====== **REVIEW** ======

Natural Activators of Autophagy

Julia A. Pavlova[1,2,3,a*#], Ekaterina A. Guseva[1,2,3#], Olga A. Dontsova[1,2,3,4], and Petr V. Sergiev[1,2,3,5,b*]

[1]*Center of Life Sciences, Skolkovo Institute of Science and Technology, 143025 Skolkovo, Russia*
[2]*Belozersky Institute of Physico-Chemical Biology, Lomonosov Moscow State University, 119991 Moscow, Russia*
[3]*Department of Chemistry, Lomonosov Moscow State University, 119991 Moscow, Russia*
[4]*Shemyakin–Ovchinnikov Institute of Bioorganic Chemistry, 117997 Moscow, Russia*
[5]*Institute of Functional Genomics, Lomonosov Moscow State University, 119991 Moscow, Russia*
[a]*e-mail: julidev@yandex.ru*
[b]*e-mail: petya@genebee.msu.ru*

Abstract—Autophagy is the process by which cell contents, such as aggregated proteins, dysfunctional organelles, and cell structures are sequestered by autophagosome and delivered to lysosomes for degradation. As a process that allows the cell to get rid of non-functional components that tend to accumulate with age, autophagy has been associated with many human diseases. In this regard, the search for autophagy activators and the study of their mechanism of action is an important task for treatment of many diseases, as well as for increasing healthy life expectancy. Plants are rich sources of autophagy activators, containing large amounts of polyphenolic compounds in their composition, which can be autophagy activators in their original form, or can be metabolized by the intestinal microbiota to active compounds. This review is devoted to the plant-based autophagy activators with emphasis on the sources of their production, mechanism of action, and application in various diseases. The review also describes companies commercializing natural autophagy activators.

INTRODUCTION

Autophagy is one of the fundamental molecular processes facilitating removal of damaged or non-operating properly cell components. Three different types of autophagy are recognized: microautophagy, macroautophagy, and autophagy associated with chaperons.

Microautophagy involves non-selective capture of macromolecules and parts of membranes followed by their digestion. Hence, the cell could receive additional energy and material for biosynthetic activity, which is essential, for example, under starvation conditions. However, it is important to note that similar processes could occur under normal conditions [1]. It should be mentioned that in this review microautophagy will not be discussed in detail, because it represents non-specific type of autophagy. More emphasis will be on macroautophagy that plays an important physiological role in human health, and dysfunction of which is a cause of numerous diseases.

Abbreviations: Akt, RAC-α serine/threonine protein kinase; AMPK, AMP-activated protein kinase; BECN1, beclin-1; LC3, microtubule-associated protein light chain 3; LKB1, liver kinase B1; mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin complex 1; p62/SQSTM1, sequestosome 1; p70S6K, ribosomal protein S6 kinase; PI3K, phosphatidylinositol-3-kinase; PINK1, PTEN-induced protein kinase 1; ROS, reactive oxygen species; SIRT1, sirtuin 1; TFE3, transcription factor E3; TFEB, transcription factor EB; UA, urolithin A; Ub, ubiquitin; ULK1, unc-51-like autophagy-activating kinase 1.

* To whom correspondence should be addressed.

# These authors contributed equally to the study.

In autophagy associated with chaperone activity, denatured proteins are transported to lysosomes, where they are digested. This process requires participation of cytoplasmic chaperons from the Hsp70–Hsp90 family, as well as membrane receptors recognizing complexes of proteins with chaperons. This type of autophagy has been observed only in mammalian cells and only under stress condition [2].

The last and selective type of autophagy, macroautophagy, seems the most interesting. In this process the organelles carrying the autophagosome label are recognized by the membrane receptors (LC3/GABARAP). Ubiquitin (Ub) is the most often found label in this case, but polysaccharide-based signals, lipids, Ub-like proteins could also be used [3]. Recognition of the signalling molecule results in separation of the part of cytoplasm from the rest by two membranes leading to formation of autophagosome. Next, autophagosome is fused with lysosome forming autophagolysosome, where digestion of the content occurs [4].

One of the features of macroautophagy is its fast and dynamic regulation. Under normal conditions the level of autophagy is rather low in the cell, but under starvation and under effect of specific signaling compounds it increases several folds. Continuous or periodic decrease in caloric intake without malnutrition is a promising strategy increasing life expectancy of organisms [5]. However, strict adherence to such diets is complicated, which facilitated development of the calorie restriction mimetics (CRM). CRMs are compounds that artificially induce pathways of calorie restriction thus facilitating autophagy. Potential of the use of calorie restriction mimetics in treatment of age-related diseases has been considered previously in the review devoted to the mechanisms of their action and possible therapeutic effects [6]. Some of the compounds described in this publication and recognized as calorie restriction mimetics (resveratrol, spermidine, quercetin, curcumin, and others) will be analyzed in the review predominantly from the point of view of the mechanism of their action.

Macroautophagy plays an important role in such physiological processes as adaptation to starvation, quality control of cellular organelles, elimination of intracellular parasites, and regulation of innate and acquired immunity [7].

Among the diverse macroautophagy processes autophagy of mitochondria (mitophagy) should be highlighted, because in the course of this process redundant and damaged mitochondria, which potentially are highly cytotoxic, are eliminated [8].

Balanced operation of the mitophagy systems is extremely important, and its disruption results in the development of cancer, cardiovascular, and neurodegenerative diseases [9]. It was demonstrated in the murine models that activation of mitophagy and au-

tophagy processes with the help of pharmaceutical preparations results in improvement in the state of model animals with myocardium infarction, various types of cardiomyopathy, and atherosclerosis [8]. This fact is especially significant, because up to now cardiovascular diseases are the leading cause of death not only in Russia, but also worldwide [10].

It was shown with different animal models that the compounds initiating activation of mitophagy promote increase in life expectancy by preventing accumulation of damaged mitochondria. Moreover, consumption of such compounds prolongs normal activity of the organism by preventing age-related decrease of muscle strength and decrease of the speed of walking [11]. This could be explained by the fact that the level of mitophagy in the skeletal muscle cells decreases with age, which, in turn, results in the decrease of energy supply in the muscles [12].

Another interesting mechanism of targeted autophagy is lipophagy – a pathway of degradation of lipid droplets (LD), which participate in various biological processes in the cells. Excessive accumulation of LD is closely associated with various diseases including metabolic diseases. Targeted degradation of lipid droplets is a potential strategy for treatment obesity [13], diabetes [14], non-alcoholic steatohepatitis [15, 16], and other diseases associated with excessive accumulation of lipids.

Hence, investigation of the mechanisms of autophagy is a promising research area aiming at extending life expectancy, and, which is no less important, improving quality of life for the elderly. Moreover, activators of autophagy have been considered more often as potential therapeutics for treatment of such diseases as diabetes [17], infection diseases [18], oncological [19, 20], autoimmune [21], cardiovascular [22], neurodegenerative diseases [23], and others. Preparations approved by the US Food and Drug Administration (FDA), for which the ability to activate autophagy was demonstrated, have been described in detail in the review devoted to the synthetic activators of autophagy [24].

This review is devoted to the natural activators of autophagy and mitophagy with emphasis on the mechanism of their action, origins, as well as potential of their use for treatment of different diseases.

MECHANISMS OF ACTIVATION OF AUTOPHAGY

A significant progress was achieved in investigation of the process of autophagy in the recent decade. The evolutionary conserved genes regulating autophagy have been identified, which facilitated investigation of their functions associated with maintenance of homeostasis and total physiological state. Moreover,
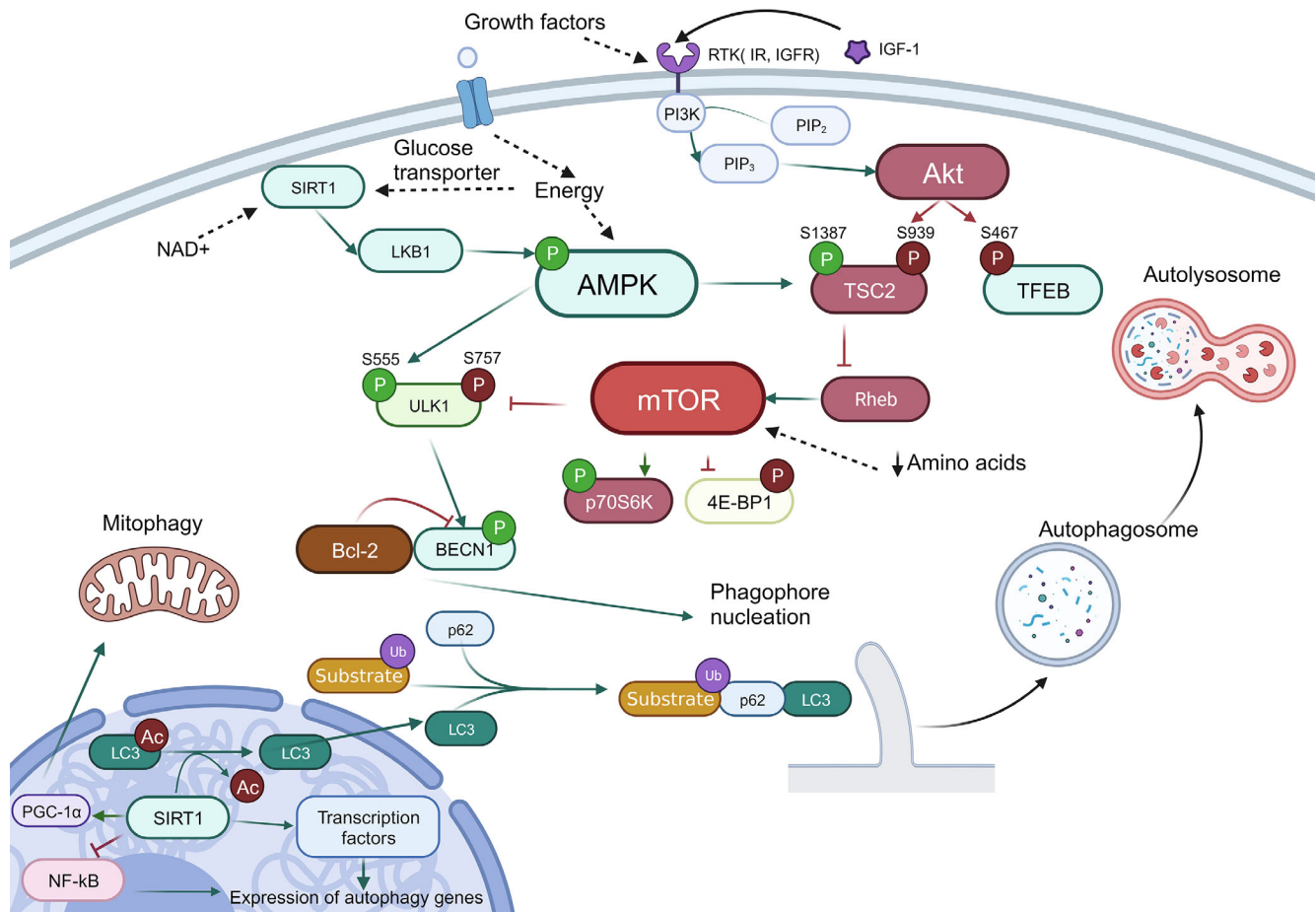
Fig. 1. Scheme of autophagy regulation. Ub, ubiquitination; P, phosphorylation (inhibitory phosphorylation is shown in red, activating – in green). Green arrows show interactions that activate target, and red arrows – interactions that inhibit target. Black arrows are used to show sequence of the stages in the process of autophagy, as well as to show targets of the compounds. Black dashed lines show effect of intracellular conditions/factors on the target.

a vast amount of data has been accumulated indicating association between the disruption of macroautophagy and various diseases. Considering that it is macroautophagy that represents a selective type of autophagy and plays the most important physiological role in the development of different diseases, in this review we will describe mechanism of this particular process and omit discussion of the non-selective type of autophagy, microautophagy.

Macroautophagy. Numerous proteins participate in autophagy that are required for fusion of autophagosomes and lysosomes, acidification of lysosomes, and lysosomal digestion, as well as for transmission of the regulatory signals that link state of the environment and autophagy system. General scheme of autophagy regulation is presented in Fig. 1.

The main signals of autophagy initiation are energy and amino acids starvation in the cell, as well as hypoxia and oxidative stress. The main sensor of energy starvation is the AMP-activated protein kinase (AMPK). Activity of this enzyme is also regulated by sirtuin 1

(SIRT1), NAD$^+$-dependent deacetylase, and ADP-ribosyl transferase. Accumulation of NAD$^+$ in the cell serves as a signal for SIRT1 activation, which, in turn, indicates exhaustion of energy sources and decrease of the mitochondrial membrane potential. In the activated state SIRT1 exhibits deacetylase activity, which, in turn, results in activation of the liver kinase B1 (LKB1) and AMPK, as well as in deacetylation of LC3 (microtubule-associated protein light chain 3), triggering its translocation from the nucleus to cytoplasm. SIRT1 also can control autophagy through the transcription factors FOXO1 and NF-κB (nuclear factor κB). Moreover, by maintaining deacetylated state of the peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC-1α), SIRT1 participates in regulation of the mitochondrial function and oxidative stress [25].

The main signals for cell survival and growth are PI3K (phosphatidylinositol-3-kinase) and Akt (RAC-α serine/threonine protein kinase). Activation of this signaling pathway results in suppression of autophagy via inhibition of the tuberous sclerosis protein 2 (TSC2),

which stops switching off the RheB regulator due to GTP hydrolysis. In addition, Akt also phosphorylate TFEB – main transcription factor regulating biogenesis of mitochondria. The phosphorylated state of TFEB is translocated from the nucleus to cytoplasm, which results in the decrease of autophagy level in the cells [26].

Serine/threonine protein kinase mTOR (mammalian target of rapamycin) is the central regulator involved in the vast majority of the pathways associated with both biogenesis and autophagy. mTOR controls cell growth and survival by recognizing intercellular signals and information on metabolism such as, for example, availability of amino acids. Activity of mTOR is also regulated via the AMPK- and Akt-dependent pathways.

In cell mTOR is in composition of two kinase complexes (mTORC1 and mTORC2), which have different functions. The role of mTORC2 involves regulation of growth factor signaling pathways by phosphorylation of the Akt and SGK kinases, which affect cell survival and suppress apoptosis [27]. At the same time, mTORC1 in active state inhibits autophagy by suppressing activity of the Unc-51-like kinase 1 (ULK1) and initiates protein biosynthesis via phosphorylation of the main mRNA translation regulators, such as proteins of the 4E-BP group inhibiting protein synthesis initiation factor eIF4E [27]. In order to be activated mTORC1 should be translocated to the lysosome surface, where it can be activated by amino acids [7]. In the case of mTOR inhibition by starvation or by the autophagy inducers, ULK1 is autophosphorylated and undergoes conformational changes, thus initiating assembly of the platform for further formation of autophagosome [28]. Beclin 1 (BECN1) is the main effector of this platform, which in composition of different complexes activates assembly of autophagophore, the two-membrane vesicle containing the eliminated organelles and part of cytoplasm.

The process of autophagophore assembly includes two main stages: nucleation and elongation of the isolating membrane. Complex of class III PI3K is required at the stage of nucleation of the phagophore membrane, which also includes BECN1. Regulation of activity of this complex is mediated by BECN1 with the help of ULK complex and also Bcl-2, anti-apoptotic protein, which inhibits autophagy by binding BECN1 under condition of excess of nutrients in the cell. Dissociation of BECN1 and Bcl-2 is required for autophagy induction [7].

PI3K complex also initiates assembly of the platform required for attracting, modification, and anchoring of LC3 in the phagophore membrane. Initially LC3 is present in the cell in the form of precursor – pro-LC3. In the first step of modification a small fragment is cleaved from the C-end. A soluble form of LC3, LC3-I, is produced as a result of this reaction [29]. In LC3-I the C-terminal glycine is exposed on the surface. In the next stage Atg7 (E1) and Atg3 (E2) carry reaction similar to ubiquitination [29]. As a result, a bond is formed between the C-terminal glycine and phosphatidylethanolamine leading to production of the protein isoform associated with the membrane – LC3-II. In the process LC3-II binds both to the outer and inner membranes of the autophagosome.

Special adapter systems exist in the cells that connect LC3 with the autophagy targets. The most thoroughly investigated among them is p62, also known as SQSTM1/sequestosome 1. p62 is a selective receptor of autophagy. Five domains are in composition of this protein: N-terminal domains Phox and Bem1p (PB1), zinc finger domain of ZZ-type, PEST site (containing presumed phosphorylation sites), and C-terminal domain binding polyubiquitin (UBA). The N-terminal domain PB1 is used for p62 polymerization and binding to other proteins containing PB1 domains [30]. It has been suggested that p62 facilitates binding of polyubiquitinated protein aggregates with LC3, which results in their incorporation into autophagosome and degradation. Hence, the cell destroys the incorrectly folded proteins together with p62 [30].

Mitophagy. Mitophagy is a selective form of macroautophagy, which is required for elimination of damaged or redundant mitochondria and, hence, is one of the most important processes maintaining cellular homeostasis. Disruption of mitophagy could result in the development of a number of diseases including cancer, cardiovascular and neurodegenerative diseases, as well as liver diseases [8, 31-35].

Mechanisms of mitophagy can be classified as Ub-dependent and Ub-independent pathways. The Ub-dependent mitophagy pathway is based on ubiquitination of the surface proteins in mitochondria to be recognized as damaged organelles. The most investigated pathway of mitophagy activations is the PINK1/Parkin system (see Fig. 2).

PINK1 is a PTEN-inducible Ser/Thr kinase 1, which is accumulated at the outer mitochondrial membrane in response to disruption of membrane potential. PINK1 phosphorylates ubiquitin ligase Parkin and its substrate, ubiquitin, which results in the labeling of damaged mitochondria with ubiquitin labels. Ubiquitin ligases SMURF1 and Gp78B also participate in this process. Ubiquitin labels on mitochondria are recognized by the autophagy receptors OPTN and NDP52, which initiates formation of autophagosomes close to mitochondria, and also play a role of adapters in binding of mitochondria with LC3-II [9]. It was also discovered that p62 participated in mitophagy via the PINK1/Parkin-mediated pathway. The phosphorylated Parkin ubiquitinates p62 and facilitates its binding with LC3-II, which, in turn, facilitates transport of mitochondria to autophagosome [36].
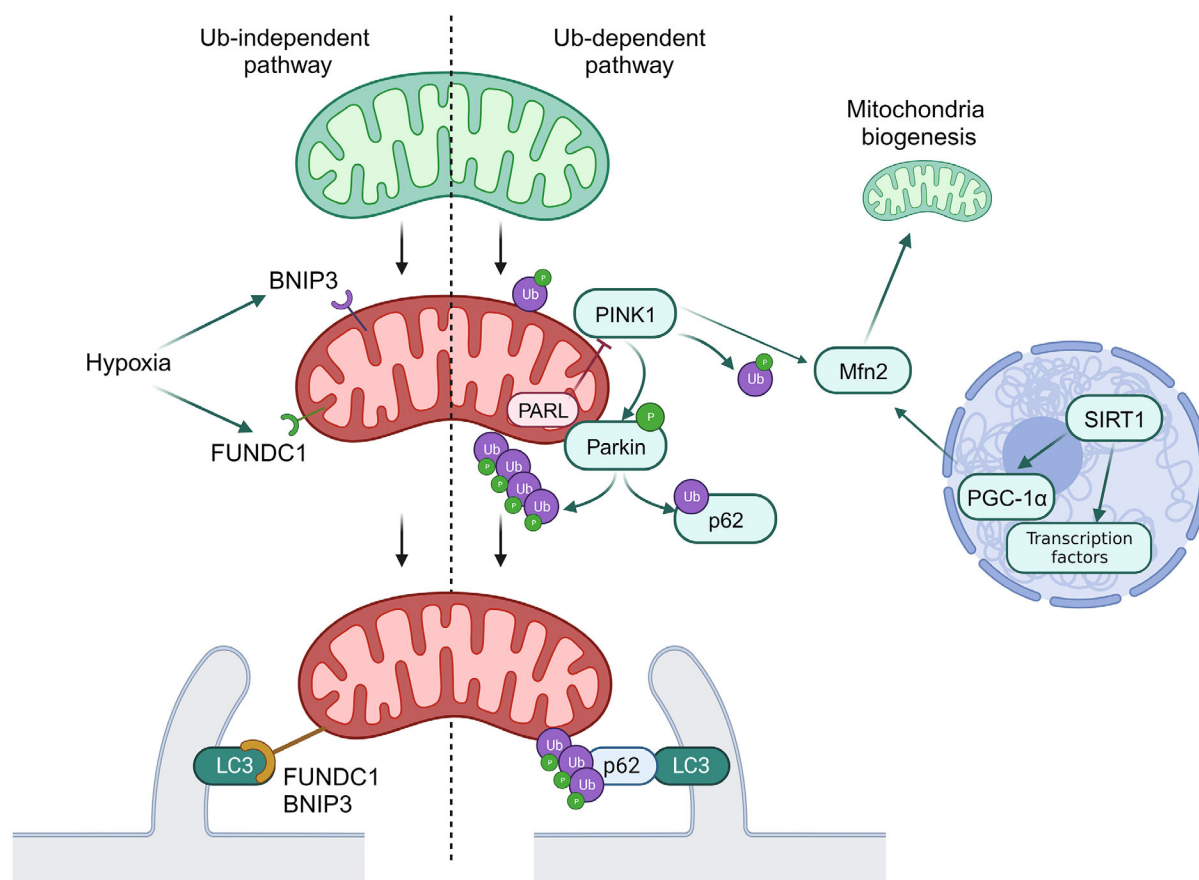
Fig. 2. General scheme of mitophagy. Normal mitochondria are shown in green, and mitochondria with disrupted functioning – in red. Ub, ubiquitination; P, activating phosphorylation. Green arrows show interactions activating the target. Red arrows show interactions inhibiting the target. Black arrows used to show sequence of stages in mitophagy.

Regulation of deacetylation of transcription factors mediated by SIRT1 could result in activation of mitophagy via the SIRT1/PGC1α/Mfn2/Parkin pathway [37]. The PINK1/Parkin system catalyzes phospho-ubiquitination of Mfn2, thus initiating the p97-dependent dissociation of the Mfn2 complexes from the outer mitochondrial membrane. This results in separation of mitochondria from endoplasmic reticulum and their fragmentation, which facilitates mitophagy [38].

In addition to the described signaling system, mitophagy receptors BNIP3, NIX/BNIP3L10, and FUNDC1B are localized on the outer mitochondrial membrane, which interact directly with LC3 through typical or atypical LIR motifs (LC3-interacting region) independent on ubiquitination. Initially NIX was identified as a key mediator of mitochondria degradation during erythrocyte maturation, but it has been shown recently that it is also activated in response to disruption of mitochondrial membrane potential. It was also demonstrated that expression of NIX and BNIP3 is under partial control of HIF-1 (hypoxia inducible factor 1), and their activation during hypoxia facilitates elimination of the damaged mitochondria. Hence, BNIP3 together with FUNDC1 are considered as the main mediators

of mitophagy induced by hypoxia. Unlike in the case of NIX and BNIP3, expression of FUNDC1 does not depend significantly on hypoxia or mitochondrial membrane potential, and its activity in controlled via post-translational modifications. Under normal conditions interaction between FUNDC1 and LC3 is suppressed by phosphorylation of the LIR domain. However, in hypoxia or in the case of disruption of mitochondrial membrane potential Ser/Thr phosphatase PGAM5 dephosphorylates FUNDC1, which increases its affinity for LC3 and promotes attachment of mitochondria to the membrane of the forming autophagosome [9].

NATURAL ACTIVATORS
OF AUTOPHAGY AND MITOPHAGY

Complex system of regulation of autophagy in general and mitophagy in particular explains the fact that a rather diverse set of natural and synthetic compounds could affect this process. Considering that activation or inhibition of autophagy are important for maintenance of the balance between the monomeric blocks such as amino acids from the one side
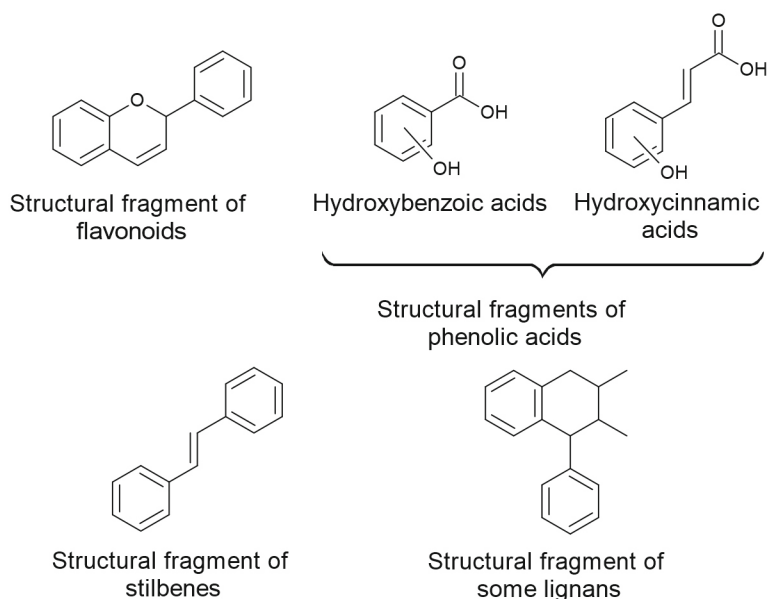
Structural fragment of
flavonoids

Hydroxybenzoic acids

Hydroxycinnamic
acids

Structural fragments of
phenolic acids

Structural fragment of
stilbenes

Structural fragment of
some lignans

Fig. 3. Main structural fragments in the composition of polyphenolic compounds.

and macromolecules and organelles from the other side, search for and investigation of the compounds regulating autophagy is an important task of the basic and applied science.

Sources of natural activators of autophagy and mitophagy. *Secondary metabolites of plants.* Plants contain large amounts of polyphenolic compounds with main structures presented in Fig. 3. These compounds affect human health exhibiting antioxidant, anti-inflammatory, antitumor, anti-adaptogenic, and neuroprotective properties [39-42]. Role of polyphenolic compounds in the processes of autophagy and apoptosis, as well as their possible use in chemotherapy of oncological diseases have been described in detail in numerous reviews [43-50].

Among the phytocompounds with anticarcinogenic properties and phytocompounds affecting processes of autophagy and apoptosis representatives of all classes of polyphenolic compounds such as flavonoids (flavonols, flavones, flavanones, isoflavones, flavan-3-ols, anthocyanins) and non-flavonoids (coumarins, curcuminoids, phenolic acids, lignans, stilbenes, xanthones) have been described [43, 48]. Majority of flavonoids are found in plants in the form bound to sugars, such as O- or C-glycosides, which interferes with their absorption in small intestine. The reactions of sugar hydrolysis leading to formation flavonoid aglycones increases their bioavailability for the organism.

Below we present examples of some polyphenolic phytocompounds; metabolism of these compounds by microorganisms results in formation of products activating autophagy. Ellagitannins found in many plant species belong to such compounds. Due to their molecular weight these compounds have very low bioavailability and are not absorbed in the intestine until they are hydrolyzed by the gut microflora to urolithins [51, 52]. Bacteria transformation of ellagitannins involves reduction of one of the two lactone groups followed by decarboxylation and sequential reduction to tetrahydroxy (urolithin D), trihydroxy (urolithin C), dihydroxy (urolithin A and isourolithin A), and monohydroxy (urolithin B) dibenzopyranones.

The ability to transform ellagitannins to urolithins was found in *Gordonibacter urolithinfaciens* and *Gordonibacter pamelaeae* (Coriobacteriaceae family), as well as in *Ellagibacter isourolithinifaciens* (Eggerthellaceae family), and in the strain *Bifidobacterium pseudocatenulatum* INIA P815 (Fig. 4) [53, 54].

Three metabolome phenotype groups (A, B, and 0) were observed in humans depending on the type of formed of urolithins [55]. In the group A (25-80%) only urolithin A is formed; in the group B (10-50%) – isourolithin A and/or B and urolithin A are detected. In the group 0 (5-25%) urolithins are not formed.

Daidzein is an example of another phytocompound transformation of which by the gut microbiota results in formation of more active and bioavailable metabolites than the initial isoflavonoid. Transformation of daidzein by the gut microbiota could result in formation of (S)-equol (isoflavandiol estrogen) or O-desmethylangolensin (O-DMA) depending on the microbiota composition (Fig. 5).

In the majority of individuals formation of O-desmethylangolensin occurs with participation of *Clostridium* species. In 30% of the tested individuals daidzein is transformed into S-equol, which exhibits stronger estrogenic effect, antioxidant activity, and
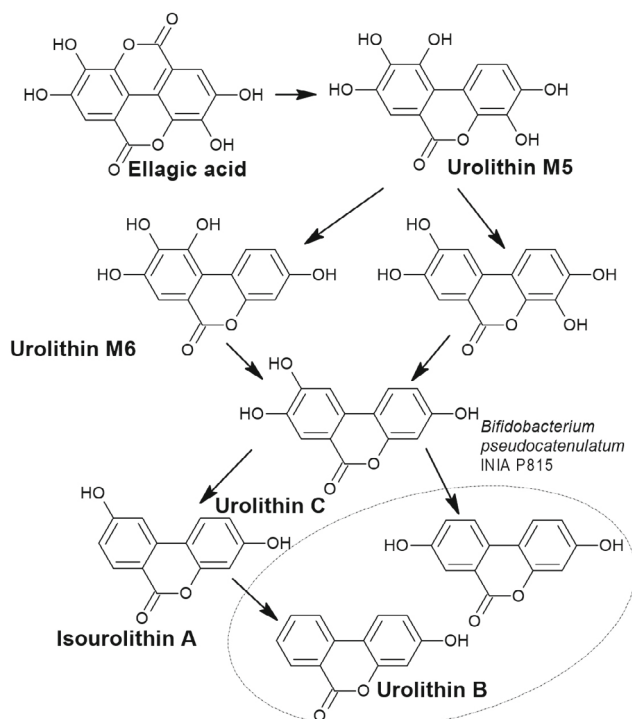
Fig. 4. Simplified scheme of formation of urolithins from ellagic acid by the bacterium *Bifidobacterium pseudocatenulatum* INIA P815.

Fig. 5. Transformation of daidzein by the human gut microbiota into bioavailable derivatives.

bioavailability than daidzein. S-equol is formed by a wide spectrum of bacteria: *Streptococcus intermedius*, *Bacteroides ovatus*, *Blautia producta*, *Eggerthella* sp. Julong 732, *Adlercreutzia equolifaciens*, *Slakia isoflavoniconvertens*, *Slakia equolifaciens*, *Asaccharobacter celatus*, *Enterorhabdus mucosicola* (Actinobacteria), and *Lactococcus garvieae* (Firmicutes) [56, 57].

Secondary bacterial metabolites. Microbiome and products of its metabolism could potentially affect activity of autophagy, as has been shown for formation of urolithin. In general, it can be presumed that microbiome formed under conditions of starvation could potentially activate autophagy. Based on suggestion on the benefits of the process of autophagy under conditions of starvation both for the host organism and for its microbiota, in this review mostly metabolites are considered that are formed by commensal gut bacteria. It has been shown in the studies that gnotobiotic (germ-free without microbiota) mice, rats, and birds have higher mortality under nutrient deficiency than the normal animals, despite the fact that the weight loss rate is the same in both cases. This is explained by the ability of gut microbiota to use alternative energy sources (fatty acids, ketone bodies, host proteins), to stimulate immunity and other protective mechanisms in the cells [58]. Under conditions of hibernation and starvation, high molecular weight glycoproteins of the intestinal mucus, atrophic epithelial cells, and dead bacterial cells are the main sources of energy
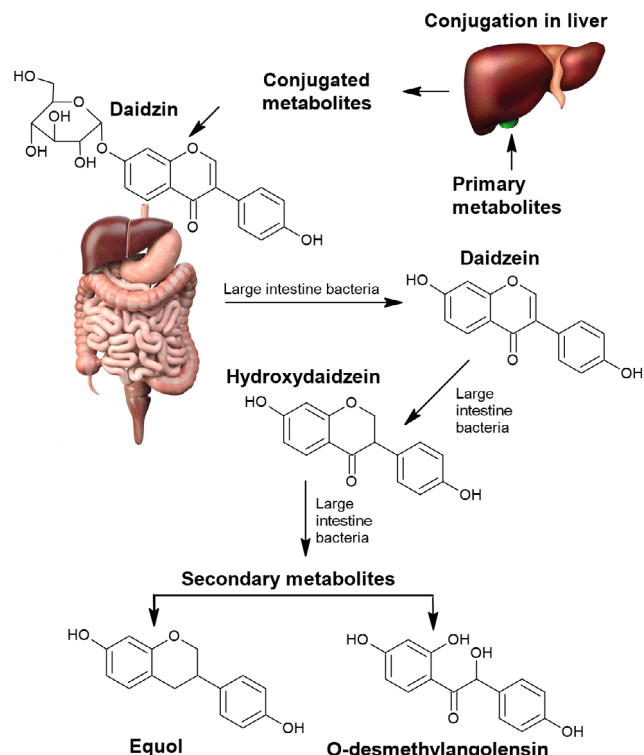
and carbon. This results in the changes of gut microbiota composition; fraction of the Bacteroidetes and *Akkermansia* bacteria that use endogenous glycosylated protein increases, and fraction of the bacteria of Firmicutes phylum that use plant polysaccharides for growth decreases [58]. Under conditions of complete starvation, bacteria that are capable of degradation of the host proteins receive competitive advantage [59, 60]. Metagenomic studies of the cecum contents in live hibernating or starving organisms demonstrated prevalence of *Bacteroides* (*B. thetaiotaomicron*, *B. fragilis*), certain Firmicutes (*Ruminococcus gnavus*), and Verrucomicrobiales (*Akkermansia muciniphila*). The bacteria *A. muciniphila* use exclusively mucins unlike the *Bacteroides* capable of consuming a wide spectrum of plant polysaccharides. The main metabolites of gut microflora in animals are short-chain (volatile) fatty acids formed as a result of fermentation of plant polysaccharides (cellulose, hemicellulose, resistant starch, pectins, dextrans, and oligosaccharides) indigestible by animal enzymes. The main products of fermentation (acetate, propionate, and butyrate) are formed, respectively, at a ratio from 75/15/10 to 40/40/20 (on average – 60/20/18) [61].

It was shown in the study by Iannucci et al. [62] that propionate and butyrate induced the UCP2/AMPK-dependent autophagy in the mouse liver cells via activation of PPARg (peroxisome proliferator-activated receptor gamma coactivator). Administration of
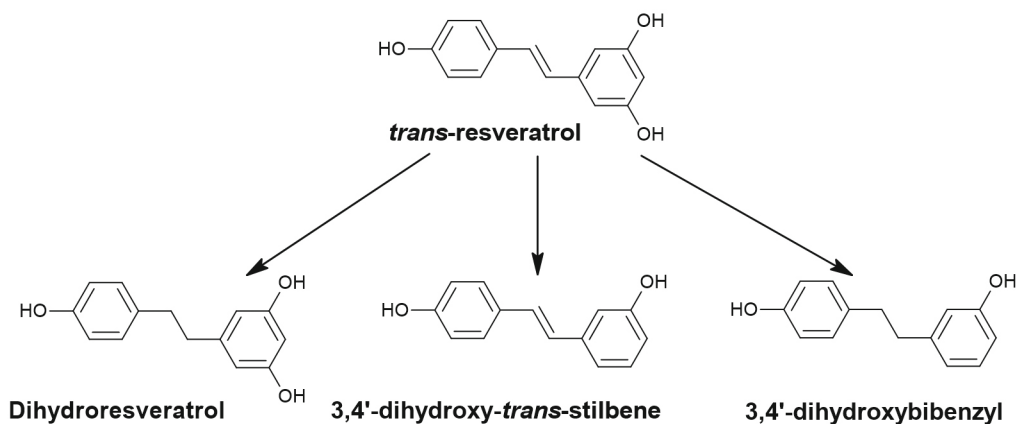
Fig. 6. Dehydrogenation of *trans*-resveratrol with formation of dihydroresveratrol, 3,4′-dihydroxy-*trans*-stilbene and 3,4′-dihydroxybibenzyl (lunularin) by the gut microbiota.

antibiotics significantly decreased basal level of autophagy in the mouse liver cells.

Hence, under starvation conditions gut microbiota both in animals and in humans predominantly contained bacteria capable of using mucins and other endogenous host substrates. It is likely that starvation is a factor for selection of bacterial species that are capable of surviving during prolonged absence of nutrients by switching metabolism to the use of available endogenous mucins and/or recyclization of dead bacterial or epithelial cells.

Natural compounds inducing autophagy. Among the activators of autophagy there are quite a few natural compounds, which often could act on several targets simultaneously. This complicates significantly elucidation of the exact mechanism of their action and could explain the fact that the data on these compounds mostly involve results of the experiments with cell cultures [63].

Let us begin the review of natural activators of autophagy considering compounds with the mechanism of action associated with the mTOR-dependent signaling pathway, inhibition of which positively regulates autophagy. There are many examples of compounds with this mechanism of action.

The natural polyphenol resveratrol, derivative of *trans*-stilbene, exerts a wide range of effects including antiproliferative activity via stimulation of both the BECN1-independent autophagy and apoptosis of cancer cells [64]. It was also shown that resveratrol inhibits the PI3K/Akt/mTOR pathway and activates AMPK, which are essential events in the suppression of adenoma growth in the mouse model of colorectal cancer [65]. However, according to another study, resveratrol induces autophagy in the ovarian cancer cells via alternative mechanism – by disruption of the BECN1–Bcl-2 complex [66]. It has been also reported that the resveratrol-induced apoptosis leads to inhibition of autophagy in the endometrial cancer cells [67] and in

the cells of esophageal squamous cell carcinoma [68]. In addition to that, it also enhances expression SIRT1, which could result in increase of autophagy [69]. It must be mentioned that the effects produced by resveratrol are multifaceted and significantly depend on the cell line and used concentrations.

Resveratrol is quickly absorbed via passive diffusion in the intestine and next is metabolized through glucuronidation and sulfation in enterocytes and in liver or is reduced to dihydroresveratrol by the gut bacteria *Sl. equolifaciens* and *Adl. equolifaciens* [70, 71]. In addition to dihydroresveratrol (Fig. 6), 3,4′-dihydroxy-*trans*-stilbene and 3,4′-dihydroxybibenzyl (lunularin) are formed as a result of metabolism by the gut microbiota [70].

There are no studies devoted to antitumor effects and effects on autophagy of the microbial metabolites of resveratrol despite the large number of such studies investigating resveratrol itself and its metabolites produced in liver and enterocytes [72].

Curcumin, the most studied biologically active compound isolated from the *Curcuma* plant species, has the same mechanism of action. Based on the results of preclinical and clinical studies this compound is recognized as an agent sensitizing cancer cells to chemo- and radiation therapy [73]. In the stomach cancer cell lines SGC-7901 and BGC-823 this compound suppresses the PI3K/Akt/mTOR pathway, which causes increase of expression of BECN1, Atg3, Atg5, p53, and p21, increases the LC3-II/LC3-I ratio, and potentiates autophagy [74]. In the cells of castration-resistant prostate cancer curcumin induces protective type of autophagy [75]. Inhibitory action of curcumin on the processes of transcription of ribosomal genes and activation of autophagy in the mouse embryonic fibroblasts (MAFs) [76], in the glioma cells [77], and in the lung carcinoma [78] has been also established. It has been mentioned in many clinical studies that curcumin exhibits very low bioavailability due to low solubility

and fast metabolism [79]. It has been suggested that the mechanism of positive effects of curcumin with its low bioavailability could be associated with its effect on the gut microbiota [80-83]. Transformation of curcumin by the gut microbiota could result in formation of compounds with high biological activity and improved bioavailability. One of the main metabolites of curcumin, tetrahydroxycurcumin, induced autophagy in the human leukemia cells HL-60 and lung cancer cells A549 NSCLC [84, 85].

Quercetin, natural flavonoid contained in many herbs, has the similar mechanism of action [86, 87]. Numerous preclinical studies have been devoted to investigation of its antiproliferative effects. Quercetin, similarly to curcumin, suppresses proliferation of the cells of stomach cancer [87], glioma [78], and lung cancer [88]. In the stomach cancer cells quercetin induces protective autophagy via the Akt/mTOR pathway and signal transduction mediated by hypoxia-inducible factor 1α (HIF-1α) [87]. In the study investigating human lung cancer cells A549 and H1299 quercetin increased the levels of SIRT1 protein and accumulation of the phosphorylated form of AMPK in dose-dependent manner [89].

There are other activators of autophagy among the flavonoids with mechanism of action associated with inhibition of mTOR. In particular, isobacachalcone from Ashitaba and Psoralea corylifolia inhibits activity of Akt and mTORC1, activates pro-autophagy transcription factors TFEB and TFE3 *in vitro*, as well as *in vivo* in the mouse model of fibrosarcoma [90]. It is important to clarify that in addition to activation of autophagy isobacachalcone also triggers endoplasmic reticulum stress manifested as endoplasmic reticulum PKR-like kinase (PERK)-dependent phosphorylation of eIF2α.

Representatives of the group of prenylated flavones, such as morusin and mulberrin, could slow down aging in the models of budding yeasts, worms, and human cells affecting the mTOR-Sch9/p70S6K system inducing autophagy. In the study with the HeLa human cells morusin and mulberrin inhibited phosphorylation of the β1 kinase of the ribosomal protein S6 (p70S6K), stimulated autophagy, and slowed down cell aging [91]. Moreover, the worms treated with morusin and mulberrin demonstrated additional benefits such as increase of reproduction without affecting the worms' health.

Another three compounds – eriocalyxin B (EriB), diterpenoid from isodon, α-hederin, triterpenoid saponin, and omega-3 polyunsaturated fatty acids – display similar mechanism of autophagy induction by inhibiting Akt/mTOR/p70S6K signaling and, simultaneously, initiating generation of reactive oxygen species (ROS) in the breast cancer [92], colorectal cancer [93], and prostate cancer [94] cells.

The FDA approved natural compound guaiazulene (1,4-dimethyl-7-isoprpylazulene) also could be assigned to the group of Akt/mTOR inhibitors [95]; previously it was used in ophthalmic preparations and later became popular as an ingredient of cosmetic products, toothpastes, and pharmaceutical preparations. This compound exhibits anticancer properties, and also can be used for pain treatment during inflammation in combination with diclofenac [96]. Guaiazulene suppresses non-small cell lung cancer (NCSLC) by initiating apoptosis induced by ROS. In the process, induction of autophagy was demonstrated in the NCSLC cells mediated by inhibition of the Akt/mTOR signaling pathway [97].

Caffeine is another interesting example of the inhibitor of mTOR signalling pathway, which initiates autophagy both *in vitro* and *in vivo* [98-100]. Caffeine decreases liver hepatosis in mice with non-alcoholic fatty liver disease [101] and protects against the prion-mediated neurotoxicity [102]. It is also worth mentioning that it was demonstrated in the studies that the coffee beans containing in addition to caffeine large amounts of polyphenols cause enhancement of autophagy, inhibition of mTORC1, decrease of the level of p70S6K phosphorylation, and translocation of LC3B into autophagosomes [103]. It could be suggested that the caffeine-induced autophagy is the cause underlying the fact that coffee decreases mortality among the middle-age individuals [104].

Autophagy induction through inhibition of the PI3K/Akt/mTOR signaling pathway could be used as an approach for obesity treatment. This has been corroborated in the study demonstrating that the flavonoids from *Pueraria montana* improved the state of obese mice with non-alcoholic fatty acid disease due to this mechanism [105]. It was also shown that puerarin, one of the isoflavones from *P. montana*, could significantly extend lifespan of *Drosophila melanogaster* via regulation of the proteasome subunit beta 5 (prosbeta5) and SIRT1 [106].

Another mechanism of autophagy activation is inhibition of the receptor of insulin-like growth factor-1 (IGF1), which regulates the PI3K/AKT/mTOR pathway. This mechanism has been observed for picropodophyllin (PPP), cyclolignan alkaloid isolated from the mayapple plant. PPP has been described as a powerful inducer of autophagy realizing its effect by inhibition of the insulin-like growth factor-1 receptor (IGF1R). Administration of PPP to mice with tumors increased efficiency of immunogenic chemotherapy, which was based on the induction of autophagy in the malignant cells [107].

Despite the fact that mTOR plays an important role in the cell metabolism participating in sensing of nutrients, there is a wide variety of mTOR-independent pathways, which are targets of other autophagy activators.

Trehalose, natural disaccharide, stimulates autophagy and decrease protein aggregation by inhibiting glucose transporters [108, 109]. It was shown that trehalose increases conversion of LC3-I into LC3-II via the mTOR-independent pathway, similarly to sucrose [110]. Hence, trehalose could be used for inducing autophagy in the Parkinson's [111] and Alzheimer's [112] diseases, as well as in prion diseases [113]. Despite this, trehalose is not used in clinical practice, because it has low bioavailability due to fast metabolism in the organism. That is why more stable analogs of trehalose, lenztrehaloses A, B, and C, were synthesized, which were shown to be active activators of autophagy [114].

The hormonally-active form of vitamin D (calcitriol) inhibits replication of HIV-1 [115] and of mycobacterium tuberculosis in human macrophages [18] and kills breast cancer cells [116] due to induction of autophagy mediated by PI3K, ATG5, and BECN1. This explains the fact that the vitamin D deficit could be the cause of enhanced susceptibility to various cancer types and infectious diseases [117].

Among the natural autophagy activators, the AMPK kinase activators could be highlighted, which positively regulate autophagy by phosphorylating the ULK1 kinase at Ser-317, Ser-555, and Ser-777. Kazinol C from the *Broussonetia kazinoki* plant is one of such compounds, which induces apoptosis at high concentrations and autophagy at low concentration through activation of AMPK [118]. Hence, owing to these properties kazinol C could serve as an effective therapeutic agent for treatment of both cancer and metabolic diseases.

Regulation of AMPK could be realized through, for example, the SIRT1/LKB1 pathway [119]. SIRT1 activation results in deacetylation and increase of kinase activity of the LKB1 protein, which could activate AMPK by phosphorylation. Examples of double activators of SIRT1 and AMPK include combination of ferulic acid with berberine, which promotes autophagy, mitophagy, mitochondrial biogenesis, and DNA repair; this process facilitates cell survival due to suppression of apoptosis, aging, and inflammation caused by NF-κB [120].

Dihydroflavonoid compound naringin, which is abundant in citrus fruits and used in traditional Chinese phytotherapy, slows down aging in the *Caenorhabditis elegans* model, decreases fat accumulation, and facilitates autophagy. Transcriptome analysis showed changes in the levels of transcription of the genes associated with regulation of biosynthesis and metabolism of lipids and autophagy (such as genes *skn-1*, *hlh-30*, *lgg-1*, *unc-51*, and *pha-4*) [121]. According to the results of the study, naringin significantly activates SIRT1 and AMPK and stimulates mitochondrial biogenesis pathway through regulation of the LKB1/AMPK/PGC-1α signals [122].

Regulation of autophagy at the level of transcription is another possible mechanism of action of some activators. In particular, 3,4-dimethoxychalcone (3,4-DC), which has been described as a calorie restriction mimetic, induces autophagy by activation transcription factors TFEB and TFE3 [123]. Sweet tea (*Rubus suavissmus S. Lee*) polysaccharide STP-60a in the study with *C. elegans* extended lifespan of the animals through the insulin-dependent and mitochondrial pathways that depend on autophagy. It activates three transcription factors (FoxO/DAF-16, Nrf-2/SKN-1, and HSF-1) that operate downstream of the insulin signaling pathway [124].

Hence, natural activators of autophagy are very diverse in their mode of action, which in the majority of cases is associated simultaneously with several targets. The scheme summarizing targets of the natural activators of autophagy is presented in Fig. 7.

It must be emphasized that on the summarizing scheme only major targets are presented, which are affected by the considered compounds; however, for numerous compounds alternative mechanisms of action have been described in the literature, as noted in this review. Many molecules affect the process of autophagy by interacting with proteins (AMPK, ULK1, SIRT1, and others) and positively regulate this process. However, quite a few molecules activate autophagy by suppressing the AKT/mTOR pathway, which inhibits autophagy. Obviously, there are compounds affecting both of the indicated pathways, such as, for example, resveratrol and quercetin. However, it must be understood that the effects of many described molecules also include interactions with other targets mentioned above depending on the cell type and concentration. Hence, common feature of the majority of natural activators of autophagy is absence of unique mechanisms of action and, as a consequence, existence of a large number of side effects that limit their application.

Natural activators of mitophagy. Many natural compounds discussed in the previous section also can trigger mitophagy, such as spermidine and resveratrol. It seems logical to elaborate on the most known mitophagy activator – urolithin A (UA). Urolithin A belongs to the class of benzocoumarins, which is formed as a result of metabolism of ellagic acid and ellagitannins by the gut microflora [125]. No foods contain urolithin, and its bioavailability depends of the individual composition of microbiota. Mechanism of mitophagy induction with the help of UA is still poorly understood, but it is clear that it maintains mitochondrial functions with the help of several proteins regulators of mitophagy such as AMPK, BECN1, PINK1, p62/SQSTM1, and others. UA can activate SKN1 (homolog of NRF2 in *C. elegans* nematode), which extends lifespan and improves mitochondrial biogenesis thus preserving population and activity of mitochondria. It was shown in
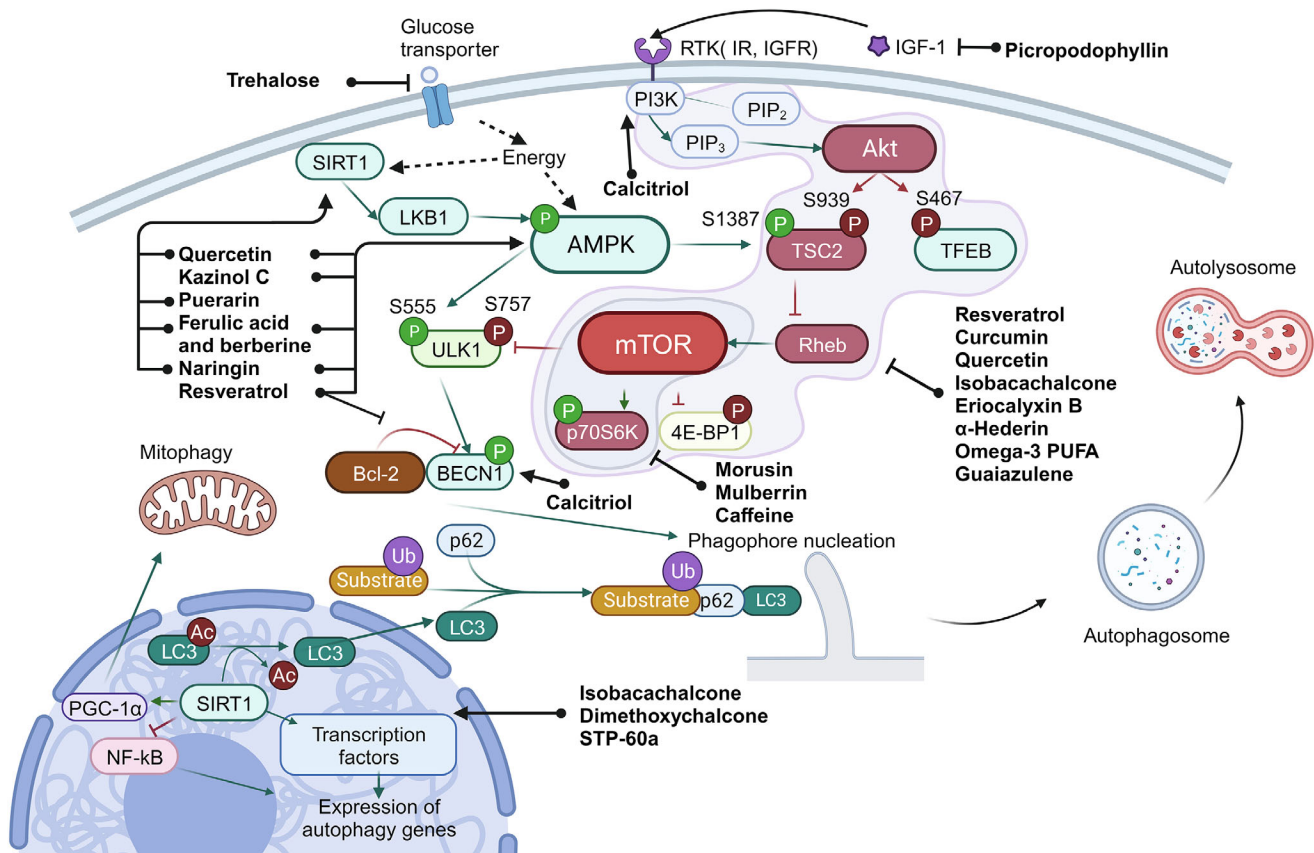
Fig. 7. Mechanism of action of natural activators of autophagy. Ub, ubiquitination; P, phosphorylation (inhibitory phosphorylation shown in red, and activating – in green). Green arrows show interaction activating the target, and red – interactions inhibiting the target. Black arrows used for presenting sequence of the stages in the process of autophagy, as well as to show targets of the compounds. Black dashed lines reflect effects of intracellular conditions/factors on the target.

the experiments with nematodes that the long-term administration of UA results in activation of mitochondrial biogenesis, which, in turn, results in the improvement of mobility, activity of pharyngeal pumping and respiration processes; moreover, these effects were shown to be independent on age and diet [11]. It was also demonstrated in the mouse models that prolonged oral administration of urolithin A results in the increase of physical endurance in the young mice and both muscle strength and endurance increase in the old mice. These results highlight therapeutic potential of urolithin A in improvement of muscle system functioning and mobility [126]. The results of *in vivo* studies did not reveal any toxic or specific side effects [127], moreover, elderly tolerate well treatment with UA [128]. In 2018 FDA included urolithin A in the list of safe food supplements.

Another natural activator of autophagy used at present as a food supplement for maintenance of mitochondrial functions is spermidine, which is a natural endogenous polyamine synthesized from diamine putrescine. Cereals, legumins, soya, hazelnuts, pistachios, as well as some fruits and berries are natural sources of spermidine [129]. Milk, eggs, as well as meat con-

tain spermidine in their composition. Spermidine is considered to exert such properties as slowing down aging, cardio protective effects [130], improvement of cognitive functions [131], protection against neurodegenerative disorders [132]; there are quite a few mechanisms suggested for possible effects of spermidine on autophagy. It was demonstrated in one study that spermidine, similarly to curcumin and quercetin, exerts properties of epigenetic regulator and induces autophagy *in vitro* by inhibiting histone acetyltransferase p300 (EP300), which suppresses function of several autophagy proteins [133]. In the female germline stem cells (FGSC) spermidine induces autophagy via inhibition of the PI3K/Akt pathway [134]. Spermidine enhanced the BECN1-dependent autophagy in fibroblasts in the bleomycin-induced idiopathic pulmonary fibrosis in mice [135].

It has been also shown that addition of spermidine affects number and morphology of mitochondria in the heart of old mice by stimulating mitophagy and mitochondrial biogenesis [136]. It was shown in the mouse models that spermidine can cross blood-brain barrier and enhance hypusination of the eukaryotic translation initiation factor 5A (eIF5A) in hippocampus

thus improving mitochondrial functions. In the same study it was shown with the model of Drosophila aging that spermidine increases respiratory capacity of mitochondria through the autophagy regulator Atg7 and PINK1/Parkin pathway [131].

Due to the large number of effects of spermidine on cellular metabolism the mechanisms of action of a particular compound differ depending on the cell type, organ, or existence of certain disease. This, from the one hand, could be beneficial for the fight with aging, which is the process with very complex mechanism. However, absence of the unique mechanism could pose serious problems for application of the particular compounds. Despite the fact that safety of spermidine used in the form of plant extract enriched with spermidine has been demonstrated for mice and elderly [132], another study with the rats treated with pure spermidine demonstrated several side effects of this compound [137].

Considering perspectives of spermidine application in different diseases, one of the approaches to overcome limitations of spermidine use is design and synthesis of new derivatives. Structurally related spermidine analogs have been produced, which in the experiments with *C. elegans* facilitate extension of life expectancy and protection of cells against oxidative stress by activation of mitophagy. In particular, the compound VL-004 (1,8-diaminooctane) has better capability to induce mitophagy than spermidine [138]. Unexpectedly it was discovered during investigation of the mechanism of action of VL-004 that the function of this compound depends on PINK1, but does not depend on PDR-1, Parkin ortholog in *C. elegans*. The authors of the study assume that another ubiquitin ligase E3 could be involved together with PINK1 inducing mitophagy.

Mitochondrial dysfunction is typical for many neurodegenerative diseases such as Parkinson's disease, and mitophagy mediated by the PRKN1/Parkin pathway could serve as an approach for treatment of such disorders. It was shown that in addition to individual molecules probiotics could also activate mitophagy thus alleviating symptoms of neurodegenerative diseases. Screening of 49 probiotic strains revealed that two probiotics, *Saccharomyces boulardii* and *Lactococcus lactis*, increased recruitment of Parkin to mitochondria, accumulation of phosphoubiquitin, and degradation of mitofusins [139].

Lactate and pyruvate that are capable of short-term acidification of cytosol were also described as agents activating mitophagy with aim to fight against Parkinson's disease [140]. Incubation of SH-SY5Y cells or primary neurons and astrocytes with these compounds resulted in activation of mitophagy after treatment with MPP+ (1-methyl-4-phenylpyridinium), which facilitated restoration of mitochondrial functions and protection of these cells from apoptotic and necrotic death. Mechanism of mitophagy activation has not been established in this study, but it was suggested that it could occurred not only via the PINK1/Parkin-dependent pathway, but also via the ubiquitin-independent pathways, such as oxidative stress accompanying Parkinson's disease.

Another active compound that provides neuroprotective effect in Parkinson's disease by inducing mitophagy is cistanoside A (CA), phenylethanoid isolated from the desert-broomrape, *Cistanche deserticola.* Exact mechanism of action has not yet been elucidated; however, it has been suggested that this compound could presumably activate the PINK1/Parkin/p62 pathway leading to degradation of damaged mitochondria and decrease of oxidative stress [141].

Nicotinamide (NAM), the FDA-approved food supplement, also has a potential for improving quality of mitochondria via activation of mitophagy. NAM decreases mitochondrial respiration and ROS production in the human primary fibroblasts and extends their replicative lifespan. NAM in the cells is converted into NAD^+ (nicotinamide adenine dinucleotide) with participation of nicotinamide phosphoribosyltransferase (Nampt). The presumed mechanism is associated with either increase of GAPDH activity, which, in turn, stimulates activation of ATG12, or with activation of SIRT1 [142].

Restoration of mitochondrial functions by activation of mitophagy is also considered as an approach for treatment of sarcopenia, syndrome of age-related muscle and strength loss. Linolenic acid was suggested as a compound with such potential, which significantly reduced sarcopenia in *C. elegans* by restoring mitochondrial functions, stimulating mitophagy, and fighting against oxidative stress. The mechanism of action is associated with upregulation of the *pink1* gene expression [143].

Another activator of the PINK1/Parkin-dependent mitophagy is L-carnitine, which maintains mitochondrial functions and normal state of heart microvessels. The described mechanism of L-carnitine action involves decrease of protease activity of the mitochondrial intramembrane cleaving protease PARL (presenilin-associated rhomboid-like protein), which mediates PINK1 cleavage by increasing interaction between PHB2 (Prohibitin-2) and PARL [144].

Hence, numerous activators of autophagy and mitophagy have been identified among the natural compounds, which exhibit a wide range of the mechanisms of action that involve several targets in the majority of cases (Fig. 8) including many proteins autophagy regulators. In addition to the effects on the PINK/Parkin pathway observed for the majority of the described molecules activators of mitophagy, they enhance autophagy via activation of AMPK and SIRT1 or by inhibiting mTOR.
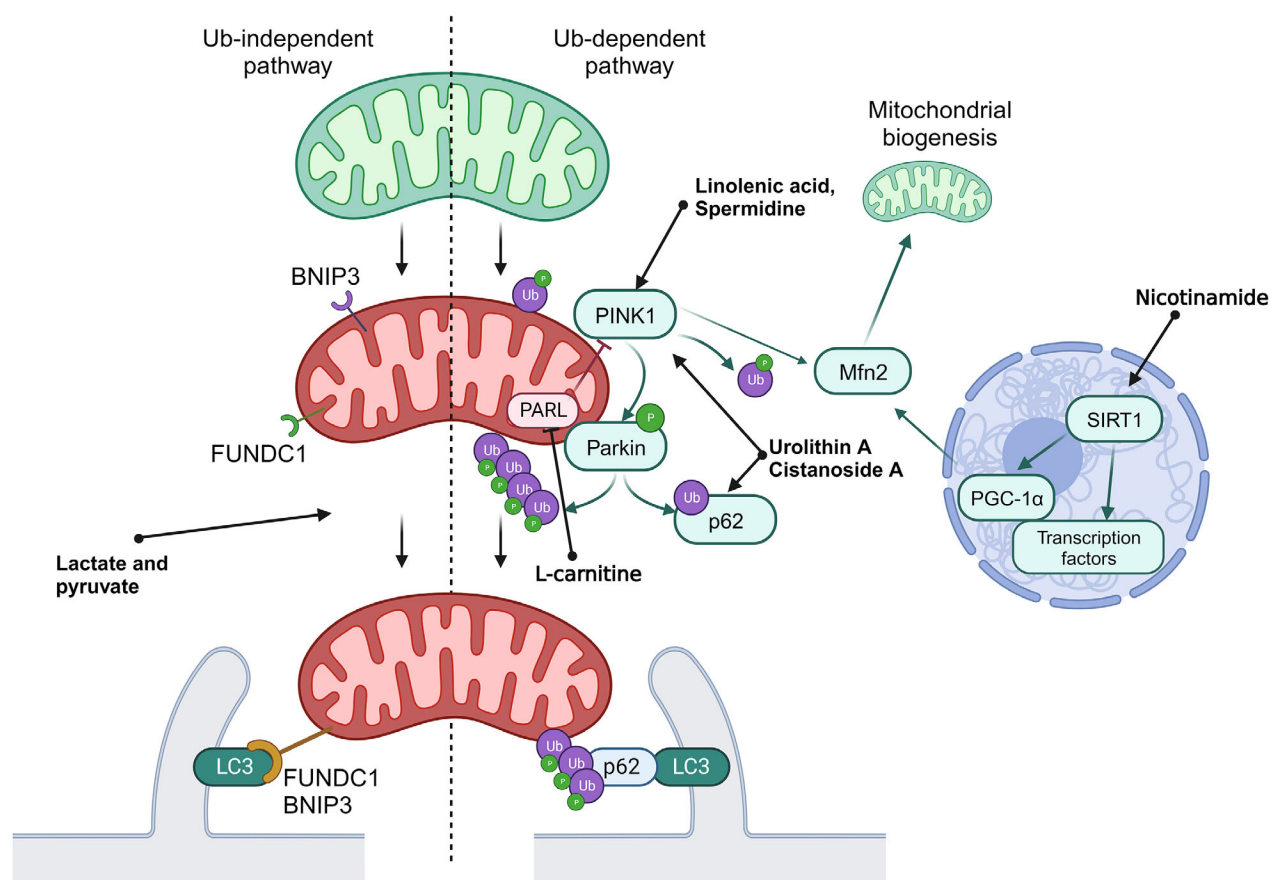
Fig. 8. Mechanism of action of natural activators of mitophagy. Normal mitochondria are shown in green, and mitochondria with disrupted function – in red. Ub, ubiquitination; P, activating phosphorylation. Green arrows show activating interaction. Red line shows interaction inhibiting the target. Black arrows show the sequence of stages in the process of mitophagy, as well as the targets of the compounds.

Summarized data on activators of autophagy and mitophagy including their structures, brief description of mechanism, and sources are presented in table.

COMMERICIAL DEVELOPMENTS
OF NATURAL AUTOPHAGY ACTIVATORS

Research and development in the area of autophagy became more and more popular in recent years as an approach for search of the compounds capable to slow down aging, improve health of elderly, and to delay onset of diverse age-related diseases. The companies Amazentis, Longevity labs, Mimio Health, Nestlé Health Science produce various biologically active supplements that aim to activate autophagy in cells and slow down aging and improve health status of an organism.

Some companies do not emphasize the fact that their product is capable of modulating autophagy, however, they use ingredients described in the literature as autophagy activators. In particular, the Napa Hills company produces drinks with resveratrol and other antioxidants, which help to reduce inflammation, facilitate improvement of cardiovascular system functioning, and slow down aging. Resveratrol also is in composition of food supplements produced by the Vinomis and Life Extension companies. The Taiyo company is a manufacturer of isoquercetin, precursor of quercetin, which provides defense against oxidative stress and also could initiate autophagy. Jarrow Formulas uses quercetin and other ingredients in their products to maintain mitochondrial functions, and Zeus Hygia uses bioavailable form of curcumin to restore muscle and joint functions. The list of companies using natural autophagy activators in compositions of their products does not end here, because natural compounds exhibit a wide spectrum of effects, and potential of their application is not limited to their use for autophagy activation.

Let us begin our detailed description with the companies that use natural autophagy activators in their products. The company Amazentis, founded in 2007 in Lausanne, Switzerland, uses modern science and clinical research for discovery and development of supplements aiming at extension of healthy life.

Natural activators of auto- and mitophagy

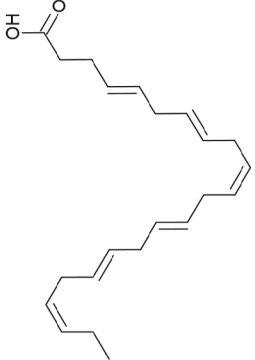| Name	Structure	Mechanism	Source	Reference
		Autophagy activators		
Resveratrol		disruption of BECN1–Bcl-2 complex; suppression of PI3K/Akt/mTOR pathway and activation of AMPK	red grape, blueberry, bog bilberry, cranberry, lingonberry, red current, roots of black mulberry, *Reynoutria sachalinensis*, and others	[64-72]
Curcumin		suppression of the PI3K/Akt/mTOR pathway	plants of *Curcuma* genus	[73-85]
Quercetin		inhibition of Akt/mTOR pathway and effect on signal transduction mediated by HIF-1α; activation of SIRT1 and AMPK	many plants, fruits, and berries of predominantly red color (red onion, grape, apples, tomatoes, lovage, capers, pepper, cherries, blueberries, and many others)	[86-89]
Isobacachalcone		inhibition of Akt and mTORC1; activation of pro-autophagy transcription factors TFEB and TFE3	*Angelica keiskei* and *Psoralea corylifolia*	[90]
Morusin		affecting mTOR-Sch9/p70S6K pathway by inhibiting phosphorylation of p70S6K	mulberry and other plants of Moraceae family	[91]
Mulberrin				[91]

Table (*cont.*)
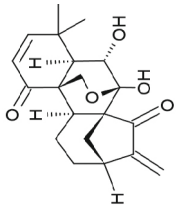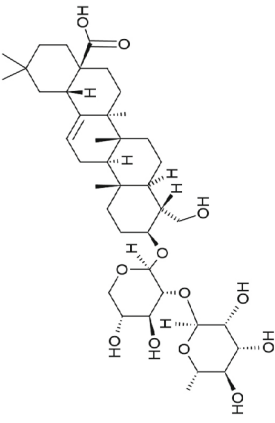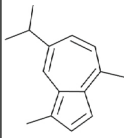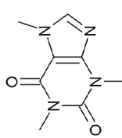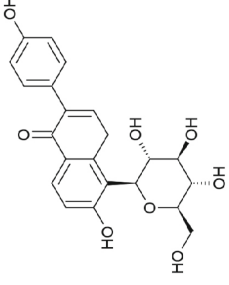
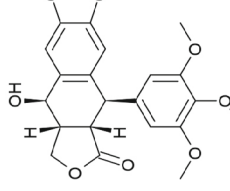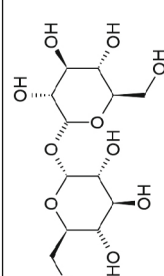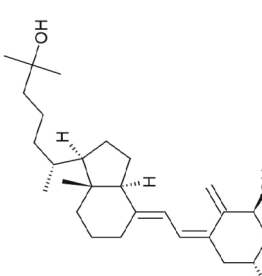| Name	Structure	Mechanism	Source	Reference
Eriocalyxin B (EriB)			*Isodon*	[92]
α-hederin		inhibition of Akt/mTOR/p70S6K	black caraway seeds and leaves of common ivy	[93]
Omega-3 polyunsaturated fatty acids (such as doco-sahexaenoic acid)			fish, chia seeds, flax seeds, sea algae and microalgae	[94]
Guaiazulene		inhibition of Akt/mTOR	some essential oils, mainly guaiac oil and chamomile oil, various soft corals	[95-97]
Caffeine		inhibitor of mTOR signaling pathway	tea leaves, coffee beans, cacao beans, kola nuts	[98-104]
Puerarin		regulation of proteasome subunit beta 5 (prosbeta5) and sirtuin-1 (SIRT1)	*Pueraria montana var. lobata*	[105-106]

Table (*cont.*)
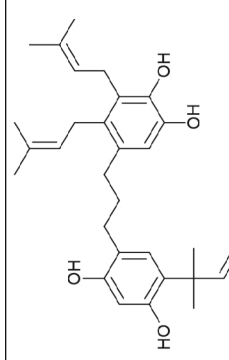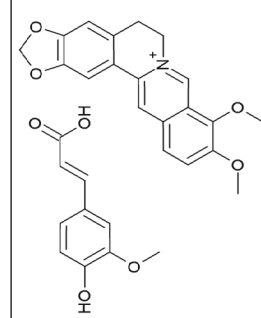
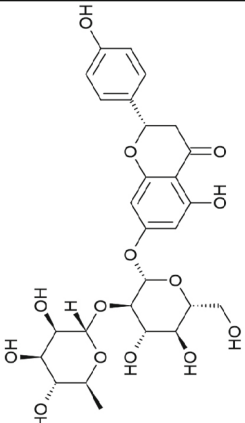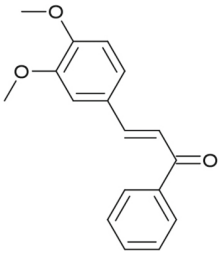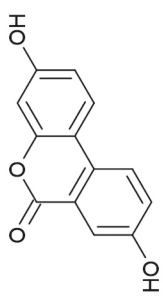| Name	Structure	Mechanism	Source	Reference
Picropodophyllin (PPP)		inhibition of insulin-like growth factor 1 receptor (IGF1)	Perennial herbaceous plant of the Berberidaceae family, *Podophyllum peltatum*	[107]
Trehalose		inhibition of glucose transporters	ergot, algae, yeast, higher fungi, lichens, some higher plants, hemolymph of some worms and insects	[108-113]
Calcitriol		induction of autophagy via PI3K, ATG5, and BECN1	produced in kidneys from cholesterol	[18, 115-117]
Kazinol C		activation of AMPK	*Broussonetia kazinoki*	[118]
Combination of ferulic acid and berberine		activation of SIRT1 and AMPK	ferulic acid is abundant in higher plants, berberine in *Berberis vulgaris)*, *Radix colombo* roots, and *Coptis chinensis*	[120]

Table (*cont.*)
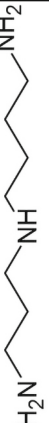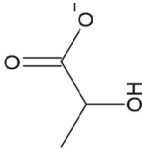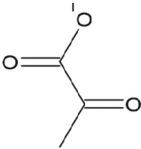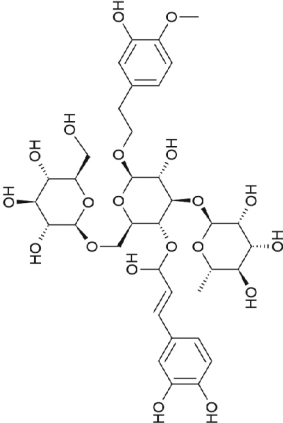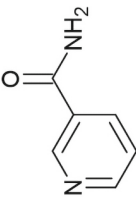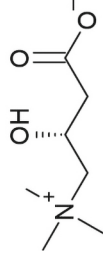
Name	Structure	Mechanism	Source	Reference
Naringin		activation of SIRT1 and AMPK, stimulation of mitochondrial biogenesis via regulation of LKB1/AMPK/PGC-1α signals	citrus fruits, especially grapefruit	[121, 122]
Dimethoxychalcone (3,4-DC)		activation of transcription factors TFEB and TFE3	Ashitaba, also known as *Angelica keiskei*	[123]
Sweet tea polysaccharide STP-60a	homogenous heteropolysaccharide consisting of rhamnose, arabinose, glucose, galactose, and glucuronic acid	activation of transcription factors FoxO/DAF-16, Nrf-2/SKN-1, and HSF-1	*Rubus Suavissmus S. Lee*	[124]

Activators of mitophagy

Name	Structure	Mechanism	Source	Reference
Urolithin A (UA)		affecting numerous proteins autophagy regulators (AMPK, BECN1, PINK1, p62/SQSTM1, SKN1)	forms in gut as a result of metabolism of ellagic acid and ellagitannins by gut microflora	[11, 51-55, 125-128]
Spermidine		inhibition of the PI3K/Akt/mTOR pathway; inhibition of EP300; activation of the PINK1/Parkin pathway	cereals, legumes, soya, hazelnuts, pistachios, as well as some fruits and berries, milk, eggs, and meat	[129-137]

Table (*cont.*)

Name	Structure	Mechanism	Source	Reference
Lactate		exact mechanism has not been elucidated; presumably activation of autophagy via ubiquitin-independent pathways	lactate – product of anaerobic metabolism of glucose (glycolysis), in the course of which it is formed from pyruvate in the reaction catalyzed by lactate dehydrogenase	[140]
Pyruvate				[140]
Cistanoside A (CA)		presumably activation of PINK1/Parkin/p62 pathway	*Cistanche deserticola*	[141]
Nicotinamide (NAM)		activation of ATG12 or activation of SIRT1	contains in such foods as liver, kidney, turkey meat, fish (tuna, salmon), yeasts, rye bread, buckwheat, beans, and others	[142]
Linolenic acid		upregulation of the *pink-1* gene expression	vegetable oils such as soya oil, corn oil, rapeseed oil	[143]
L-carnitine		decrease of PARL activity mediating PINK1 cleavage	meat, fish, poultry, milk, cheese, cottage cheese	[144]

The company targets age-related mitochondrial dysfunctions. History of the company starts with the Mitopure™ ingredient (patented highly purified form of urolithin A). Despite the fact that urolithin could be produced in an organism by the gut microflora, microflora composition in individuals could be very different and synthesis of urolithin could occur with varying efficiency. That is why the Amazentis team created the Mitopure preparation protected by the patents (EP-3393467-B1, US-9994542-B2, US-10906883-B2, and others), efficiency of which was verified in several clinical trials [145, 146]. The company patented the method of urolithin synthesis and well as use of the compositions containing this ingredient in food supplements, food products, and drinks. Mitopure induces mitophagy and supports improved mitochondrial functions and muscle strength. By using the Mitopure ingredient, the Timeline company (subsidiary of Amazentis) produces food supplements and well as anti-aging cosmetics.

Commercialization of urolithin A attracted attention of the Nestlé Health Science company, which took an equity stake in Amazentis and received global rights for using the patented ingredient Mitopure. That is why urolithin A in the form of Mitopure ingredient is also in the composition of the Celltrient Cellular Nutrition line of the dietary supplements produced by the Nestlé Health Science company.

Among the companies producing biologically active supplements for modulation of autophagy the Austrian company Longevity Labs+ should be mentioned. This company was established in 2016, although its history begins six years earlier in 2010. Professor Frank Madeo, discoverer of spermidine, was at that time the head of research group investigating polyamine spermidine in the Graz university. This research attracted attention of Doctor Gerald Sitte and professional engineer Herbert Pock, founders of the company. Immediately they started collaboration with the researchers from Graz university in the area of development of special extraction process, which eventually led to establishment of the Longevity Labs+ company. The company produces supplements Spermidine LIFE, which contain 100% natural and clinically tested spermidine from wheat germ. The company patented the use of spermidine in dietary supplements and pharmaceutical preparations for treating diseases or disorders associated with mitochondrial dysfunction.

Despite the fact that the Longevity Labs+ company was the first company to introduce supplements with spermidine on the market in 2019, at present it is not the only one using this biologically active substance. The USA company Mimio Health also uses spermidine as an ingredient of the patented composition mimicking fasting effects and intended for activation of the natural capability of cells for self-cleaning, restoration, and defence. Clinical study conducted by the compa-ny revealed that intermittent long-term fasting activates effects of several biologically active metabolites (spermidine, 1-methylnicotinamide, palmitoylethanolamide, and oleoylethanolamide), which were capable to increase average lifespan of *C. elegans* by as much as 96% [5]. The compounds mentioned above are in composition of the food supplements produced by the company. With regards of the mechanism of action, this composition helps to activate autophagy via regulation of mTOR, Akt, and histone acetyl transfer, as well as stimulation of AMPK and SIRT1.

Despite the fact that spermidine is recognized as a promising autophagy activator, its mechanism of action could vary depending on the cell type and type of disease. A complicated and poorly understood mechanism of action in combination with high activity with regard to autophagy regulation promoted the idea of development of more specific analogues of spermidine. At present the Israeli startup Vitalunga actively develops the methods for production of clinical preparations and conducts investigation of the properties of spermidine analogues that enhance mitophagy and autophagy. The startup's founding researchers already tested a family of compounds structurally related to spermidine and demonstrated that the 1,8-diaminooctane (VL-004) molecule induced mitophagy and protected from oxidative stress more effectively than spermidine, which facilitated extension of the *C. elegans* lifespan [138].

Research in the Vitalunga startup has a goal of developing preparations for prophylactics of numerous diseases associated with aging, such as Alzheimer's and Parkinson's diseases, heart failure, sarcopenia, and others.

CONCLUSIONS

Autophagy plays an important role among the cellular processes, and its dysfunction is associated with many human diseases. Disruption of the autophagy process could lead to the development of cardiovascular, neurodegenerative diseases, as well as diabetes, cancer, and other disorders. However, the role of natural compounds in prevention of these diseases is quite complicated due to pleiotropic mechanism of their action. Moreover, depending on concentration, cell type, and type of the disease natural compounds could exert not only activating effect on autophagy, but also an inhibitory effect. In particular, the well-known and described in this review natural compound resveratrol activates autophagy via several mechanisms, and also initiates apoptosis of cancer cells. Another good example is the compound Kazinol C, which was shown to induce autophagy at low concentrations and apoptosis – at high concentrations. Use of many natural

compounds in food supplements and pharmaceutical preparations is limited, because mechanisms of their action are not fully understood, and there are quite a few of side effects.

Despite the large number of studies devoted to natural autophagy activators, it is necessary in future studies to address the issue of elucidation of exact targets of the plant-derived autophagy activators, as well as to search for new compounds with more targeted action. Deeper investigation of novel plant-derived sources seems very promising for the discovery of new natural activators of autophagy, which should involve establishing of exact formulas of the molecules in the plant composition, as well as investigation of the metabolites of these compounds produced by microbiota of the animals resistant to long-term starvation, because starvation is one of the well-known conditions facilitating activation of autophagy in an organism.

It should be noted that autophagy attracts attention not only from the medical point of view, but also as a process, which could be instrumental in extension of human longevity and delay onset of the age-related diseases. In this regard, the compounds activating mitophagy are the most interesting. It is remarkable that several companies already produce biologically active supplements based on natural compounds activating autophagy such as urolithin A (Amazentis, Nestlé Health Science) and spermidine (Longevity labs, Mimio Health) that are intended for improving the state of cells and slow down aging. It must be emphasized that at present there are no companies in Russia that produce food supplements based on autophagy activators. Considering the fact that investigation of autophagy activators becomes more and more popular worldwide, the number of dietary supplements or clinical preparations on their bases introduced to the market would only grow in future. That is why it is very important to develop this research area in Russia in order to establish our own industry of functional food supplements targeting extension of healthy life and, as a consequence, quality of life of humans.

Ethics declarations. This work does not describe any studies involving human participants and animals performed by and of the authors. The authors of this work declare that they have no conflicts of interest.

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