy. This review is primarily concerned with the activation and utilization of autophagy. Based on this review, the function of autophagy There are three types of glaucoma. On the one hand, autophagy may be neuroprotective, protecting retinal ganglion cells from stress and death, but it may also accelerate the disease's predictable progression if it is not controlled.

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Declaration of interest statement

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Authors' contributions

HIN: Conceptualization, data analysis; KJJ, ISD, UBG: Literature search and data analysis, writing original draft preparation

Conflict of Interest

The authors declare that they have no conflicts of interest.

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