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Autophagy in benign prostatic hyperplasia: insights and therapeutic potential

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Abstract

Autophagy is a cellular homeostatic mechanism characterized by cyclic degradation. It plays an essential role in maintaining cellular quality and survival by eliminating dysfunctional cellular components. This process is pivotal in various pathophysiological processes. Benign prostatic hyperplasia (BPH) is a common urological disorder in middle-aged and elderly men. It frequently presents as lower urinary tract symptoms due to an increase in epithelial and stromal cells surrounding the prostatic urethra. The precise pathogenesis of BPH is complex. In recent years, research on autophagy in BPH has gained significant momentum, with accumulating evidence indicating its crucial role in the onset and progression of the disease. This review aims to outline the various roles of autophagy in BPH and elucidate potential therapeutic strategies targeting autophagy for managing BPH.

Keywords Autophagy, Benign prostatic hyperplasia, BPH, Cell death pathways, Herbal therapy, Signaling pathways

Introduction

Benign Prostatic Hyperplasia (BPH) is characterized by the non-malignant proliferation of prostatic urethral tissues, which can lead to a cascade of lower urinary tract symptoms (LUTS), including obstructed urine flow and difficulties in urination, significantly impacting male health and quality of life [1]. Furthermore, BPH is highly prevalent among elderly men, and its incidence continues to rise as the population ages. The prevalence of histologically diagnosed BPH among males aged 31 to 40 is approximately 8%, while it escalates to over 80% among males aged 80 and above [2]. In 2019, the estimated global burden of BPH reached 11.26 million cases, significantly surpassing the 5.48 million cases reported in 1990 [3]. Modern medicine has made significant advancements in the treatment of BPH, with molecular mechanisms such as hormonal factors [4, 5], cytokines [6], and autoimmunity [7] receiving widespread attention in recent years.

Autophagy, meaning self-phagocytosis, refers to the process by which eukaryotic cells degrade their cytoplasmic proteins and damaged organelles via lysosomes. This process is regulated by autophagy-related genes (ATGs). Autophagy is classified into basal autophagy and inducible autophagy based on its level. Basal autophagy is stably and continuously present in most cells and is crucial for the renewal of cellular components under normal physiological conditions and the maintenance of internal environmental balance. Inducible autophagy, on the other hand, can provide protection to cells under specific conditions, defending against damage. As a protective response to stress conditions, autophagy degrades damaged organelles and proteins via the lysosomal pathway, preventing the accumulation of harmful substances within the cell, thereby helping to maintain cellular homeostasis and promoting cell survival [8].

BPH is a proliferation resulting from the disruption of the balance between cell proliferation and cell death [1]. Autophagy is widely present in the prostate tissues of

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BPH patients [9]. Additionally, as a survival mechanism, autophagy helps human prostatic stromal cells survive in mildly hypoxic environments caused by reduced blood flow to the prostate [10]. However, the ultimate outcome of autophagy's role remains controversial. Some believe that the continuous progression of BPH is due to the upregulation of autophagy [9]. Conversely, others have found that autophagy in BPH tissue cells decreases under both basal and inducible conditions [11]. In this review, we will elucidate the process and regulatory mechanisms of autophagy and analyze its various specific mechanisms of action in BPH. Finally, potential methods of utilizing autophagy to treat BPH will also be described.

The process and regulatory mechanisms of autophagy

Autophagy is a multi-stage process, including autophagy induction, autophagosome formation, autolysosome formation, and the degradation and recycling of its contents. The initiating factor of autophagy is UNC-51-like autophagy-activating kinase 1 (ULK1), which forms a complex with proteins such as Atg13 and FIP200, and is regulated by the mammalian target of rapamycin complex 1 (mTORC1). mTORC1, acting as a sensor of external stimuli in cells, typically inhibits ULK1 to maintain autophagy at low levels [12]. When mTORC1 is inhibited by external interventions such as rapamycin, ULK1 activity is released, significantly enhancing the autophagic response. AMP-activated protein kinase (AMPK) is a key regulator of cellular energy balance, activated when ATP supply is depleted during cellular stress responses, leading to an increased AMP/ATP ratio. AMPK activates autophagy either directly by phosphorylating mTORC1 and ULK1, or indirectly by regulating the expression of ATGs [13]. Additionally, the PI3K/AKT signaling pathway plays a central role in cell growth, proliferation, survival, and metabolism, and is an upstream regulator of mTORC1 [14]. Upon activation, Class I PI3K converts PIP2 to PIP3, attracting AKT to the cell membrane. Activated AKT then phosphorylates various proteins, including mTORC1, thereby inhibiting autophagy [15].

The autophagosome, a double-membrane structure formed from a phagophore, is the primary structure involved in autophagic degradation of intracellular material. The class III PI3K complex, composed of Vps34, Beclin-1, p150, and Atg14L, initiates autophagosome formation by producing PI3P [16]. Beclin-1 is a component of the class III PI3K complex Vps34 and is crucial for PI3P synthesis and autophagosome formation [17]. The activity of Beclin-1 is positively regulated by ATG14L1 and AMBRA1, and can also be negatively regulated by anti-apoptotic proteins [18]. AMBRA1 promotes the interaction between Beclin-1 and Vps34, activating the class III PI3K complex [19]. Subsequently, ATG5 conjugates with ATG12 and forms a complex with ATG16, promoting phagophore maturation [20]. LC3 is a key protein in the autophagy process. LC3-I, under the action of ATG7 and ATG3, binds to phosphatidylethanolamine (PE) to form LC3-II, participating in phagophore elongation and autophagosome formation [21]. Autophagosomes move along the microtubule cytoskeleton and fuse with lysosomes to form autolysosomes, where the encapsulated contents are degraded by a series of hydrolases (Fig. 1).

Interaction of androgens, apoptosis, and autophagy

Although the specific pathogenesis of BPH remains unclear, the growth and development of prostate tissue are related to the action of androgens, and the maintenance of normal prostate tissue morphology also depends on androgen action [1]. The PI3K-AKT-mTOR pathway is considered one of the main pathways regulating autophagy, exerting a negative regulatory effect on cellular autophagy [22]. In androgen-induced BPH rats, testosterone can inhibit autophagy by activating the PI3K/Akt/mTOR pathway, reducing the expression of Beclin1 and LC3-II. It also promotes proliferation by reducing the expression of caspase-3 in prostate tissue and increasing the expression of Bcl-2 protein, thereby reducing apoptosis [23]. The presence of testosterone may affect autophagy and apoptosis, thereby contributing to the progression of BPH. Studies have also shown that the use of the autophagy inducer rapamycin can enhance autophagy by inhibiting mTOR, thereby suppressing the testosterone-induced proliferation of prostate tissue in rats [23]. As a hormone-responsive organ, androgen receptor (AR) signaling plays an important role in the progression of BPH. 5-alpha reductase inhibitors (5-ARIs) impair AR signaling by blocking the conversion of testosterone to dihydrotestosterone (DHT), often used as an androgen deprivation (AD) therapy to induce prostate cell apoptosis, thus treating BPH. Lowering androgen levels is widely considered an effective method for treating BPH by inducing apoptosis in prostate epithelial cells [24]. However, studies have found that the apoptosis induced by this method is not enduring, with more than 17% of BPH patients undergoing long-term 5-ARI treatment still experiencing clinical progression [25, 26]. In BPH patients treated with 5-ARIs, the expression of Beclin-1 and LC3 is significantly higher than in untreated control groups [27]. This suggests that autophagy is promoted during 5-ARI treatment. Research has also indicated that long-term use of 5-ARIs reduces the secretion of IGF-1 by prostate stromal cells, thereby inducing autophagy in prostate epithelial cells [28].

Autophagy plays a crucial role in maintaining cell survival while also being decisive in the process of cell death. In many cases, the autophagy pathway dynamically interacts with various cell death pathways,

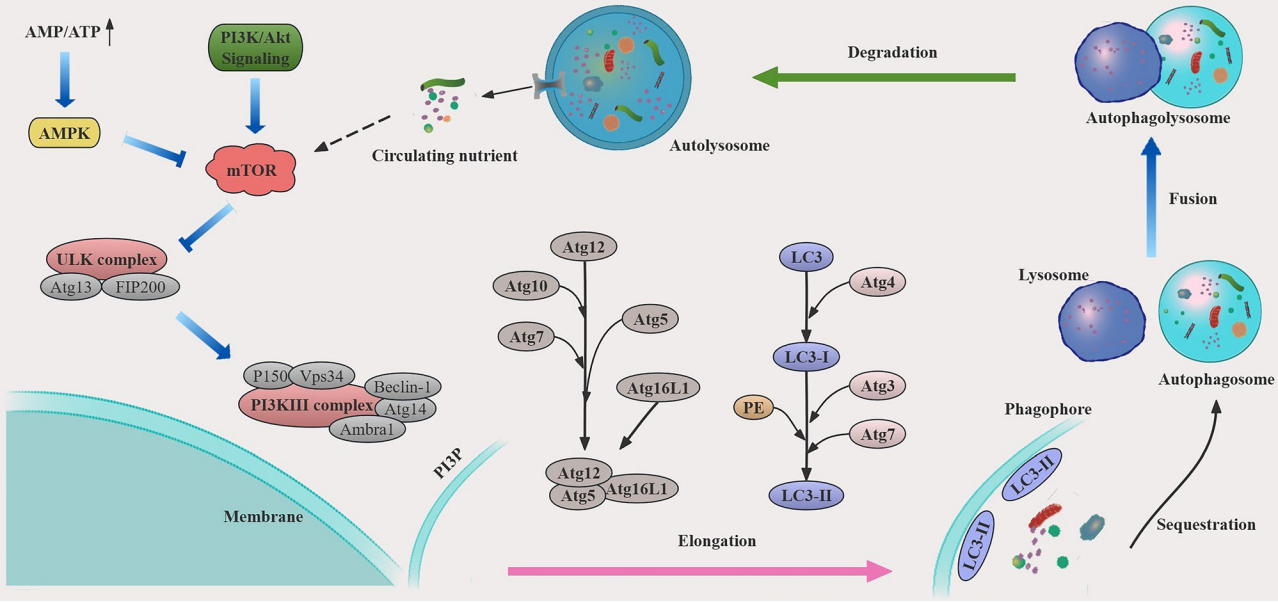

Fig. 1 The process of cellular autophagy: The autophagy process begins with the initiation by the ULK1 complex, which is regulated by mTORC1. Upon inhibition of mTORC1, ULK1 activates the formation of the phagophore. Beclin 1, in conjunction with the PI3K complex, nucleates the autophagic membrane. The ATG12-ATG5 complex, along with ATG16L1, facilitates the elongation of the membrane. LC3 is cleaved and lipidated to form LC3-II, which is then incorporated into the autophagosome membrane. The autophagosome engulfs cellular debris and subsequently fuses with a lysosome, forming an autophagolysosome where the contents are degraded and recycled

including apoptosis, necrosis, and ferroptosis [29]. Li et al. [30] found through experiments that 5-ARI treatment increased autophagy in prostate epithelial cells and reduced apoptosis, whereas blocking autophagy significantly increased the apoptosis rate in PWR-1E cells. This demonstrates that autophagy may be activated as a survival mechanism under androgen suppression, leading to reduced apoptosis. Some studies indicate that the increase in prostate volume is not due to excessive proliferation of prostate tissue but is related to reduced apoptosis of prostate cells caused by crosstalk between autophagy and apoptosis [31–33]. Autophagy and apoptosis are tightly regulated biological processes that play a central role in tissue homeostasis, development, and disease. Autophagy and apoptosis share some common molecular components, especially the Beclin1 protein. The anti-apoptotic protein Bcl-2 inhibits autophagy through its interaction with Beclin1, thereby maintaining autophagy levels compatible with cell survival [34]. Depending on the levels of reactive oxygen species (ROS) within the cell, Beclin1 can dissociate from Bcl-2, initiating the autophagy process. Under intense stress signals, Beclin1 may be cleaved by caspases, blocking autophagy, while the cleavage products promote the release of pro-apoptotic factors, accelerating cell apoptosis [15, 35]. Additionally, autophagy-related molecules Atg5 and Atg12 can independently promote cell apoptosis when present in an unconjugated form [36]. Liu et al. [37] found that in the early stages of AD, autophagy has a compensatory function, while throughout the process, autophagy and apoptosis are antagonistic. They suggested that Beclin-1 protein fragments provide positive feedback to the apoptosis process, which may be a potential mechanism for AD therapy in BPH. Studies have pointed out that under AD conditions, silencing Beclin-1 leads to blocked autophagy and activated apoptosis. Silencing this gene can decrease Bcl-2 expression and increase Bax protein expression, leading to a reduced Bcl-2/Bax ratio, thereby promoting prostate cell apoptosis [38]. Similarly, after AD therapy, knocking down the ATG9A gene significantly inhibited autophagy in prostate stromal fibroblasts and reduced the volume of prostate stromal fibroblast and epithelial cell recombined grafts in nude mice [9]. This suggests that AD and autophagy inhibition may have a synergistic effect, potentially treating BPH by further enhancing apoptosis levels (Table 1).

Interaction of Estrogen, Age, and autophagy

Several studies have indicated that although androgens play a role in inducing and maintaining benign prostatic hyperplasia (BPH), their impact alone is insufficient, as testosterone supplementation in men does not appear to elevate BPH risk or decrease LUTS [39]. In the human body, testosterone levels decrease with age, while serum estradiol (E2) levels remain relatively stable. Consequently, there is an increase in the ratio of serum E2 to testosterone (T) [40]. Moreover, locally produced E2 is implicated in prostate hyperplasia. Research has

Table 1 Autophagy vs. BPH

Context	Study Subject	Autophagy	Gene/Protein (oE*, uE*)	BPH	Ref
Aging	C57 mice, WPMY-1 cells	Decreased	Beclin-1↓, ATG14L↓, ERα↑, LC3-II/LC3-I↓	Promoted	[50] Hong GL et al. 2022
Androgen deprivation (5ARi)	BPH-1 cells	Increased	LC3-II↑, PARP-1↓, caspase-3↓	Promoted	[37] Liu RF et al. 2018
Androgen deprivation (5ARi)	BPH-1 cells	Decreased	Beclin-1↓, PARP-1↑, Caspase-3↑, Bcl-2/Bax↓	Inhibited	[38] Liu R et al. 2022
Androgen deprivation (5ARi)	Human BPH tissue, WPMY-AR cells, nude mouse prostate stromal and epithelial	Increased	ATG9A↑, Beclin-1↑, LC3↑	Promoted	[9] Jiang CY et al. 2018
Androgen deprivation (5ARi)	Prostate epithelial and stromal cells	Increased	IGF-1↓, mTOR↑, Beclin-1↑, LC3↑	Promoted	[28] Yang BY et al. 2019
Androgen deprivation (5ARi)	PWR-1E cells	Increased	LC3↑	Promoted	[30] Li M et al. 2014
Androgen excess	Castrated rat prostate epithelial cells	Decreased	Beclin-1↓, LC3-II↓, caspase-3↓, Bcl-2↑	Promoted	[23] Liu RF et al. 2018
Blocking cholinergic innervation	Spontaneously hypertensive rats	Increased	LC3-II/LC3-I↑	Inhibited	[86] Cai JL et al. 2017
Estrogen excess	BPH-1 cells	Decreased	LLGL2↑, LC3-B↓, ATG7↓, p-beclin↓	Promoted	[42] Kim KH et al. 2022
Fasting	Normal albino rats (15 months)	Increased	Beclin-1/P62↑	Inhibited	[87] Gamal El-Tahawy NF et al. 2023
Hypoxic conditions	WPMY-1 cells	Increased	LC3B-II↑, Beclin1↑, ATG5↑	Promoted	[80] Zhang N et al. 2015
Inflammation	Human normal prostate tissue, BPH-1 cells, RWPE-1 cells	Decreased	PRDX3↑, LC3-II↓, caspase-1↑	Promoted	[69] Jiang MY et al. 2017
Obesity (potentially associated with insulin resistance)	Patients with prostate hyperplasia (overweight/obese)	Decreased	LC3B↓, p62↑	Promoted	[85] De Nunzio C et al. 2021
Role of GPX3 in BPH	BPH-1 cells	Increased	GPX3↓, AMPK↑, Nrf2/GPX4↓	Promoted	[6363] Li Y et al. 2023

Note:

• "oE" stands for "overexpressed" and "uE" stands for "underexpressed"

• "↑" indicates an increase and "↓" indicates a decrease

demonstrated that a reduction in aromatase expression results in decreased estrogen-induced prostate hyperplasia [40, 41]. Consequently, a high E2 to T ratio in prostatic serum may exacerbate benign prostatic hyperplasia. Studies have found that autophagy levels are low in E2-induced BPH-1 cell proliferation. However, silencing the LLGL2 gene can enhance autophagy, thereby inhibiting E2-induced BPH-1 cell proliferation [42]. This suggests that the level of autophagy plays a role in estrogen-induced proliferation.

Aging is linked to the gradual degradation of tissues, impairing the structure and function of vital organs [43]. Mitophagy, involving the selective removal of excess or damaged mitochondria through autophagosomes and double-membrane vesicles, significantly impacts age-related mitochondrial dysfunction and associated diseases, with its regulatory mechanisms pivotal in disease onset and progression. Dysfunction in mitochondrial autophagy has been observed in the hearts [44], skeletal muscles [45], and brains [46] of aged mice. Mitophagy induces degradation by fusion with lysosomes and is categorized as macro autophagy [47]. External stimuli such as nutrient deprivation and cellular senescence cause mitochondrial depolarization and damage. Autophagosomes selectively engulf these damaged mitochondria, which are then fused with lysosomes for degradation, maintaining cellular homeostasis [48, 49]. Studies have suggested that age-related decline in mitochondrial autophagy may contribute to the development of BPH in aged mice. The study observed mitochondrial fragmentation and reduced autophagy in the prostatic tissues of aged mice, correlated with decreased phosphorylation levels of the mitochondrial division factor Dynamin-Related Protein 1 (DRP1) and the autophagy-related protein parkin. Additionally, elderly mice exhibited decreased expression of androgen receptors and increased expression of estrogen receptor alpha (ERα). Blocking estrogen receptor alpha significantly increased autophagy and decreased cell

proliferation [50]. These findings suggest that reduced autophagy may contribute to BPH development in aged mice by modulating ERα expression levels, offering a novel perspective on the potential etiology of age-related prostate hyperplasia (Table 1).

Interaction between programmed cell death (ferroptosis and pyroptosis) and autophagy

Uncontrolled excessive activation of autophagy can also lead to cell death, a phenomenon known as "autophagic cell death" [51, 52]. Ferroptosis is a recently discovered form of programmed cell death, primarily activated by the accumulation of iron and lipid peroxidation products. Its major biochemical characteristics include increased soluble iron, elevated ROS generation, reduced GPX4 activity, and accumulation of lipid metabolites [53]. Autophagy regulates intracellular iron balance, lipid metabolism, and redox status [54, 55]. When ferroptosis occurs, autophagy is triggered, leading to the degradation of iron storage proteins and nuclear receptor coactivator 4 (NCOA4), resulting in increased unstable iron levels and a dramatic rise in ROS within the cell [56]. Research has identified that ferroptosis plays a role in several tumors, including prostate cancer [57], and that BPH often involves abnormal elevation of oxidative stress (OS) and ROS levels, leading to cellular dysfunction and tissue damage. This may be related to autophagy's regulation of ferroptosis [58, 59]. Studies have found that significant increases in ROS expression in BPH tissue lead to upregulation of HIF-1α expression through induction of PI3K/AKT and ERK phosphorylation [60]. HIF-1 can increase iron uptake, thereby affecting sensitivity to ferroptosis [10]. Glutathione peroxidase 3 (GPX3) exerts its antioxidant effect by consuming glutathione (GSH) to reduce H2O2 and hydroperoxides [61]. The deficiency of GPX3 can promote cell proliferation in prostate cancer (PCa) tissue and reduce apoptosis of PCa cells [62]. In BPH tissue, GPX3 expression is downregulated. The downregulation of GPX3 promotes autophagy-related ferroptosis by activating the AMPK/mTOR pathway and downregulating Nrf2/GPX4 [63]. This suggests that in the development of BPH, autophagy and ferroptosis may serve as mechanisms regulating cell death, and the antioxidant role of GPX3 may influence these processes, thereby affecting the progression of BPH (Fig. 2).

Studies have found that inflammation induces compensatory growth of epithelial and stromal cells, leading to prostate enlargement [64, 65]. Pyroptosis (inflammatory cell death) is a form of programmed cell death activated by inflammasomes, characterized by rapid rupture of the cell membrane and release of inflammatory mediators, playing a crucial role in clearing infections and promoting inflammatory responses [66]. Autophagy has been shown to reduce inflammasome activation by removing

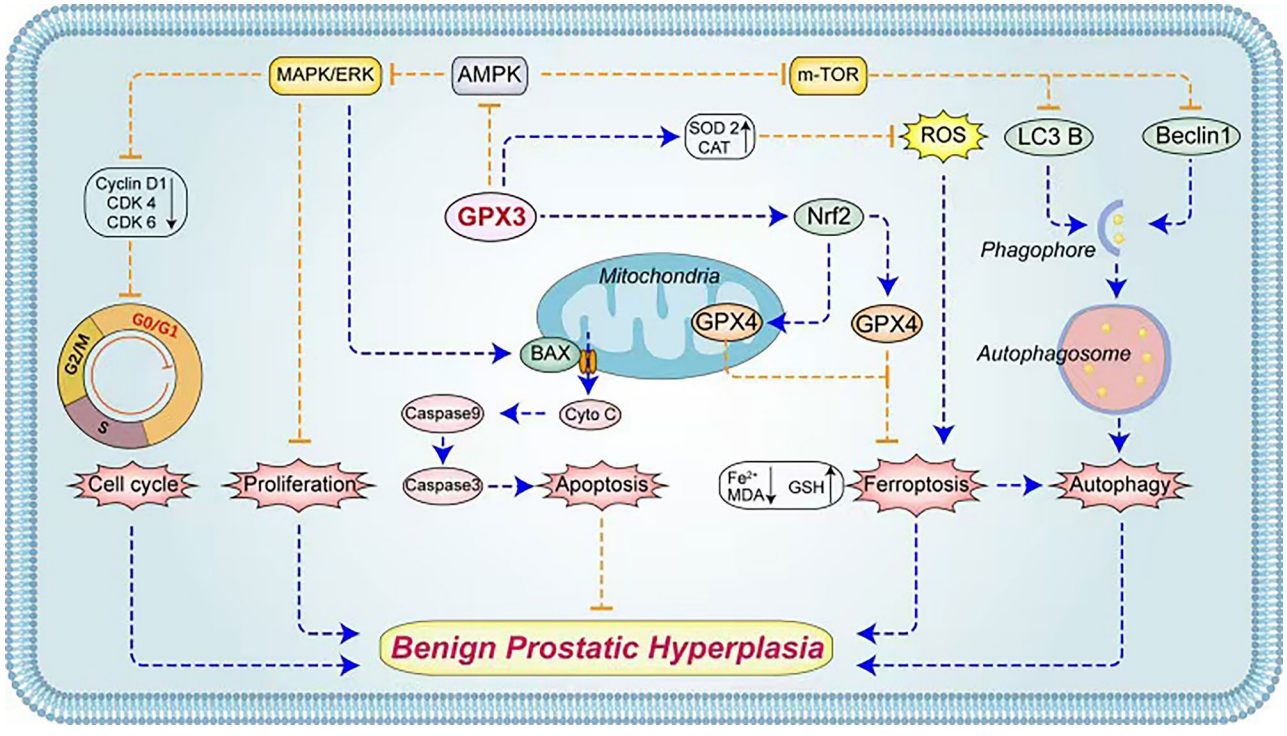

Fig. 2 The mechanism of GPX3 on prostate cells. Adapted with permission from Li Y, Zhou Y, Liu D, Wang Z, Qiu J, et al. Glutathione Peroxidase 3 induced mitochondria-mediated apoptosis via AMPK/ERK1/2 pathway and resisted autophagy-related ferroptosis via AMPK/mTOR pathway in hyperplastic prostate, J Transl Med, 2023, 21:575. This image is licensed under the Creative Commons Attribution 4.0 International License (CC BY 4.0)

DAMPs (damage-associated molecular patterns) and PAMPs (pathogen-associated molecular patterns). Additionally, autophagy can directly degrade inflammasomes and their downstream molecules, such as pro-IL-1β, thereby reducing IL-1β release. Autophagy also decreases the levels of cleaved GSDMD (gasdermin D), effectively inhibiting pyroptosis [67]. Oxidative stress is one of the key triggers of inflammation and also a factor that induces increased autophagy [68]. Autophagy is the primary mechanism for degrading damaged mitochondria and clearing ROS. Mitochondrial protein peroxiredoxin 3 (PRDX3) is a member of the peroxiredoxin family associated with mitochondria and provides protective antioxidant effects through its peroxidase activity. In the prostate tissue of BPH patients, PRDX3 expression levels are significantly higher than those in healthy donors. The high expression of PRDX3 is associated with the inhibition of autophagy in prostate epithelial cells, leading to the activation of pyroptosis [69]. Defects in autophagy can lead to increased oxidative stress or lysosomal rupture, thereby activating the NLRP3 inflammasome [70, 71]. Activation of the NLRP3 inflammasome recruits and activates Caspase-1, which then cleaves Gasdermin D (GSDMD), generating GSDMD-N-terminal fragments that form pores in the cell membrane, leading to the release of cellular contents and exchange of the internal and external environment. Additionally, Caspase-1 cleaves precursors of pro-inflammatory cytokines IL-1β and IL-18, promoting their maturation and release [72, 73]. These cytokines attract more inflammatory cells, amplifying the inflammatory response and inducing pyroptosis, which ultimately leads to excessive growth of prostate tissue (Table 1).

Other factors and their interaction with autophagy

Hypoxia and endoplasmic reticulum stress (ERS)

Increasing evidence suggests that hypoxia resulting from impaired blood flow can trigger the development of BPH [74, 75]. ERS is an important regulatory factor in the development of BPH following hypoxia due to impaired prostate blood flow, leading to widespread alterations in downstream signaling pathways such as angiogenesis, glucose metabolism, and cell survival [76, 77]. Upon exposure of prostate stromal cells to hypoxic conditions, ERS is activated in a time-dependent manner, leading to the secretion of various growth factors and pro-inflammatory cytokines (TGF-β1, FGF-2, and IL-8), which subsequently induce BPH [78]. Recent investigations have found that ERS plays a crucial role in determining cell survival or death and can induce autophagy in various cell lines [79]. Previously, we mentioned that autophagy might serve as a survival mechanism, assisting human prostate stromal cells to survive in a mildly hypoxic environment caused by reduced blood flow [10]. Studies have also shown that autophagy acts as a cellular protective response, promoting the survival of human prostate stromal cells under hypoxic conditions through ERS [80]. (Table 1)

Energy metabolism

Autophagy is a cellular self-digestion process that degrades intracellular proteins, damaged organelles, and other molecules to release amino acids, fatty acids, and other energy sources [81]. It helps cells maintain macromolecular synthesis and energy homeostasis under conditions of starvation and other stressors, and regulates various metabolic pathways [82, 83]. Obesity, resulting from energy intake exceeding energy expenditure, is often associated with insulin resistance, diabetes, and other metabolic disorders. These metabolic changes can affect cellular energy status and function, leading to dysregulation of autophagy. For instance, insulin resistance may reduce autophagic activity, thereby impacting the cell's response to energy and nutritional status [84]. A study analyzing prostatectomy specimens from 150 patients with BPH/LUTS found that obese and overweight patients (BMI > 25 kg/m²) exhibited lower LC3B and higher P62 expression, suggesting impaired autophagic function in obese BPH patients [85]. In spontaneous BPH, the characteristics of rat prostate glandular epithelium include metabolic hyperactivity, accumulation of metabolic waste, accelerated organelle regeneration and remodeling, as well as an increase in byproducts and abnormal organelles [86]. These conditions require sufficient activation of autophagy to meet the demands of proliferating cells, suggesting that full activation of autophagy may be a key factor in benign hyperplasia of the prostate glandular epithelium. However, studies have found that pharmacologically induced blockade of cholinergic nerve innervation significantly activates autophagy in glandular cells, thereby slowing the process of BPH in rat prostate glandular epithelium [86]. Similarly, fasting-induced autophagy is a crucial biological process that helps cells and tissues survive and adapt under conditions of limited nutrients and energy. Studies have found that intermittent fasting can improve age-related prostatic hyperplasia in rats, with the specific mechanism involving enhancement of autophagy through the Beclin-1/P62 pathway, suppression of oxidative stress, and exertion of anti-inflammatory and anti-proliferative effects [87] (Table 1).

Plant medicine's potential in regulating autophagy for BPH treatment

The conventional pharmacological treatments for BPH primarily involve 5α-reductase inhibitors and α-receptor blockers. However, their side effects, including sexual dysfunction, breast swelling and pain, dizziness, and

fatigue, can significantly impact treatment adherence and effectiveness [88]. Furthermore, previous studies have indicated that autophagy may contribute to the reduced efficacy of these treatments. Therefore, it is imperative to find safe and effective therapies that can target autophagy in the treatment of BPH. Phytotherapy, which uses the medicinal properties of plant-derived compounds to address physical and mental health issues, has gained increasing attention for BPH treatment due to its efficacy and low side effect profile. Additionally, active compounds extracted from medicinal plants, such as terpenes, flavonoids, alkaloids, steroids, and lignans, may influence the growth and survival of prostate cells by modulating autophagy. Therefore, we have summarized the current applications of autophagy-related phytotherapy in the treatment of BPH.

Extract of stauntonia hexaphylla (Thunb) decne

Stauntonia hexaphylla, a traditional medicinal plant widely found in Korea, Japan, and China, is frequently utilized in folk medicine for its fever-reducing properties and notable anti-inflammatory and analgesic effects [89]. Extracts from this plant have shown significant reductions in prostate weight and epithelial cell thickness. In a study using Sprague-Dawley rats and a testosterone-treated LNCaP cell line, an extract of S. hexaphylla, hederacoside D, inhibited type 2 5α-reductase, enhanced the expression of the crucial autophagy protein LC3, thereby inducing autophagosome formation [90]. Consequently, the decrease in dihydrotestosterone (DHT) levels leads to the downregulation of androgen receptor (AR) and prostate-specific antigen (PSA) levels, effectively mitigating prostate hyperplasia.

Extract of celtis choseniana nakai

Celtis choseniana, a member of the Ulmaceae family, is utilized as a medicinal plant in China, Korea, and Japan for detoxification, heat-clearing, anti-swelling, and analgesic effects. Its primary medicinal constituents consist of anti-inflammatory flavonoids, including quercetin, kaempferol, and isorhamnetin [91]. Celtis choseniana extract, in a testosterone-induced rat study, reduced prostate weight and epithelial cell thickness in BPH treatment. It diminished the expression of Akt, nuclear NF-κB, cytoplasmic I-κB and attenuated AR signal transduction. AR activation was inhibited, and AMPK phosphorylation induced. This resulted in up-regulation of LC3 and reduced expression of p62, thereby inducing autophagy. Concurrently, NF-κB activation up-regulated the expression of pro-apoptotic markers (Bax) and down-regulated the expression of anti-apoptotic markers (Bcl-2), resulting in enhanced apoptosis [92].

Extract of rauwolfia vomitoria (RWF)

Rauwolfia vomitoria, a valuable herbaceous plant widely found in tropical regions of Africa and Asia, contains biologically active monoterpenes and β-carboline alkaloids in its extract [93]. The RWF extract triggers apoptosis in BPH-1 epithelial cells and WPMY-1 stromal cells, as well as in human BPH samples, through the activation of ERS and autophagy signaling pathways. It enhances autophagy by upregulating the expression of autophagy genes (ULK2 and SQSTM1/p62) and increasing the LC3II: LC3I ratio. Moreover, the RWF extract initiates downstream apoptosis pathways through the activation of the ERS response, leading to cell apoptosis and notable inhibition of the vitality of BPH epithelial cells and stromal fibroblasts [94].

Extract of herba epimedii

Herba Epimedii, a traditional Chinese medicine long used in China, contains active compounds like total flavonoids, icariin, polysaccharides, alkaloids, plant sterols, and anthraquinones [95, 96]. Relevant studies have confirmed that Herba Epimedii extract significantly inhibits mouse prostate hyperplasia [97]. The therapeutic effect of Herba Epimedii may be associated with the downregulation of autophagy-related proteins Beclin-1 and LC3 in prostate hyperplasia tissues, inhibiting excessive autophagy [98].

Qianlienin capsule

Qianlienin Capsule, a standardized traditional Chinese herbal preparation, consists of 14 traditional ingredients such as stone chive, dandelion, hoelen, sword bean, safflower, cardamom, and others. Qianlienin Capsule has been shown to inhibit the reduction in Beclin-1 expression, reverse the decrease in LC3-II levels, restore Atg4B levels in the rat prostate, reduce p62 expression, and promote autophagy. This action weakens the activation of NLRP3 inflammasomes in BPH [99]. The capsule promotes autophagy by increasing Beclin-1 expression and the LC3II/I ratio, thus achieving the goal of treating BPH.

Extract of tripterygium wilfordii (TGV)

Tripterygium wilfordii, derived from the root of the plant in the Celastraceae family, is a traditional medicinal herb widely used in Chinese medicine and has been studied for its anti-inflammatory, anti-tumor, and immunomodulatory effects. TGV contains various active components, among which triptolide and celastrol are closely associated with autophagy. Celastrol is one of the most potent active ingredients in TGV and is a typical triterpene compound. Studies have found that celastrol can inhibit proteasome function, leading to the accumulation of ubiquitinated proteins, inducing apoptosis, and thus inhibiting the growth of human PCa in nude mice

Table 2 Plant Medicine's potential in regulating autophagy for BPH Treatment

Treatment methods	Effects on autophagy	Study Subject	Ref
Celtis choseniana Nakai Extract	Increased Autophagy	Male SD rats	[92] Hong GL et al. 2022
Curcumin	Increased Autophagy	LNCaP cells	[110] Yang C et al. 2017
Herba Epimedii Extract	Decreased Autophagy	Male SD rats	[98] Tu ML et al. 2020
Oleanolic acid, Ursolic acid	Increased Autophagy	BPH-1 cells, WPMY-1 cells	[107] Smith DK et al. 2020
Qianlienin capsule	Increased Autophagy	Male SD rats	[99] Zang L et al. 2021
Rauwolfia vomitoria Extract	Increased Autophagy	BPH-1 cells, WPMY-1 cells	[94] Huang G et al. 2022
Stauntonia hexaphylla (Thunb) Decne Extract	Increased Autophagy	LNCaP cells, Male SD rats	[90] Hong GL et al. 2020
Tripterine	Increased Autophagy	LNCaP cells	[101] Guo J et al. 2015
Triptolide	Increased Autophagy	LNCaP cells	[106] Zhao F et al. 2016

[100]. In AR-positive PCa cells, celastrol induces protective autophagy [101].

Celastrol is considered a potential autophagy regulator [102]. Celastrol can induce ROS accumulation in gastric cancer cells by directly targeting peroxidase 2, thereby inducing apoptosis and protective autophagy [103]. Celastrol can inhibit the proliferation of nasopharyngeal carcinoma cells and induce their apoptosis through the PI3K/Akt pathway [104], while it induces autophagy and apoptosis in glioma cells by upregulating ROS/JNK and downregulating the Akt/mTOR signaling pathway [105]. In PCa cells, celastrol has been shown to induce protective autophagy by activating the CaMKKβ-AMPK signaling pathway [106]. Current research on TGV and its active components in the treatment of BPH is relatively limited. However, the mechanisms explored in the aforementioned studies, particularly in cancer and prostate cancer, involving autophagy, may be closely related to BPH treatment and warrant further investigation.

Similarly, Natural compounds such as oleanolic acid (OA) and ursolic acid (UA) can inhibit the growth of BPH cells by inducing autophagy and reducing the expression of the IL-8 axis [107]. Traditional Chinese medicines and extracts, such as tribulosin, brusatol, ecliptasaponin A, and matrine, can also regulate autophagy [108]. Particularly, compounds like curcumin have been found in related studies to influence the progression of prostate cancer through the modulation of autophagy [109, 110]. Therefore, exploring the mechanisms of promising anti-BPH herbs and extracts in relation to autophagy is worthy of further investigation (Table 2).

Conclusions and perspectives

All data discussed in this review emphasize that autophagy is a crucial process affecting the onset and progression of BPH. However, the specific mechanisms and roles of autophagy activation or inhibition in BPH must be considered based on the factors influencing the disease and its different developmental stages. Furthermore, the crosstalk between autophagy and other forms of programmed cell death significantly impacts BPH development, but related research is limited and warrants further investigation. Many studies suggest that targeting autophagy for treating established BPH, particularly through AD combined with autophagy inhibition, is a viable strategy. This approach can effectively increase prostate cell apoptosis, achieving better therapeutic outcomes. Researchers have been seeking relevant strategies and specific autophagy modulators for treating BPH. Phytotherapy, a traditional and effective treatment method, has made new advancements under modern molecular biology research. Using herbal medicines and their extracts to treat BPH also shows good efficacy. Many herbal medicines and extracts can treat BPH by regulating autophagy, making this a potentially effective research area. Therefore, when planning new autophagy-based treatment strategies for BPH, this aspect should be considered.

Abbreviations

BPH	Benign Prostatic Hyperplasia
LUTS	Lower Urinary Tract Symptoms
ATGs	Autophagy-related Genes
ULK1	UNC-51-like autophagy-activating kinase 1
mTORC1	Mammalian target of rapamycin complex 1
AMPK	Adenosine 5′-monophosphate (AMP)-activated protein kinase
PI3P	Phosphatidylinositol 3-phosphate
PI3KIII	Class III phosphatidylinositol 3-kinase
LC3	Microtubule-associated Proteins 1A/1B Light Chain 3
DHT	Dihydrotestosterone
AR	Androgen Receptor
5-ARIs	5-Alpha Reductase Inhibitors
AD	Androgen Deprivation
AMBRA1	Activating Molecule in BECN1-Regulated Autophagy Protein 1
ROS	Reactive Oxygen Species
E2	Estradiol
T	Testosterone
DRP1	Dynamin-Related Protein 1
GPX3	Glutathione Peroxidase 3
ERα	Estrogen Receptor Alpha
HIF-1α	Hypoxia-inducible Factor 1-alpha
IGF-1	Insulin-like Growth Factor 1
ERS	Endoplasmic Reticulum Stress
NCOA4	Nuclear receptor coactivator 4
GSH	Consuming glutathione
LLGL2	LLGL scribble cell polarity complex component 2
PRDX3	Peroxiredoxin 3
PCa	Prostate cancer
GSDMD	Gasdermin D
PSA	Prostate-specific antigen

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XZZ and JS conceived and designed the manuscript. XZZ, PH, YKW, and JBY contributed to the literature collection and data acquisition. XZZ and JS drafted the manuscript. All authors read and approved the final manuscript.

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Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This article does not have ethics-related issues.

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The authors declare no competing interests.

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References

1. Wein AJ, Partin AW, Peters CA, editors. Campbell-Walsh-Wein Urology. 12th ed. Philadelphia: Elsevier; 2020.
2. Gu FL, Xia TL, Kong XT. Preliminary study of the frequency of benign prostatic hyperplasia and prostatic cancer in China. Urology. 1994;44:688–91.
3. Awedew AF, Han H, Abbasi B, Abbasi-Kangevari M, Ahmed MB, Almidani O, et al. The global, regional, and national burden of benign prostatic hyperplasia in 204 countries and territories from 2000 to 2019: a systematic analysis for the global burden of Disease Study 2019. Lancet Healthy Longev. 2022;3:e754–76.
4. Chang WH, Tsai YS, Wang JY, Chen HL, Yang WH, Lee CC. Sex hormones and oxidative stress mediated phthalate-induced effects in prostatic enlargement. Environ Int. 2019;126:184–92.
5. Kristal AR, Schenk JM, Song Y, Arnold KB, Neuhouser ML, Goodman PJ, et al. Serum steroid and sex hormone-binding globulin concentrations and the risk of incident benign prostatic hyperplasia: results from the prostate cancer prevention trial. Am J Epidemiol. 2008;168:1416–24.
6. Fiard G, Stavrinides V, Chambers ES, Heavey S, Freeman A, Ball R, et al. Cellular senescence as a possible link between prostate diseases of the ageing male. Nat Rev Urol. 2021;18:597–610.
7. Vickman RE, Aaron-Brooks L, Zhang R, Lanman NA, Lapin B, Gil V, et al. TNF is a potential therapeutic target to suppress prostatic inflammation and hyperplasia in autoimmune disease. Nat Commun. 2022;13:2133.
8. Hasan KMM, Haque MA. Autophagy and its lineage-specific roles in the hematopoietic system. Oxid Med Cell Longev. 2023;2023:8257217.
9. Jiang CY, Yang BY, Zhao S, Shao SH, Bei XY, Shi F, et al. Deregulation of ATG9A by impaired AR signaling induces autophagy in prostate stromal fibroblasts and promotes BPH progression. Cell Death Dis. 2018;9:431.
10. Saito M, Tsounapi P, Oikawa R, Shimizu S, Honda M, Sejima T, et al. Prostatic ischemia induces ventral prostatic hyperplasia in the SHR; possible mechanism of development of BPH. Sci Rep. 2014;4:3822.
11. Oh SH, Lee DW, Choi YB, Lee YH, Ju JS. Measurement of autophagy flux in benign prostatic hyperplasia in vitro. Prostate Int. 2020;8:70–7.
12. Zachari M, Ganley IG. The mammalian ULK1 complex and autophagy initiation. Essays Biochem. 2017;61:585–96.
13. Alers S, Löffler AS, Wesselborg S, Stork B. Role of AMPK-mTOR-Ulk1/2 in the regulation of autophagy: cross talk, shortcuts, and feedbacks. Mol Cell Biol. 2012;32:2–11.
14. Ravikumar B, Sarkar S, Davies JE, Futter M, Garcia-Arencibia M, Green-Thompson ZW, et al. Regulation of mammalian autophagy in physiology and pathophysiology. Physiol Rev. 2010;90:1383–435.
15. Kma L, Baruah TJ. The interplay of ROS and the PI3K/Akt pathway in autophagy regulation. Biotechnol Appl Biochem. 2022;69:248–64.
16. Gallagher LE, Chan EYW. Early signalling events of autophagy. Essays Biochem. 2013;55:1–15.
17. Boya P, Reggiori F, Codogno P. Emerging regulation and functions of autophagy. Nat Cell Biol. 2013;15:713–20.
18. Bento CF, Renna M, Ghislat G, Puri C, Ashkenazi A, Vicinanza M, et al. Mammalian autophagy: how does it work? Annu Rev Biochem. 2016;85:685–713.
19. Sun WL. Ambra1 in autophagy and apoptosis: implications for cell survival and chemotherapy resistance. Oncol Lett. 2016;12:367–74.
20. Lystad AH, Carlsson SR, Simonsen A. Toward the function of mammalian ATG12-ATG5-ATG16L1 complex in autophagy and related processes. Autophagy. 2019;15:1485–6.
21. Ye Y, Tyndall ER, Bui V, Bewley MC, Wang G, Hong X, et al. Multifaceted membrane interactions of human Atg3 promote LC3-phosphatidylethanolamine conjugation during autophagy. Nat Commun. 2023;14:5503.
22. Yu X, Long YC, Shen HM. Differential regulatory functions of three classes of phosphatidylinositol and phosphoinositide 3-kinases in autophagy. Autophagy. 2015;11:1711–28.
23. Liu RF, Fu G, Li J, Yang YF, Wang XG, Bai PD, et al. Roles of autophagy in androgen-induced benign prostatic hyperplasia in castrated rats. Exp Ther Med. 2018;15:2703–10.
24. Azzouni F, Mohler J. Role of 5α-reductase inhibitors in benign prostatic diseases. Prostate Cancer Prostatic Dis. 2012;15:222–30.
25. Roehrborn CG, Siami P, Barkin J, Damião R, Major-Walker K, Nandy I, et al. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. Eur Urol. 2010;57:123–31.
26. McConnell JD, Bruskewitz R, Walsh P, Andriole G, Lieber M, Holtgrewe HL, et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long-Term Efficacy and Safety Study Group. N Engl J Med. 1998;338:557–63.
27. Liu C, Xu P, Chen D, Fan X, Xu Y, Li M, et al. Roles of autophagy-related genes Beclin-1 and LC3 in the development and progression of prostate cancer and benign prostatic hyperplasia. Biomedical Rep. 2013;1:855–60.
28. Yang BY, Jiang CY, Dai CY, Zhao RZ, Wang XJ, Zhu YP, et al. 5-ARI induces autophagy of prostate epithelial cells through suppressing IGF-1 expression in prostate fibroblasts. Cell Prolif. 2019;52:e12590.
29. Jung S, Jeong H, Yu S-W. Autophagy as a decisive process for cell death. Exp Mol Med. 2020;52:921–30.
30. Li M, Yang X, Wang H, Xu E, Xi Z. Inhibition of androgen induces autophagy in benign prostate epithelial cells. Int J Urology: Official J Japanese Urol Association. 2014;21:195–9.
31. Quiles MT, Arbós MA, Fraga A, de Torres IM, Reventós J, Morote J. Antiproliferative and apoptotic effects of the herbal agent Pygeum Africanum on cultured prostate stromal cells from patients with benign prostatic hyperplasia (BPH). Prostate. 2010;70:1044–53.
32. Boya P, Kroemer G. Beclin 1: a BH3-only protein that fails to induce apoptosis. Oncogene. 2009;28:2125–7.
33. Ciechomska IA, Goemans GC, Skepper JN, Tolkovsky AM. Bcl-2 complexed with Beclin-1 maintains full anti-apoptotic function. Oncogene. 2009;28:2128–41.
34. Pattingre S, Tassa A, Qu X, Garuti R, Liang XH, Mizushima N, et al. Bcl-2 antiapoptotic proteins inhibit beclin 1-dependent autophagy. Cell. 2005;122:927–39.
35. Chen Y, Zhang W, Guo X, Ren J, Gao A. The crosstalk between autophagy and apoptosis was mediated by phosphorylation of Bcl-2 and beclin1 in benzene-induced hematotoxicity. Cell Death Dis. 2019;10:772.
36. Cooper KF. Till death do us part: the marriage of Autophagy and apoptosis. Oxid Med Cell Longev. 2018;2018:4701275.
37. Liu RF, Li J, Zhang J, Bai PD, Yang YF, Li W, et al. Crosstalk between apoptosis and autophagy in prostate epithelial cells under androgen deprivation. Exp Ther Med. 2018;15:2263–8.

38. Liu R, Zhang S, Wan R, Deng J, Fang W. Effect of Beclin-1 gene silencing on autophagy and apoptosis of the prostatic hyperplasia epithelial cells. Clin (Sao Paulo Brazil). 2022;77:100076.
39. Morales A. Androgen replacement therapy and prostate safety. Eur Urol. 2002;41.
40. Nicholson TM, Ricke WA. Androgens and estrogens in benign prostatic hyperplasia: past, present and future. Differentiation. 2011;82:184–99.
41. Ellem SJ, Risbridger GP. The dual, opposing roles of estrogen in the prostate. Ann N Y Acad Sci. 2009;1155:174–86.
42. Kim KH, Hong GL, Kim YJ, Lee HJ, Jung JY. Silencing of LLGL2 suppresses the Estradiol-Induced BPH-1 cell proliferation through the regulation of Autophagy. Biomedicines. 2022;10:1981.
43. MacNee W, Rabinovich RA, Choudhury G. Ageing and the border between health and disease. Eur Respir J. 2014;44:1332–52.
44. Hoshino A, Mita Y, Okawa Y, Ariyoshi M, Iwai-Kanai E, Ueyama T, et al. Cytosolic p53 inhibits parkin-mediated mitophagy and promotes mitochondrial dysfunction in the mouse heart. Nat Commun. 2013;4:2308.
45. García-Prat L, Martínez-Vicente M, Perdiguero E, Ortet L, Rodríguez-Ubreva J, Rebollo E, et al. Autophagy maintains stemness by preventing senescence. Nature. 2016;529:37–42.
46. Fivenson EM, Lautrup S, Sun N, Scheibye-Knudsen M, Stevnsner T, Nilsen H, et al. Mitophagy in neurodegeneration and aging. Neurochem Int. 2017;109:202–9.
47. Rüb C, Wilkening A, Voos W. Mitochondrial quality control by the Pink1/Parkin system. Cell Tissue Res. 2017;367:111–23.
48. Randow F, Youle RJ. Self and nonself: how autophagy targets mitochondria and bacteria. Cell Host Microbe. 2014;15:403–11.
49. Green DR, Van Houten B, SnapShot. Mitochondrial quality control. Cell. 2011;147:950.
50. Hong GL, Kim KH, Kim YJ, Lee HJ, Kim HT, Jung JY. Decreased mitophagy aggravates benign prostatic hyperplasia in aged mice through DRP1 and estrogen receptor α. Life Sci. 2022;309:120980.
51. Denton D, Kumar S. Autophagy-dependent cell death. Cell Death Differ. 2019;26:605–16.
52. Han S, Li X, Wang K, Zhu D, Meng B, Liu J, et al. PURPL represses autophagic cell death to promote cutaneous melanoma by modulating ULK1 phosphorylation. Cell Death Dis. 2021;12:1070.
53. Li J, Cao F, Yin HL, Huang ZJ, Lin ZT, Mao N, et al. Ferroptosis: past, present and future. Cell Death Dis. 2020;11:88.
54. Liu J, Kuang F, Kroemer G, Klionsky DJ, Kang R, Tang D. Autophagy-dependent ferroptosis: Machinery and Regulation. Cell Chem Biol. 2020;27:420–35.
55. Zhou B, Liu J, Kang R, Klionsky DJ, Kroemer G, Tang D. Ferroptosis is a type of autophagy-dependent cell death. Semin Cancer Biol. 2020;66:89–100.
56. Gao M, Monian P, Pan Q, Zhang W, Xiang J, Jiang X. Ferroptosis is an autophagic cell death process. Cell Res. 2016;26:1021–32.
57. Ghoochani A, Hsu E-C, Aslan M, Rice MA, Nguyen HM, Brooks JD, et al. Ferroptosis Inducers are a Novel Therapeutic Approach for Advanced prostate Cancer. Cancer Res. 2021;81:1583–94.
58. Udensi UK, Tchounwou PB. Oxidative stress in prostate hyperplasia and carcinogenesis. J Exp Clin Cancer Res. 2016;35:139.
59. Vital P, Castro P, Ittmann M. Oxidative stress promotes benign prostatic hyperplasia. Prostate. 2016;76:58–67.
60. Du J, Xu R, Hu Z, Tian Y, Zhu Y, Gu L, et al. PI3K and ERK-induced Rac1 activation mediates hypoxia-induced HIF-1α expression in MCF-7 breast cancer cells. PLoS ONE. 2011;6:e25213.
61. Brigelius-Flohé R, Maiorino M. Glutathione peroxidases. Biochim Biophys Acta. 2013;1830:3289–303.
62. Chang SN, Lee JM, Oh H, Park J-H. Glutathione Peroxidase 3 inhibits prostate tumorigenesis in TRAMP mice. Prostate. 2016;76:1387–98.
63. Li Y, Zhou Y, Liu D, Wang Z, Qiu J, Zhang J, et al. Glutathione peroxidase 3 induced mitochondria-mediated apoptosis via AMPK /ERK1/2 pathway and resisted autophagy-related ferroptosis via AMPK/mTOR pathway in hyperplastic prostate. J Transl Med. 2023;21:575.
64. Chughtai B, Lee R, Te A, Kaplan S. Role of inflammation in benign prostatic hyperplasia. Rev Urol. 2011;13:147–50.
65. St Sauver JL, Jacobson DJ, McGree ME, Girman CJ, Lieber MM, Jacobsen SJ. Longitudinal association between prostatitis and development of benign prostatic hyperplasia. Urology. 2008;71:475–9. discussion 479.
66. Ryter SW, Mizumura K, Choi AMK. The impact of autophagy on cell death modalities. Int J Cell Biol. 2014;2014:502676.
67. Guo R, Wang H, Cui N. Autophagy regulation on pyroptosis: mechanism and medical implication in Sepsis. Mediators Inflamm. 2021;2021:9925059.
68. Lin W, Kuang H. Oxidative stress induces autophagy in response to multiple noxious stimuli in retinal ganglion cells. Autophagy. 2014;10:1692–701.
69. Jiang MY, Han ZD, Li W, Yue F, Ye J, Li B, et al. Mitochondrion-associated protein peroxiredoxin 3 promotes benign prostatic hyperplasia through autophagy suppression and pyroptosis activation. Oncotarget. 2017;8:80295–302.
70. Mizushima N, Noda T, Yoshimori T, Tanaka Y, Ishii T, George MD, et al. A protein conjugation system essential for autophagy. Nature. 1998;395:395–8.
71. Hornung V, Bauernfeind F, Halle A, Samstad EO, Kono H, Rock KL, et al. Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization. Nat Immunol. 2008;9:847–56.
72. Lamkanfi M, Dixit VM. Mechanisms and functions of inflammasomes. Cell. 2014;157:1013–22.
73. Xia S, Zhang Z, Magupalli VG, Pablo JL, Dong Y, Vora SM, et al. Gasdermin D pore structure reveals preferential release of mature interleukin-1. Nature. 2021;593:607–11.
74. Lekas AG, Lazaris AC, Chrisofos M, Papatsoris AG, Lappas D, Patsouris E, et al. Finasteride effects on hypoxia and angiogenetic markers in benign prostatic hyperplasia. Urology. 2006;68:436–41.
75. Bostanci Y, Kazzazi A, Momtahen S, Laze J, Djavan B. Correlation between benign prostatic hyperplasia and inflammation. Curr Opin Urol. 2013;23.
76. Dai Y, Bae K, Siemann DW. Another road leads to HIF-1 activation: implications for prostate cancer progression. Asian J Androl. 2012;14:241–2.
77. Mirzoeva S, Kim ND, Chiu K, Franzen CA, Bergan RC, Pelling JC. Inhibition of HIF-1 alpha and VEGF expression by the chemopreventive bioflavonoid apigenin is accompanied by akt inhibition in human prostate carcinoma PC3-M cells. Mol Carcinog. 2008;47:686–700.
78. Berger AP, Bartsch G, Deibl M, Alber H, Pachinger O, Fritsche G, et al. Atherosclerosis as a risk factor for benign prostatic hyperplasia. BJU Int. 2006;98:1038–42.
79. Malhotra JD, Kaufman RJ. ER stress and its functional link to mitochondria: role in cell survival and death. Cold Spring Harb Perspect Biol. 2011;3:a004424.
80. Zhang N, Ji N, Jiang W-M, Li Z-Y, Wang M, Wen J-M, et al. Hypoxia-induced autophagy promotes human prostate stromal cells survival and ER-stress. Biochem Biophys Res Commun. 2015;464:1107–12.
81. Jeong SH, An HK, Ha S, Yu SW. Distinct signaling pathways for autophagy-driven cell death and survival in adult hippocampal neural stem cells. Int J Mol Sci. 2023;24:8289.
82. Yoshizaki T, Kusunoki C, Kondo M, Yasuda M, Kume S, Morino K, et al. Autophagy regulates inflammation in adipocytes. Biochem Biophys Res Commun. 2012;417:352–7.
83. Giatromanolaki A, Sivridis E, Mendrinos S, Koutsopoulos AV, Koukourakis MI. Autophagy proteins in prostate cancer: relation with anaerobic metabolism and Gleason score. Urol Oncol. 2014;32:e3911–18.
84. Frendo-Cumbo S, Tokarz VL, Bilan PJ, Brumell JH, Klip A. Communication between autophagy and insulin action: at the crux of insulin action-insulin resistance? Front Cell Dev Biol. 2021;9:708431.
85. DE Nunzio C, Giglio S, Baldassarri V, Cirombella R, Mallel G, Nacchia A, et al. Impairment of autophagy may represent the molecular mechanism behind the relationship between obesity and inflammation in patients with BPH and LUTS. Minerva Urol Nephrol. 2021;73:631–7.
86. Cai JL, Yao WM, Na YQ. Correlation between cholinergic innervation, Autophagy, and etiopathology of Benign Prostatic Hyperplasia. Chin Med J (Engl). 2017;130:1953–60.
87. Gamal El-Tahawy NF, Ahmed Rifaai R. Intermittent fasting protects against Age-Induced Rat Benign Prostatic Hyperplasia via Preservation of Prostatic Histomorphology, modification of oxidative stress, and Beclin-1/P62 pathway. Microscopy and Microanalysis: the Official Journal of Microscopy Society of America, Microbeam Analysis Society. Microscopical Soc Can. 2023;29:1267–76.
88. Yu ZJ, Yan HL, Xu FH, Chao HC, Deng LH, Xu XD, et al. Efficacy and Side effects of drugs commonly used for the treatment of lower urinary tract symptoms Associated with Benign Prostatic Hyperplasia. Front Pharmacol. 2020;11:658.
89. Kim J, Lee G, Kang H, Yoo JS, Lee Y, Lee HS et al. Stauntonia hexaphylla leaf extract (YRA-1909) suppresses inflammation by modulating Akt/NF-κB signaling in lipopolysaccharide-activated peritoneal macrophages and rodent models of inflammation. Food Nutr Res. 2021;65.
90. Hong GL, Park SR, Jung DY, Karunasagara S, Lee KP, Koh EJ, et al. The therapeutic effects of stauntonia hexaphylla in benign prostate hyperplasia are mediated by the regulation of androgen receptors and 5α-reductase type 2. J Ethnopharmacol. 2020;250:112446.

91. Miean KH, Mohamed S. Flavonoid (myricetin, quercetin, kaempferol, luteolin, and apigenin) content of edible tropical plants. J Agric Food Chem. 2001;49:3106–12.
92. Hong GL, Kim TW, Lee HJ, Kim YJ, Kim KH, Jung JY. The extract of Celtis choseniana Nakai alleviates testosterone-induced benign prostatic hyperplasia through inhibiting 5α reductase type 2 and the Akt/NF-κB/AR pathway. Chin J Nat Med. 2022;20:518–26.
93. Kumar S, Singh A, Bajpai V, Srivastava M, Singh BP, Ojha S, et al. Simultaneous determination of Bioactive Monoterpene Indole Alkaloids in Ethanolic Extract of Seven Rauvolfia Species using UHPLC with Hybrid Triple Quadrupole Linear Ion Trap Mass Spectrometry. Phytochem Anal. 2016;27:296–303.
94. Huang G, He X, Xue Z, Long Y, Liu J, Cai J, et al. Rauwolfia Vomitoria extract suppresses benign prostatic hyperplasia by inducing autophagic apoptosis through endoplasmic reticulum stress. BMC Complement Med Ther. 2022;22:125.
95. Meng N, Kong K, Li SW. Research Progress on Chemical constituents and pharmacological activities of Epimedium plants. Acta Bot Boreali-Occidentalia Sinica. 2010;30(5):1063–73. [in Chinese].
96. Pei LK, Sun SQ, Guo BL, Huang WH, Xiao PG. Fast quality control of Herba Epimedii by using Fourier transform infrared spectroscopy. Spectrochim Acta Mol Biomol Spectrosc. 2008;70:258–64.
97. Geng ZK, Lv J, Zhang L. Comparison of intervention effects of different solvent extracts of Raw and Fried Epimedium on Benign Prostatic Hyperplasia Mice. Chin Traditional Patent Med. 2017;39(1):185. [in Chinese].
98. Tu ML, Yang XG, Zhuang TT. Therapeutic effects of Epimedium on Benign Prostatic Hyperplasia Model rats and its influence on the expression of Autophagy proteins Beclin-1 and LC3. J Traditional Chin Med Materia Med. 2020;31(5):1102–6. [in Chinese].
99. Zang L, Tian F, Yao Y, Chen Y, Shen Y, Han M, et al. Qianliexin capsule exerts anti-inflammatory activity in chronic non-bacterial prostatitis and benign prostatic hyperplasia via NF-κB and inflammasome. J Cell Mol Med. 2021;25:5753–68.
100. Yang H, Chen D, Cui QC, Yuan X, Dou QP. Celastrol, a triterpene extracted from the Chinese Thunder of God Vine, is a potent proteasome inhibitor and suppresses human prostate cancer growth in nude mice. Cancer Res. 2006;66.
101. Guo J, Huang X, Wang H, Yang H. Celastrol induces autophagy by targeting AR/miR-101 in prostate Cancer cells. PLoS ONE. 2015;10:e0140745.
102. Wei Y, Wang Y, Xue H, Luan Z, Liu B, Ren J. Triptolide, a potential Autophagy Modulator. Chin J Integr Med. 2019;25:233–40.
103. Chen P, Zhong X, Song Y, Zhong W, Wang S, Wang J, et al. Triptolide induces apoptosis and cytoprotective autophagy by ROS accumulation via directly targeting peroxiredoxin 2 in gastric cancer cells. Cancer Lett. 2024;587:216622.
104. Wang M, Chen B, Chai L. Triptolide suppresses the proliferation and induces the apoptosis of nasopharyngeal carcinoma cells via the PI3K/Akt pathway. Oncol Lett. 2019;17:1372–8.
105. Liu X, Zhao P, Wang X, Wang L, Zhu Y, Gao W. Triptolide induces Glioma Cell Autophagy and apoptosis via Upregulating the ROS/JNK and downregulating the Akt/mTOR signaling pathways. Front Oncol. 2019;9:387.
106. Zhao F, Huang W, Zhang Z, Mao L, Han Y, Yan J, et al. Triptolide induces protective autophagy through activation of the CaMKKβ-AMPK signaling pathway in prostate cancer cells. Oncotarget. 2016;7:5366–82.
107. Smith DK, Hasanali SL, Wang J, Kallifatidis G, Morera DS, Jordan AR, et al. Promotion of epithelial hyperplasia by interleukin-8-CXCR axis in human prostate. Prostate. 2020;80:938–49.
108. Luo C, Ye YH, Tu JW. Research Progress on Traditional Chinese Medicine regulating autophagy-related pathways to resist Lung Cancer. J Nanjing Univ Traditional Chin Med. 2023; (11): 1155–64. [in Chinese].
109. Liu J, Li M, Wang Y, Luo J. Curcumin sensitizes prostate cancer cells to radiation partly via epigenetic activation of miR-143 and miR-143 mediated autophagy inhibition. J Drug Target. 2017;25:645–52.
110. Yang C, Ma X, Wang Z, Zeng X, Hu Z, Ye Z, et al. Curcumin induces apoptosis and protective autophagy in castration-resistant prostate cancer cells through iron chelation. Drug Des Devel Ther. 2017;11:431–9.

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