



Original Articles

Natural compounds modulating mitophagy: Implications for cancer therapy

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ABSTRACT

Cancer is considered as the second leading cause of mortality, and cancer incidence is still growing rapidly worldwide, which poses an increasing global health burden. Although chemotherapy is the most widely used treatment for cancer, its effectiveness is limited by drug resistance and severe side effects. Mitophagy is the principal mechanism that degrades damaged mitochondria via the autophagy/lysosome pathway to maintain mitochondrial homeostasis. Emerging evidence indicates that mitophagy plays crucial roles in tumorigenesis, particularly in cancer therapy. Mitophagy can exhibit dual effects in cancer, with both cancer-inhibiting or cancer-promoting function in a context-dependent manner. A variety of natural compounds have been found to affect cancer cell death and display anticancer properties by modulating mitophagy. In this review, we provide a systematic overview of mitophagy signaling pathways, and examine recent advances in the utilization of natural compounds for cancer therapy through the modulation of mitophagy. Furthermore, we address the inquiries and challenges associated with ongoing investigations concerning the application of natural compounds in cancer therapy based on mitophagy. Overcoming these limitations will provide opportunities to develop novel interventional strategies for cancer treatment.

1. Introduction

Cancer is one of the leading causes of premature death, even surpassing cardiovascular disease as the primary cause in many high Human Development Index countries [1]. According to the latest statistics from the World Health Organization (WHO) in 2020, a staggering 9.95 million people worldwide lost their lives due to cancer. Among the different types of cancer, lung cancer tops the list as the leading cause of cancer-related deaths, accounting for 18.0 % of all cancer fatalities, followed by colorectal cancer (9.4 %), liver cancer (8.3 %), stomach cancer (7.7 %), and female breast cancer (6.9 %) [2]. Despite significant progress in cancer research over the decades, the anticancer therapy

continues to face serious challenges. Therefore, substantial effort has been focused on exploring novel molecular mechanisms and developing new therapeutic strategies or drugs for anticancer therapy.

Autophagy is an evolutionarily conserved catabolic process to degrade intracellular components through lysosome. Historically, Thomas Ashford and Keith Porter first observed the autophagy process and found that cells ate themselves [3], while de Duve coined the term of 'autophagy' when describing the function of lysosome after glucagon treatment [4]. At present, it is usually stated that there are three different types of autophagy in mammalian cells: macroautophagy, microautophagy and chaperone-mediated autophagy (CMA) [5]. Among them, macroautophagy is the most common and well-studied type of

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autophagy, which is referred as autophagy hereafter in this review. It has been well studied that the process of autophagy is orchestrated by a number of autophagy related genes (ATG) in four consecutive stages [6, 7]: (1) Induction or initiation, involving the emergence of phagophore, is regulated by Unc-51 like autophagy activating kinase 1 (ULK1)/ATG1 kinase complex which functions directly downstream of the key autophagy regulators mechanistic target of rapamycin complex 1 (mTORC1) and AMP-activated protein kinase (AMPK); (2) Nucleation, the process which is mediated by Beclin1-ATG14L and hVPS34/class III phosphatidylinositol 3-kinases (PI3K) complex; (3) Elongation and the formation of autophagosome, is regulated by several crucial ATG complexes including ATG2-WD repeat domain, phosphoinositide interacting 4 (WIPI4) complex, ATG9-containing vesicles and two ubiquitin-like conjugation systems: ATG12-conjugation system and ATG8/microtubule associated protein 1 light chain 3 (LC3)-family protein conjugation system; (4) Maturation and degradation processes, in which the autophagosome is fused with a lysosome to form an autolysosome and degrade the sequestered cargos through the acidic hydrolases of lysosome. Accumulating evidence has highlighted that autophagy not only plays crucial roles in various physiological processes such as cell stress responses and cell fate, but also has important function in the pathogenesis of human diseases including cancer, neurodegenerative disorders, innate immunity, metabolic disorders as well as ageing.

In the past decades, the mechanisms of autophagy have been increasingly understood. Autophagy can be further divided to non-selective autophagy and selective autophagy. For non-selective autophagy, it is generally thought that the uptake of cargos into the phagophore is indiscriminate, especially under more general stress conditions such as starvation. For selective autophagy, it can target specific or selective cargos in a context-dependent manner. So far a number of selective forms of autophagy have been reported, including mitophagy (mitochondria), ER-phagy (endoplasmic reticulum, ER), lysophagy (lysosome), aggrephagy (protein aggregates), ribophagy (ribosome), and xenophagy (bacteria) [8]. Among them, mitophagy is the main type of selective autophagy, where the damaged or superfluous mitochondria are selectively degraded via the autophagy/lysosome pathway [9]. Mitochondria function as “the powerhouse of the cell” due to their vital roles in energy production. In addition, mitochondria are involved in many other cellular events, including cell death, cell growth, cell differentiation and cell cycle regulation. Thus, mitochondrial homeostasis is critical for almost all cellular activities through life, and mitophagy is the key quality control mechanism for maintaining healthy mitochondrial network [9,10].

Natural products derived from diverse natural sources have gained significant attention in biomedical fields due to their potential health benefits. Over the past decade, there has been a rapid expansion in studying various natural compounds for their possible roles in preventing and treating cancer. Emerging studies are shedding light on the crucial role of these naturally occurring compounds in combating cancer. However, there is still a lack of clarity concerning the involvement of natural products as modulators of mitophagy in anticancer therapy, although the roles of natural compounds regulating general autophagy have been extensively reviewed in the literatures [11,12]. Understanding how natural products interact with mitophagy is valuable for the development of promising therapeutic strategies for anticancer therapy. In this review, we discuss the current understanding of mitophagy during cancer developments, and also provide a comprehensive summary of certain natural compounds in treating cancers as well as their properties in regulating mitophagy, which will be valuable for the development of promising therapeutic strategies for anticancer therapy.

2. Mitophagy: one selective type of autophagy

Mitophagy was named by John J. Lemasters and his colleagues in 2005 when they observed that damaged mitochondria were engulfed with autophagosome vesicles and coated with LC3 upon serum

starvation in rat hepatocytes [13]. Although the mechanism of mitophagy is still much unclear, explosive progresses have been made to understand its molecular mechanisms and pathophysiological roles in human diseases in the past decades, and several key signaling pathways have been identified. Among them, the PTEN-induced kinase1 (PINK1)-Parkin-mediated ubiquitin-driven pathway appears to be particularly important, to be described in details below. In addition, BCL2 and adenovirus E1B 19-KD-interacting protein 3 (BNIP3)/BNIP3-like (BNIP3L, also known as NIX) and FUN14 domain-containing 1 (FUNDC1) receptor-mediated mitophagy also play distinct and non-overlapping roles to regulate mitophagy (Fig. 1).

2.1. PINK1-Parkin-mediated ubiquitin-driven signaling pathway in mitophagy

PINK1, encoded by *PINK1/PARK6*, is a serine/threonine kinase, containing a mitochondrial targeting sequence (MTS) in its N-terminal. Parkin is a multiprotein E3 ubiquitin ligase encoded by the *PARK2* gene. At present, it has been well established that PINK1 and Parkin work closely to remove dysfunctional mitochondria through regulating mitophagy process [9]. Moreover, mutations of PINK1 and Parkin are the key etiologic factors for autosomal recessive Parkinson's disease (PD), a process due to the defective mitophagy [14].

In healthy mitochondria, PINK1 shuttles from cytosol to mitochondria via its N-terminal MTS, and then PINK1 is imported into mitochondria through TOM and TIM complex. After import, PINK1 is cleaved by the inner mitochondrial membrane (IMM)-resident protease, pre-senilin associated rhomboid like (PARL) and zinc metallopeptidase OMA1 [15–17]. Cleaved PINK1 is retro-translocated into the cytosol and degraded by the proteasome through the N-end rule pathway to maintain a very low level [18]. However, once mitochondria are damaged and depolarized such as in cells treated with a mitochondrial uncoupler carbonyl cyanide *m*-chlorophenylhydrazone (CCCP), the import of PINK1 is impaired and PINK1 is stabilized on the outer mitochondrial membrane (OMM) via TIM23 and TOM complex including TOM7 and TOM20 [17,19,20]. After accumulation at OMM, PINK1 phosphorylates its key substrate ubiquitin (Ub) at serine 65 (pSer65-Ub) which recruits Parkin from cytosol to mitochondria, then PINK1 phosphorylates Parkin also at serine 65 (pSer65-Parkin) [21,22]. In the normal condition, Parkin exists in an auto-inhibited conformation [23,24]. After phosphorylation by PINK1, Parkin is activated and mediates the poly-ubiquitination of OMM proteins. The ubiquitinated substrates can

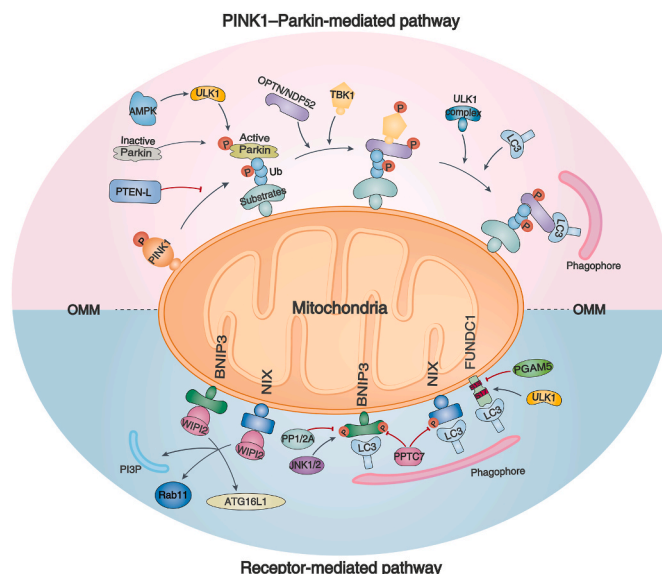


Fig. 1. Molecular mechanisms of mitophagy.

recruit a group of autophagy receptors such as NDP52 and optineurin (OPTN); then TANK binding kinase 1 (TBK1) binds and phosphorylates these receptors which in turn promotes their binding to various ubiquitin chains; next, ULK1 complex is recruited to mitochondria, leading to LC3 recruitment and phagophore generation [9]. Interestingly, ULK1 can phosphorylate cytosolic Parkin in an AMPK-dependent manner, which is important for the following mitochondrial recruitment of Parkin [25].

As discussed above, phosphorylation of key mitophagy effectors is crucial during the whole process of mitophagy, and it is speculated that dephosphorylation mediated by phosphatases exists to maintain a delicate balance of mitophagy and mitochondrial homeostasis. Phosphatase and tensin homolog (PTEN)-long (PTEN-L) is the first identified isoform of PTEN, which is reported to function as a secreted tumor suppressor [26]. PTEN-L is translated from a CUG start codon, adding an additional alternatively translated region (ATR) at the N-terminus of PTEN [27]. Intriguingly, our studies provided convincing evidence that PTEN-L is the first identified negative phosphatase of mitophagy through dephosphorylation of ubiquitin [28,29]. PTEN-L resides at the OMM. Overexpression of PTEN-L prevents mitophagy induced by multiple mitochondrial damage agents, while deletion of PTEN-L accelerates mitophagy. Moreover, PTEN-L effectively inhibits Parkin mitochondrial recruitment. More importantly, PTEN-L is able to dephosphorylate various types of pSer65-Ub chains. Finally, PTEN-L disrupts the feed-forward amplification loop formed by PINK1, pSer65-Ub and Parkin, leading to the inhibition of mitophagy.

2.2. BNIP3 and NIX receptor-mediated signaling pathway in mitophagy

BNIP3 and NIX are two mitochondrial localized mitophagy receptors. BNIP3 encoded by the *BNIP3* contains a C-terminal transmembrane (TM) domain inserting into the OMM and a N-terminal domain exposing to the cytosol [30]. NIX is a homolog of BNIP3 encoded by the *BNIP3L* gene. Both of them are the member proteins of the BCL2 family [31].

Distinct from autophagy receptors such as OPTN and NDP52, BNIP3 and NIX only contain LC3-interacting regions (LIR) motifs but lack ubiquitin-binding domains. Lots of studies have highlighted the crucial roles of BNIP3 and NIX in hypoxia-induced mitophagy. Under hypoxia, hypoxia inducible factor 1 subunit alpha (HIF-1 α) or forkhead box O3 (FOXO3) binds the promoters of BNIP3 and NIX, and then upregulates their expression [32]. After that, BNIP3 and/or NIX interact with LC3s/GABA type A receptor-associated protein (GABARAP) subfamilies through the LIR motifs, which fosters the recruitment of autophagosomes to damaged mitochondria. Phosphorylation and dephosphorylation are also important for the function of BNIP3 and NIX in the regulation of mitophagy [33,34]. He et al. reported that in response to hypoxia c-Jun N-terminal kinases 1/2 (JNK1/2) can phosphorylate BNIP3 to prevent its proteasome degradation and promote mitophagy, while protein phosphatase 1/2A (PP1/2A) is able to dephosphorylate BNIP3 and inhibit mitophagy [35]. Furthermore, Niemi et al. reported that the mitochondrial resident protein phosphatase targeting COQ7 (PPTC7) directly interact with and dephosphorylate BNIP3 and NIX to inhibit mitophagy [36]. In addition, NIX but not BNIP3 plays essential roles in reticulocyte maturation [37,38] as well as epidermal differentiation [39]. Intriguingly, latest study showed that despite of the LIR motifs, a minimal essential region (MER) of NIX is also indispensable for robust mitophagy via interaction and recruitment of WIPI2 [40].

2.3. FUNDC1 receptor-mediated signaling pathway in mitophagy

FUNDC1 as an OMM protein is another vital ubiquitin-independent mitophagy receptor. Similar to BNIP3 and NIX, FUNDC1 promotes hypoxia-induced mitophagy [41]. FUNDC1 contains a typical LIR motif near the N-terminal region, which is exposed to the cytosol and interacts with LC3 family members [41]. The activity of FUNDC1 is also tightly

regulated by phosphorylation and dephosphorylation. Under hypoxia, FUNDC1 is phosphorylated by Src and CK2 at Tyr18 and Ser13, respectively, which hinders its activity [41,42]. In contrast, upon hypoxia or mitochondrial stresses, FUNDC1 is phosphorylated by ULK1 at Ser17 and dephosphorylated by phosphoglycerate mutase 5 (PGAM5) at Ser13, which promotes its interaction with LC3 to recruit autophagosome to damaged mitochondria and facilitate mitophagy [42,43]. In addition, in the initial phase of hypoxia, membrane associated ring-CH-type finger 5 (MARCH5) ubiquitinates FUNDC1 at Lys119, leading to its degradation [44], while USP19 deubiquitinates and stabilizes FUNDC1 to recruit dynamin-related protein 1 (DRP1) and promote mitochondrial fission and mitophagy [45].

3. The roles of mitophagy in cancer

Although the exact effects of autophagy in cancer have been controversial for years, the double-edged sword effects of autophagy in cancer have been supported by a myriad of studies: (i) autophagy plays a tumor suppressor role in the initiation stage of tumorigenesis or oncogenic transformation processes; (ii) to be contrary, autophagy provides a survival advantage for the established and metastasizing tumor, which can prevent cell death induced by chemotherapeutic drugs. Thus, blocking autophagy has been suggested as a promising strategy for cancer treatment.

So far, the majority of mitophagy-related research is focusing on neurodegenerative disorders such as PD and Alzheimer disease (AD), while the implication of mitophagy in tumorigenesis and cancer chemotherapy has received much less attention. In recent years, there has been a growth in research on mitophagy and cancer, in particularly on anticancer therapy. Similar with autophagy, mitophagy can exhibit dual effects in cancer, with both cancer-inhibiting or cancer-promoting function. The context in which mitophagy operates, including the stage of cancer, the type of cancer, and the cellular microenvironment, influences its impact on tumor development and progression.

3.1. The cancer-inhibiting function of mitophagy

The strong indication for a cancer-inhibiting function of mitophagy came from studies that demonstrated the loss of key mitophagy regulators in various types of cancer, leading to defective mitophagy and accumulation of damaged mitochondria. For instance, *PARK2* locates at a fragile site of human chromosome 6q25.2-q26 which is frequently deleted or mutated in multiple cancers including glioblastoma [46,47], ovarian cancer [48,49], lung cancer [50,51], breast cancer [51–53] and hepatocellular carcinoma [54,55]. Consistently, *PARK2* knockout mice are found to be susceptible to liver cancer [54], colorectal cancer [56] and lung cancer [50]. Thus, Parkin has been supposed as a tumor suppressor. The cancer-inhibiting function of Parkin can be attributed to its critical roles in maintaining mitophagy and mitochondrial homeostasis. Damaged mitochondria are the major source of reactive oxygen species (ROS) and dysfunction of mitophagy leads to more production of ROS which can activate different signaling pathways to promote cancer cell survival [57]. In addition, Parkin can promote the antitumor function of p53 via regulating energy metabolism and the Warburg Effect [58]. Intriguingly, another study showed that Parkin deletion activates PI3K/AKT pathway via promoting PTEN S-nitrosylation and inactivation [59]. Similarly, *PARK6/PINK1* is deleted or mutated in glioblastoma [60], neuroblastoma [61], and colorectal cancer [62]. When mitophagy is inhibited, PINK1 can directly phosphorylate p53 and promote its nucleus translocation to inhibit the activity of Octamer (ATGCAAT)-binding transcriptional factor 4 (OCT4) and SRY-Box 2 (SOX2), resulting in the reduction of hepatic cancer stem cells (CSCs) populations [63]. In addition, both Parkin and PINK1 can negatively regulate HIF-1 α expression, leading to Warburg Effect and inflammation activation [64].

The key factors of receptor-mediated mitophagy such as BNIP3 and

FUNDC1 have also been implicated in cancer suppression. BNIP3 is frequently lost in triple negative breast cancer which increases HIF-1 α expression and promotes tumor progression through upregulated glycolytic metabolism and ROS production [65]. Epigenetic silencing of BNIP3 such as hypermethylation is involved in the development and progression of pancreatic cancer [66,67], colorectal cancer [68] and gallbladder cancer [69]. FUNDC1 also plays pivotal roles in hepatocellular carcinomas [70]. Knockout of FUNDC1 in mice resulted in the accumulation of dysfunctional mitochondria, the release of mitochondrial DNA to cytosol, hyperactivation of inflammatory response, and tumorigenesis at the early stage of hepatocellular carcinoma [70].

3.2. The cancer-promoting function of mitophagy

At present, more evidence shows that some types of solid tumors are “addicted” to mitophagy to promote cancer cell survival and tumor development through adjusting the microenvironment of limited oxygen and nutrient [71]. In oncogenic K-Ras-driven transformation, mitophagy promotes cancer development via autophagy-mediated organelle degradation to provide ATP and nutrients to cancer cells when there is insufficient glucose up-take (Kim et al., 2011). In addition, many studies have shown that mitophagy factors regulate the activity of CSCs. For example, PINK1 promotes mitochondrial function and activation of mTORC2/AKT signaling pathway to maintain the human brain tumor stem cell function; knockdown of PINK1 by shRNA blocks glioblastoma multiforme CSCs proliferation which is potentially via the Notch signaling pathway [72]. PINK1 could also suppress neuronal cell death in response to oxidative stress through positively regulating histone deacetylase 3 (HDAC3) by phosphorylation; then stabilized HDAC3 interacts with p53 and hyper-acetylates p53 to inhibit p53 activity [73]. Moreover, when mitophagy is enhanced, p53 can be degraded through co-localization with mitochondria, promoting the activity of hepatic CSCs [63].

The cancer-promoting function of mitophagy is mostly limited to hypoxia conditions. In a number of hypoxic solid tumors, HIF-1 α is increased to adjust the cancer cells to the Warburg Effect. As mentioned above, HIF-1 α is a positive regulator of BNIP3 and NIX to promote mitophagy, thus induction of mitophagy is proposed to be the step of adaptation for the cancer cell survival. BNIP3 is upregulated in human colorectal CSCs by doxorubicin treatment, leading to drug resistance [74]. In pancreatic ductal adenocarcinoma, oncogenic KRAS mutations increases NIX expression and induces mitophagy to promote cancer cell growth [75]. And several studies have shown that FUNDC1 is able to promote the progress of cervical cancer [76], breast cancer [77], and the late stage of hepatocellular carcinoma [70].

4. Natural compounds modulating mitophagy with potential implication of cancer

In recent years, natural compounds have received increasing interest as sources for novel anticancer agents due to the high efficacy and few side effects. However, the specific molecular mechanisms underlying their actions have not always been fully elucidated, which restricts their application. Emerging studies have shown that a variety of natural compounds can affect mitochondrial function, including ATP production, mitochondrial membrane potential, Warburg Effect as well as ROS production. Mitophagy as the most important quality control process maintains mitochondrial homeostasis, whose dysfunction is closely linked with cancer as discussed above. Here we summarize recent advance to highlight the potential anticancer function of natural compounds via regulating mitophagy (Fig. 2).

4.1. Magnolol

Magnolol is a bioactive compound isolated from the bark of *Magnolia officinalis* or *Magnolia grandiflora*. Studies have shown that magnolol has

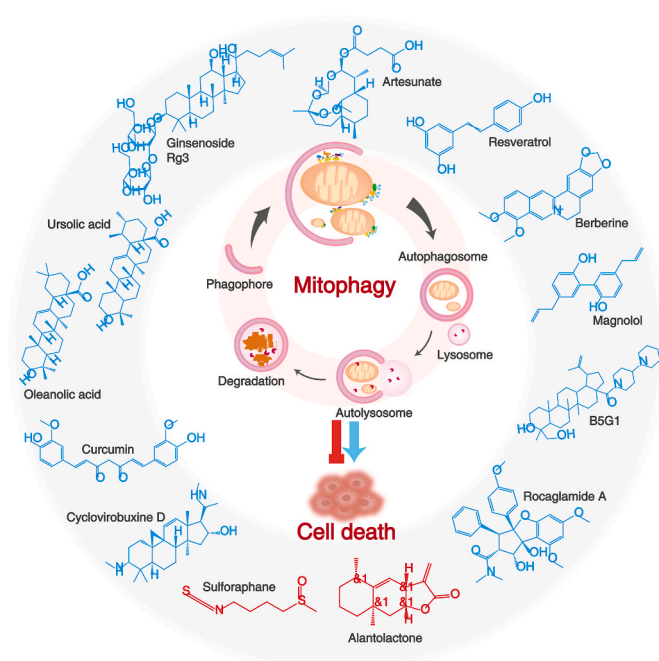


Fig. 2. Natural compounds modulating mitophagy in cancer therapy.

anticancer effects on different types of cancers, such as liver cancer [78], lung cancer [79], bladder cancer [80], prostate cancer [81], and breast cancer [82]. Magnolol is able to induce apoptosis, inhibit cell proliferation and suppress cell metastasis, thus to exhibit its antitumor activity. In addition, magnolol can regulate autophagy in different types of cancer cells [79,83,84]. Mito-magnolol, a mitochondrial targeting analog of magnolol, effectively inhibits mitochondrial respiration and melanoma cell proliferation through the regulation of oxidative phosphorylation and mitophagy [85]. Our previous study showed that in neuroblastoma cell line and xenograft mouse model, magnolol can cause mitochondrial damage, induce mitochondrial apoptosis and PINK1–Parkin-mediated mitophagy, while inhibition of mitophagy at different stages significantly promotes magnolol-induced cell death and enhances magnolol’s anticancer efficacy [86,87]. We found that magnolol positively regulates mitophagy via the two-round feedforward amplification loops: (i) PINK1–pSer65-Ub–Parkin to mediate the initiation stage of mitophagy; (ii) LC3–OPTN/NDP52 to mediate the recognition and sequestration stages of mitophagy.

4.2. Ginsenoside Rg3

Ginsenosides are glycosylated triterpenoid saponins found in *Panax ginseng*, a traditional Chinese herbal medicine known for its various health benefits [88]. Ginsenosides display anticancer effects in various types of cancers such as breast cancer, gastric cancer, lung cancer and brain cancer through inhibition of cancer cell proliferation, viability, invasion and metastasis [89]. Previous study showed that ginsenosides have multiple targets and can affect various signaling pathways including mitochondrial apoptosis pathway, PI3K/AKT pathway, nuclear factor- κ B (NF- κ B) pathway, etc [90]. The most well-studied ginsenosides are Rb1, Rg1, Rg3, Rh1 and Rh2. Among them, Rg3 has been extensively studied and applied to treat cancers [91]. In lung cancer cells, Rg3-enriched red ginseng extract (Rg3-RGE) is able to induce mitochondrial-dependent apoptosis and PINK1–Parkin-mediated mitophagy, while co-treatment with Rg3-RGE and mitophagy inhibitor Mdivi-1 further increases lung cancer cell death [92]. Another study showed that Rg3 can cause mitochondrial damage and induce Parkin mitochondrial recruitment [93]. Moreover, they revealed that Rg3 activates Parkin-mediated ubiquitination of GAPDH, which further

regulates cancer cell death by exerting its non-glycolytic activity [93]. Recently, another study showed that Rg3 can activate FUNDC1-mediated mitophagy through binding and activating ULK1 to protect against heart failure [94], while further studies are needed to explore whether Rg3 can regulate this pathway in cancers.

4.3. Resveratrol

Resveratrol, a polyphenol found in grapes, berries, and red wine, exhibits anti-inflammatory, antioxidant, and anticancer properties [95]. It has been reported that resveratrol possesses anticancer properties in various types of cancers including lung cancer, gastric cancer, breast cancer, liver cancer, etc [96]. Resveratrol can affect cancer initiation and progression through multiple signaling pathways such as mitochondrial apoptosis pathway, PI3K/AKT pathway, janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) pathway, and autophagy. For instance, resveratrol induces autophagic cell death in human promyelocytic leukemia cells [97,98], prostate cancer cells [99], and oral cancer cells [100]. Emerging studies have indicated that resveratrol activates mitophagy *in vitro* and *in vivo*. Resveratrol is able to upregulate the expression of several mitophagy-related proteins such as PINK1 and Parkin, leading to increased ROS production and cell death [101]. In contrast, another study showed that resveratrol induces LC3/p62-mediated mitophagy to protect A549 lung cancer cells against apoptosis [102]. Resveratrol can also induce BNIP3-mediated mitophagy [103]. However, other study showed that resveratrol can inhibit mitophagy on cardiomyocytes [104]. The discrepancy may be due to different experimental models used, and more work will be necessary to reconcile the different studies.

4.4. Artesunate

Artesunate, a semi-synthetic water-soluble derivative of artemisinin, is widely used for the treatment of malaria [105]. It has been documented that artesunate regulates autophagy in multiple cancer cells including breast cancer cells [106], colorectal cancer cell [107], hepatocellular carcinoma [108], and endometrial cancer cells [109]. Artesunate treatment can also affect mitochondrial function, leading to the accumulation of mitochondrial ROS, the reduction of mitochondrial membrane potential as well as the induction of mitochondrial apoptosis [110–113]. Consistently, our study has shown that artesunate treatment induces autophagy and increases mitochondrial ROS [114]. Furthermore, we found that artesunate mainly localizes at mitochondria, binds to a large number of mitochondrial proteins, induces PINK1–Parkin-mediated mitophagy, while inhibition of mitophagy leads to more cancer cell apoptosis, suggesting that targeting mitophagy could enhance the anticancer function of artesunate [114]. Another study showed that artesunate intelligent prodrug liposomes can inhibit breast cancer via regulating the expression of prohibitin 2 (PHB2), one crucial mitophagy receptor in mitochondrial inner membrane [115], and PINK1 [116]. In addition, another study demonstrated that artesunate can rescue A β -inhibited mitophagy and alleviate neuronal injury [117].

4.5. Berberine

Berberine is a natural alkaloid found in a variety of plant including *Berberis Linn*, *Coptis chinensis*, *Hydrastis canadensis*, and *Mahonia aquifolium*. Berberine has been widely used as over-the-counter (OTC) drug (Huang Lian Su Tablet) to treat diarrhea in China. It has also been commonly used for type 2 diabetes, high blood pressure, and high cholesterol. Emerging studies have shown that berberine possesses anticancer properties in various types of cancer such as breast cancer, colon cancer, liver cancer, prostate cancer, etc [118]. Berberine can induce autophagic cell death in various cancer cells including lung cancer cell [119], melanoma cell [120], and thyroid carcinoma cell

[121]. Recently, Mori et al. utilized three gastrointestinal cancer cell lines to study the anticancer mechanism of berberine, and found that berberine suppresses oxidative phosphorylation, increases mitochondrial superoxide, and reduces mitochondrial membrane potential [122]. Furthermore, berberine treatment induces PINK1–Parkin-mediated mitophagy via upregulating the expression of PINK1, Parkin, LC3-II and ATG5, while ATG5 knockdown abrogates berberine's inhibitory effects on cancer cell growth [122].

4.6. Curcumin

Curcumin, known as turmeric, is a hydrophobic polyphenol isolated from *Curcuma longa*. It has been well recognized that curcumin has good antioxidant and anti-inflammatory properties with low cytotoxicity. Curcumin displays anticancer effects through different mechanisms including cell cycle arrest, apoptosis activation, autophagy induction, tumorigenesis and metastasis regulation [123]. Curcumin is able to regulate autophagy pathways at different stages in lung cancer cells, thyroid cancer cells, renal cell carcinoma, and glioblastoma [123]. Previous study showed that curcumin changes mitochondrial morphology and induces mitophagy after ultrasound treatment in nasopharyngeal carcinoma cells [124]. Consistently, another study revealed that curcumin promotes the formation of autophagic vacuoles containing degraded mitochondria and induces mitophagy in liver cancer cells [125]. Interestingly, it has been observed that in thyroid cancer cells rather than normal epithelial cells, curcumin can accumulate in mitochondria, leading to mitochondria depolarization and lethal mitophagy [126]. However, another study reported that in glioblastoma multiforme cells, curcumin can induce autophagy via the upregulation of key autophagy factors such as ATG5, ATG7, Beclin1 and LC3, while curcumin inhibits mitophagy via the downregulation of key mitophagy factors such as PINK1, BNIP3, NIX and FUNDC1 [127]. The discrepancy of how curcumin modulate mitophagy needs further research.

4.7. Rocaglamide A

Rocaglamide A is a natural compound that is derived from the genus *Aglaia*. Rocaglamide A exhibits a wide range of anticancer effects in breast cancer, lung cancer, acute lymphoid leukemia, and glioblastoma through multiple mechanisms [128]. Among them, the translation inhibition function of rocaglamide A has elicited much interest. For instance, lots of studies have shown that rocaglamide A can specifically target eukaryotic translation inhibition factor 4A (eIF4A) [129,130]. It has been documented that rocaglamide A triggers pancreatic cancer cell apoptosis by inducing mitochondrial dysfunction and mitophagy, while inhibition of mitophagy sensitizes pancreatic cancer cell death to rocaglamide A [131]. Intriguingly, rocaglamide A can also bind to PHB2 [132]. Yan et al. revealed that rocaglamide A is able to inhibit PINK1–Parkin-mediated mitophagy via targeting PHB2 and promotes cancer cell death including cervical cancer cell, lung cancer cell and colorectal cancer cell [133]. Consistently, another study reported the similar results that rocaglamide A inhibits Parkin-dependent mitophagy [134].

4.8. Oleanolic acid and ursolic acid

Oleanolic acid and ursolic acid are isomeric triterpenoids, which are the ubiquitous ingredients of our diet such as many vegetables, fruits and Chinese medicine [135]. Previous studies have shown that oleanolic acid and ursolic acid regulate autophagy and exhibit anticancer activity in pancreatic cancer cells [136], gastric cancer cells [137], and breast cancer cells [138]. In lung cancer cells, oleanolic acid and ursolic acid can promote cytoprotective mitophagy via upregulation of PINK1 and p62 expression [139]. Intriguingly, recent study showed that oleanolic acid is able to protect against cardiac aging via FUNDC1-mediated mitophagy [140]. It remains to be explored whether ursolic acid or

oleanolic acid can regulate receptor-mediated mitophagy in cancers.

4.9. B5G1

Betulinic acid belongs to the lupine-type pentacyclic triterpenoids that are widely distributed in plants such as *Rhamnaceae* Juss., *Myrtaceae* Juss. and *Betulaceae* Gray. It has been well documented that betulinic acid and its derivatives exhibit broad-spectrum anticancer activity via diverse pathways such as mitochondrial apoptosis pathway and STAT3 pathways [141]. B5G1, a new derivative of betulinic acid, has been found to have effective anticancer activity against multidrug-resistant cancer cells HepG2/ADM and MCF-7/ADR [142]. B5G1 can upregulate PINK1 and recruit Parkin from cytosol to mitochondria followed by ubiquitination of mitofusion2, which is not dependent on ATG5 and Beclin1. Furthermore, inhibition of mitophagy through genetic or pharmacological approaches sensitizes B5G1-induced cell death [142].

4.10. Cyclovirobuxine D

Cyclovirobuxine D is the main steroidal alkaloid extracted from *Buxus microphylla*. Due to its antioxidant and anti-inflammatory, cyclovirobuxine D has been clinically used to treat cardiovascular and cerebrovascular diseases [143]. Various studies also reported that cyclovirobuxine D displays anticancer effects in colorectal cancer [144], glioblastoma [145], and lung cancer [146]. Previous study has shown that cyclovirobuxine D promotes autophagic cell death in breast cancer cells through the AKT/mTOR pathway [147]. In addition, cyclovirobuxine D can enhance apoptosis in lung cancer cells by inducing mitophagy [148]. Cyclovirobuxine D increases the expression of BNIP3 by downregulation its suppressor of p65, and enhances the interaction between BNIP3 and LC3, leading to mitophagy initiation [148].

4.11. Alantolactone

Alantolactone is a sesquiterpene lactone compound mainly extracted from the root of *Inula helenium* L. Alantolactone displays diverse biological activities including anti-inflammatory, antibacterial and anticancer effects. Previous study has shown that in pancreatic cancer cells, alantolactone inhibits autophagy via downregulation of transcription factor EB (TFEB), the key factor for lysosome biogenesis, leading to apoptosis induction and chemosensitivity [149]. Consistently, another study reported that alantolactone inhibits autophagy, reduces mitochondrial membrane potential and induces apoptosis in acute lymphoblastic leukemia cells [150]. Intriguingly, in liver cancer cells, alantolactone can inhibit mitophagy through downregulation the expression of PINK1 and Parkin, and mitophagy inhibitor enhances alantolactone-induced apoptosis [151].

4.12. Sulforaphane

Sulforaphane is a phytochemical that is derived from cruciferous vegetables like cabbage, broccoli, and cauliflower. Due to its potent antioxidant properties, sulforaphane is widely used as dietary supplement. Emerging studies have shown that sulforaphane possesses anticancer activity [152–154]. Sulforaphane can induce protective autophagy which attenuates its anticancer effects [155,156]. Intriguingly, Sulforaphane can inhibit mitophagy, leading to apoptosis in lung cancer cells [157]. Sulforaphane reduces the expression of BNIP3 and NIX, inhibits the interaction between NIX and LC3, and hinders the fusion of mitochondria and lysosomes [157]. Recent study showed that sulforaphane can alleviate podocyte injury via inducing Nrf2/PINK1-mediated mitophagy [158]. Future investigation needs to explore whether sulforaphane can modulate PINK1-mediated mitophagy in cancers.

5. Conclusion

Mitochondria is one of the most important organelles in eukaryote. As “the powerhouse of the cell”, mitochondria generate ATP to support almost all cellular activities. However, more and more studies have suggested that the function of mitochondria is not limited to energy production. Mitochondria are also involved in ROS production, biosynthetic metabolism, inflammation, cell death and cell survival regulation. Thus, mitochondria are also the crucial hub for signal transduction and the dysfunction of mitochondria is tightly linked with cancer [159,160]. Mitophagy as the key mitochondrial quality control process has caught emerging interest in cancer therapy. Remarkably, a variety of natural compounds can modulate mitophagy to regulate cancer cell death and survival (Table 1). The mitophagy-based application of natural compounds may provide new therapeutic intervention for cancer treatment. However, there are still numerous questions and challenges for future studies. First, there are no available *in vivo* methods to monitor mitophagy level in human tumor. Second, there are no specific mitophagy inhibitors for clinical applications. At this stage, the most widely used methods to inhibit mitophagy are either to block general autophagy, inhibit lysosome function or disrupt mitochondrial fission and fusion, which cannot rule out the possibilities that these inhibitors affect other signaling pathways. Third, most current studies detect the expression of level of key mitophagy regulators such PINK1, Parkin, BNIP3 or NIX, but not examine their activities, which may be not accurate and need more future work to reconcile the findings. Such knowledge will open new window for studying the biological function of mitophagy and offer new opportunities in the development of strategies for treating cancers.

Ethics approval and consent to participate

Not applicable.

Availability of data and materials

Not applicable.

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CRediT authorship contribution statement

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Tabel 1

Effect of natural compounds on cancers via regulating mitophagy.

NO	Natural compound	Source	Model	Mechanism of action on mitophagy	Ref.
1	Magnolol	<i>Magnolia officinalis/Magnolia grandiflora</i>	Neuroblastoma cells (SH-SY5Y); Melanoma cells (UACC-62)	Activate PINK1–Parkin-mediated mitophagy pathway	[86,87]
2	Ginsenoside Rg3	<i>Panax ginseng</i>	Lung cancer cells (A549, H460); Colon cancer cells (HCT116)	Activate PINK1–Parkin-mediated mitophagy pathway	[92,93]
3	Resveratrol	<i>Vitis vinifera</i>	Lung cancer cells (A549)	Activate LC3/p62-, PINK1–Parkin-, and BNIP3-mediated mitophagy pathway;	[101–103]
4	Artesunate	<i>Artemisia caruifolia</i>	Cervix cancer cells (HeLa); Breast cancer cells (MCF-7, MDA-MB-231)	Activate PINK1–Parkin- and PHB2-mediated mitophagy pathway	[114–116]
5	Berberine	<i>Berberis Linn, Coptis chinensis, Hydrastis canadensis, and Mahonia aquifolium</i>	Gastrointestinal cancer cells (CT26, HT29, TMK-1)	Activate PINK1–Parkin-mediated mitophagy pathway	[122]
6	Curcumin	<i>Curcuma longa</i>	Nasopharyngeal carcinoma cells (CNE2); Liver cancer cells (Huh-7)	Target mitochondria and increase SDH activity to activate mitophagy	[124–126]
7	Rocaglamide A	<i>Aglaia</i>	Glioblastoma multiforme cells (U-87MG, GL261, F98 and N2a)	Inhibit PI3K–AKT/mTOR-mediated mitophagy pathway	[127]
			Pancreatic cancer cells (MIA PaCa2, PANC-1)	Activate PINK1–Parkin-mediated mitophagy pathway	[131]
			Cervical cancer cells (HeLa); Lung cancer cells (A549); Colorectal cancer cells (HCT116)	Inhibit PINK1–Parkin-mediated mitophagy pathway; Inhibit Parkin-dependent mitophagy pathway	[132–134]
8	Oleanolic acid and Ursolic acid	Plants and Fruits	Lung cancer cells (A549)	Activate PINK1–Parkin-mediated mitophagy pathway	[139]
9	B5G1	<i>Rhamnaceae</i> Juss., <i>Myrtaceae</i> Juss. and <i>Betulaceae</i> Gray	Hepatoma cells (HepG2/ADM); Breast cancer cells (MCF-7/ADR)	Activate PINK1–Parkin-mediated mitophagy pathway	[142]
10	Cyclovirobuxine D	<i>Buxus microphylla</i>	Lung cancer cells (A549, H446 and 95-D)	Activate BNIP3-mediated mitophagy pathway	[148]
11	Alantolactone	<i>Inula helenium</i> L.	Acute lymphoblastic leukemia cells (BV173, NALM6); Liver cancer cells (HepG2)	Inhibit PINK1–Parkin-mediated mitophagy pathway	[150,151]
12	Sulforaphane	Cruciferous vegetables	Lung cancer cells (A549, SK-1)	Inhibit BNIP3/NIX-mediated mitophagy pathway	[157]

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

List of Abbreviations

AD	Alzheimer disease
AMPK	AMP-activated protein kinase
ATG	Autophagy related genes
ATR	Alternatively translated region
BNIP3	BCL2 and adenovirus E1B 19-KD-interacting protein 3
BNIP3L/NIX	BCL2 and adenovirus E1B 19-KD-interacting protein 3-like
CCCP	Carbonyl cyanide <i>m</i> -chlorophenylhydrazone
CMA	Chaperone-mediated autophagy
CSCs	Cancer stem cells
DRP1	Dynamin-related protein 1
eIF4A	Eukaryotic translation inhibition factor 4A
ER	Endoplasmic reticulum
FOXO3	Forkhead box O3
FUNDC1	FUN14 domain-containing 1
GABARAP	GABA type A receptor-associated protein
HDAC3	Histone deacetylase 3
HIF-1 α	Hypoxia inducible factor 1 subunit alpha
IMM	Inner mitochondrial membrane
JAK2	Janus kinase 2
JNK1/2	C-Jun N-terminal kinases 1/2
LC3	Microtubule associated protein 1 light chain 3
LIR	LC3-interacting regions
MARCH5	Membrane associated ring–CH–type finger 5
MER	Minimal essential region

mTORC1	Mechanistic target of rapamycin complex 1
MTS	Mitochondrial targeting sequence
NF- κ B	Nuclear factor- κ B
OCT4	Octamer (ATGCAAAT)-binding transcriptional factor 4
OMA1	Zinc metalloproteinase (OMA1)
OMM	Outer mitochondrial membrane
OPTN	Optineurin
OTC	Over-the-counter
PARL	Presenilin associated rhomboid like
PD	Parkinson's disease
PGAM5	Phosphoglycerate mutase 5
PHB2	Prohibitin 2
PI3K	Phosphatidylinositol 3-kinases
PINK1	PTEN-induced kinase protein 1
PP1/2A	Protein phosphatase 1/2A
PPTC7	Protein phosphatase targeting COQ7
PTEN	Phosphatase and tensin homolog
PTEN-L	PTEN-long
Rg3-RGE	Rg3-enriched red ginseng extract
ROS	Reactive oxygen species
SOX2	SRY-Box 2
STAT3	Signal transducer and activator of transcription 3
TBK1	TANK binding kinase 1
TFEB	Transcription factor EB
TM	Transmembrane
Ub	Ubiquitin
ULK1	Unc-51 like autophagy activating kinase 1
WHO	World Health Organization
WIPI4	WD repeat domain, phosphoinositide interacting 4

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