

# Natural Compounds As Modulators of Non-apoptotic Cell Death in Cancer Cells



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**Abstract:** Cell death is an innate capability of cells to be removed from microenvironment, if and when they are damaged by multiple stresses. Cell death is often regulated by multiple molecular pathways and mechanism, including apoptosis, autophagy, and necroptosis. The molecular network underlying these processes is often intertwined and one pathway can dynamically shift to another one acquiring certain protein components, in particular upon treatment with various drugs. The strategy to treat human cancer ultimately relies on the ability of anticancer therapeutics to induce tumor-specific cell death, while leaving normal adjacent cells undamaged. However, tumor cells often develop the resistance to the drug-induced cell death, thus representing a great challenge for the anticancer approaches. Numerous compounds originated from the natural sources and biopharmaceutical industries are applied today in clinics showing advantageous results. However, some exhibit serious toxic side effects. Thus, novel effective therapeutic approaches in treating cancers are continued to be developed. Natural compounds with anti-cancer activity have gained a great interest among researchers and clinicians alike since they have shown more favorable safety and efficacy than the synthetic marketed drugs. Numerous studies *in vitro* and *in vivo* have found that several natural compounds display promising anticancer potentials. This review underlines certain information regarding the role of natural compounds from plants, microorganisms and sea life forms, which are able to induce non-apoptotic cell death in tumor cells, namely autophagy and necroptosis.

**Keywords:** Cancer, Autophagy, Necroptosis, Paraptosis, Natural compounds.

## 1. INTRODUCTION

Tumor cells often display the well-known and expanding traits (“hallmarks”) of cancer designated as “sustained proliferative signaling, resistance to cell death, tumor angiogenesis, enabling replicative immortality (self-sufficiency in growth signals), activating invasion and metastasis, evasion of growth suppression (insensitivity to anti-growth signals), metabolic reprogramming and deregulated metabolism, genome instability (mutations and epigenetics), tumor-promoting inflammation, and evasiveness from immune destruction”, as reviewed elsewhere [1, 2]. Accumulating evidence shows that ubiquitous disruptive environmental chemical exposures, especially associated with a late industrial revolution that have been shown to greatly increase the tumor incidence in humans affecting practically each of cancer hallmarks [3]. Moreover, these factors might to disrupt

key pathways and mechanisms inducing oncogenic factors and repressing tumor-suppressing regulators, as reviewed elsewhere [4-14].

Programmed cell death is natural way of removing aged or damaged cells from the body, as reviewed elsewhere [4, 15-17]. Most of the anti-cancer therapies trigger various cell death mechanisms and pathways to eliminate tumor cells, while leaving normal cells unscathed as much as possible, as reviewed in [4, 15-17]. However, in cancer, de-regulated apoptotic signaling, particularly the activation of an anti-apoptotic systems, allows tumor cells to escape these treatments leading to uncontrolled proliferation resulting in tumor survival, and chemotherapeutic resistance often displayed by tumors [4, 15-17]. Up to date various pathways underlying the programmed cell death include apoptosis, autophagy, and necroptosis, as reviewed elsewhere [18-23]. While numerous reviews focused on the apoptotic pathways, extrinsic and intrinsic alike, we concentrate our efforts on the latest developments regarding autophagy and necroptosis induced by natural compounds in tumor cells [24-29]. Apoptosis is the most often occurred mechanism of tumor cell

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death induced upon chemotherapeutic treatment. Apoptosis is characterized by specific morphological and biochemical features distinct from other cell death pathways, including blebbing, cell shrinkage, nuclear fragmentation, and chromatin condensation, as well as activation of caspase cascade and mitochondrial processes, as reviewed in [30-32].

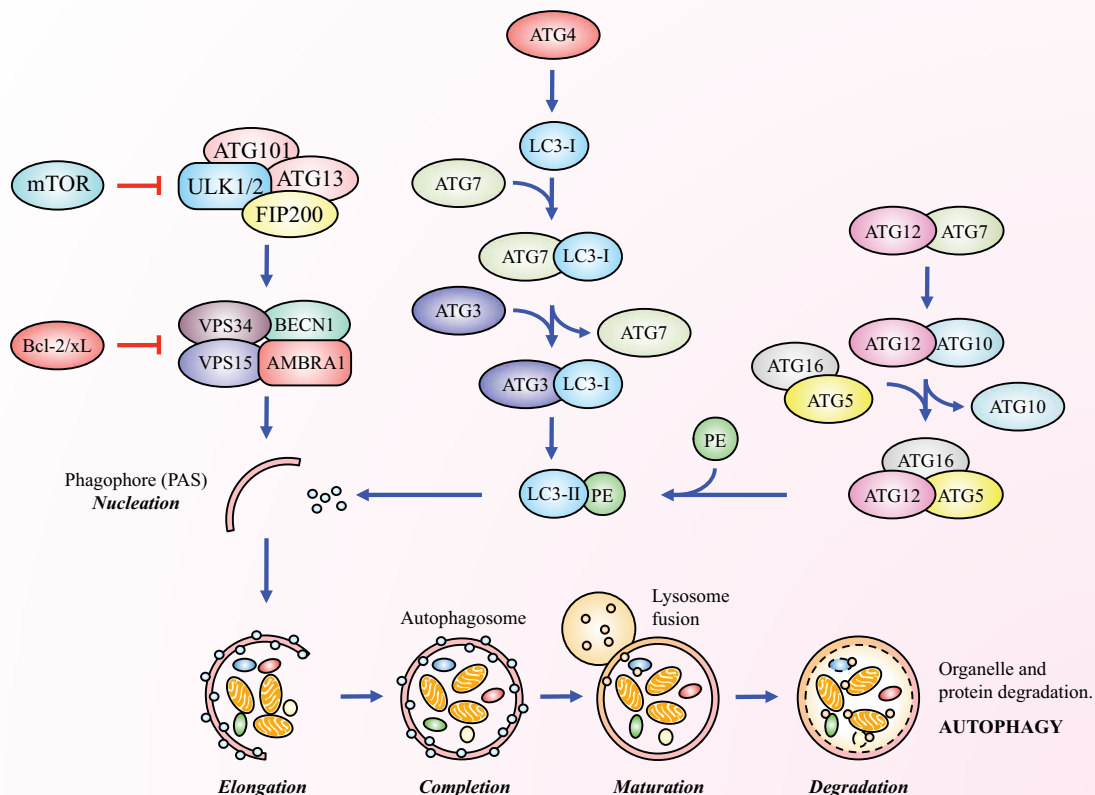
Autophagy is characterized by the formation of specific vesicles “autophagosomes”, which envelope denatured proteins, damaged protein aggregates and disintegrated cellular organelles. The content of autophagosomes is subsequently dumped into lysosomes for subsequent enzymatic degradation, as depicted in (Fig. 1) and reviewed elsewhere [30-33]. Additionally, a necroptotic process, which is characterized by alterations in plasma membranes leading to inflammatory cell functions, was recently found to be under genetically controlled program. Necroptosis can be induced by cytokines, pathogens, ischemia, heat, and irradiation triggering various pathways (e.g. death receptors, kinase cascades, and mitochondrial), as depicted in (Fig. 2) and reviewed in [34-36].

Naturally compounds originated from the diverse plants, microorganisms and marine life forms were widely shown to display anti-carcinogenic, anti-proliferative anti-survival effects inducing tumor cell death via various pathways, in-

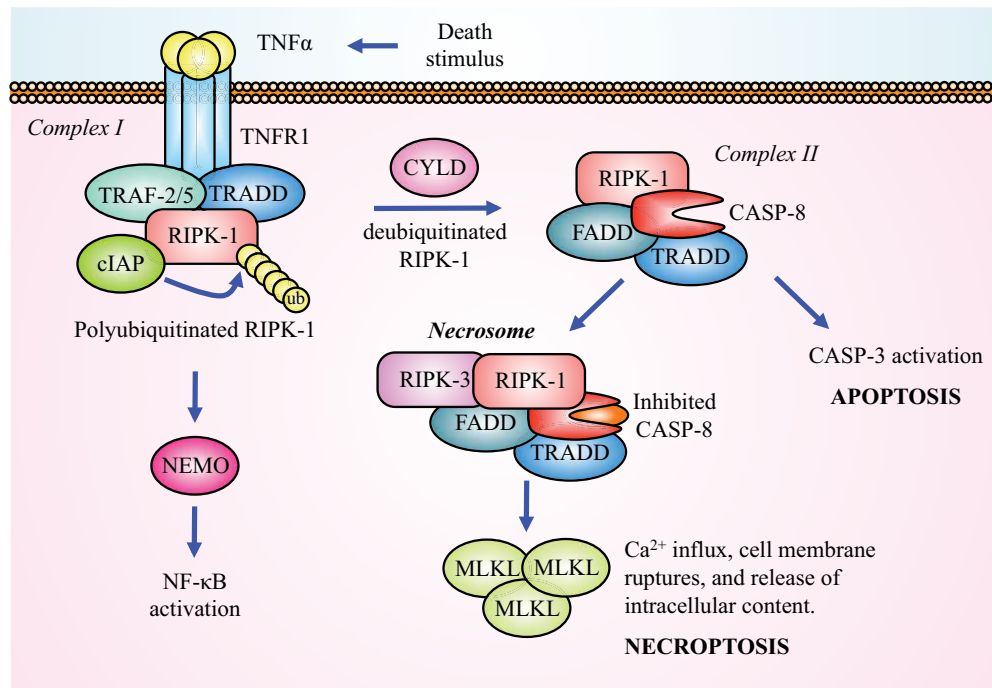
cluding apoptosis, autophagy, necroptosis, paraptosis, parthanatos or mitotic catastrophe, and through multiple molecular mechanisms, such as epigenetic regulation, protein kinase and protease cascades, nuclear and mitochondrial processes leading to cell death, as reviewed in [8, 24-29, 37-44]. Many natural compounds exhibited the ability to inhibit proliferation and cell viability of numerous tumor cells and inhibit tumor growth in animal models, suggesting the potential venue to generate novel anticancer therapeutics, as reviewed in [24-45]. Various compounds were found to induce tumor cell death by deregulating of signaling pathways leading to autophagy [8, 17, 24, 28, 29, 45-49].

## 2. AUTOPHAGY SIGNALING PATHWAYS

Autophagy is an intrinsic tightly controlled catabolic cellular process in which denatured proteins and damaged organelles are enveloped into autophagic vesicles and subsequently delivered to lysosomes for degradation, as reviewed elsewhere [50]. Autophagy is increased when cell under stress conditions, including metabolic alterations, genome instability, and oxygen deficiency, as well as chemotherapeutic treatments [50]. Notably, an overactive autophagy might cause tumor cell death process [51, 52]. Autophagy processes are designated as macroautophagy, microauto-



**Fig. (1). Schematic representation of autophagic pathway.** Several cytoplasmic proteins interact to upregulate autophagy. mTOR, which inhibit autophagy, is regulated negatively by different steps modulated by MAPKs or p53. Once mTOR is inhibited, the formation of ULK complex, which is composed of FIP200, ULK1/2 and ATG13/101, is stimulated. In turn, ULK complex phosphorylates AMBRA1, leading to the activation of a complex that includes p-AMBRA1, BECN1, and VPS15/34 to the formation of phagophoro in the nucleation step. The elongation step is controlled by LC3B-II, which is conjugated to PE and regulated by ATG5/12/16 complex. The completion step includes the formation of an Autophagosome carrying the proteins or organelles, which fuses to Lysosome in the Maturation step, forming an Autolysosome. The final step consists in the Degradation of the content in the Autolysosome.



**Fig. (2). Schematic representation of necroptosis pathway.** Different events occur in the necroptosis activation pathway. The interaction of the TNFRs with their specific ligand TNF- $\alpha$ , induce the formation of the Complex I, which is composed by TRADD, TRAF-2/6 and RIPK-1. RIPK-1 is polyubiquitinated by cIAP to lead the activation of NF- $\kappa$ B pathway. In other context, RIPK-1 is deubiquitinated by CYLD to form the Complex II, composed by TRADD, FADD, RIPK-1, and CASP-8, leading to the activation of the apoptotic pathway. However, CASP-8 is inhibited by the interaction of RIP-3 to the Complex II, inducing to the formation of a third complex named Necrosome, this last complex stimulate MLKL, as a last step of necroptosis pathway activation.

phagy and chaperone-mediated autophagy [50-52]. Autophagy can promote a survival to stressful conditions; however, when stress exceeds certain level autophagy could induce a cell death process [50-52].

Autophagy-related genes, *Atg* (human homologs designated as *ATG*) were found to regulate autophagy [30, 31]. The autophagic signaling comprises several molecular events: autophagy induction, regulated by the ATG1/unc51-like kinase (ULK) complex; vesicle nucleation involving the BECN1/class III PI3K complex; vesicle elongation controlled by two ubiquitin-like conjugation systems (ATG12 and ATG8/LC3B); retrieval, in which the transmembrane ATG9 and associated proteins provide lipids and recruit other ATG proteins; and fusion between autophagosomes and lysosomes, involving proteins, such as lysosome-associated membrane protein 2 (LAMP2) and RAS-related protein-7 (RAB7A), resulting in vesicle breakdown and degradation by lysosomal hydrolases, as reviewed elsewhere [53-59]. Autophagy is initiated by the ULK1 kinase complex, consisting of ULK1, ATG13, and ATG17 proteins, as described in [53-59]. Meanwhile, vesicle-mediated vacuolar protein sorting (VPS34) protein (possessing the lipid kinase activity) forms a complex with BECN1 proteins after interacting with activating molecule in BECN1-regulated autophagy protein 1 (AMBRA1), SH3-domain GRB2-like endophilin B1 (also known as BIF1), and B-cell lymphoma 2 (BCL-2) proteins, as indicated in [53-59]. BECN1 phosphorylation induced by ULK1 kinase leads to activation of the ATG14L-containing VPS34 complex, which in turn promotes autophagy induction [53-59]. ATG12 and LC3B proteins, which exert the conjugation activities, are critical

for transport of matured autophagosome [53-59]. After maturation, autophagosome joins with lysosomes to degrade its content [53-59].

Autophagy pathway involves two ubiquitin-like binding pathways, such as ATG5-ATG12 complex and microtubule-associated protein 1 light chain 3-beta (MAP1LC3B), which is encoded by one of the human homologue of the yeast *Atg8*, as indicated [60, 61]. Upon induction of autophagy, LC3B protein is cleaved by human ATG4 cysteine protease to produce LC3B-I isoform [60, 61]. As a result of that, LC3B-I is activated by ATG7 protein and is transferred to ATG3, before phosphatidylethanolamine (PE) is conjugated to the carboxyl glycine of LC3B-I to generate a LC3B-II isoform [60, 61]. The synthesis and processing of LC3B is increased during autophagy, making it a key marker of autophagy [30, 31]. The matured autophagosomes integrate with lysosomes, whose enzymes degrade the content of autophagosome generating small molecules, such as amino acids, subsequently used for *de novo* protein synthesis, thereby supporting cell survival and homeostasis [61].

### 3. AUTOPHAGIC SIGNALING IN CANCER

In normal cells, autophagy presents a mechanism, which cells develop to fight against malignant transformation, as reviewed elsewhere [62-64]. Various oncoproteins were found to inhibit, whereas and tumor suppressive proteins were shown to activate autophagy, as reviewed elsewhere [64]. However, autophagy contributes to cellular responses associated with extreme stress conditions, thus "favoring tumor progression" [64]. Therefore, autophagy can poten-

tially modulate the pro-survival and pro-death mechanisms in tumor initiation and progression underlying its dual nature, as reviewed in [65]. Defective autophagy might contribute to tumorigenesis via accumulation of damaged organelles and protein aggregates, leading to a production of reactive oxygen species (ROS) and causing genome instability [65]. Altering autophagic signaling in order to induce tumor cell death, inhibit pro-survival of tumor cells and initiate crosstalk of autophagy with tissue-specific apoptosis might provide promising anticancer chemotherapeutic venues [65].

Many reports showed the tumor suppressive function of autophagy, as reviewed in [62, 63]. For example, BECN1 (a human homolog of yeast *Atg6*) is a key tumor suppressor protein, which acts through a modulating of initiation and regulation of autophagy. Frequent mono-allelic deletions of BECN1 were found in human breast, ovarian and prostate, lung and liver cancers [66, 67]. Autophagy is a central component of the integrated stress response, functioning to suppress apoptosis or just delay apoptotic cell death, as discussed in [50, 68]. Cisplatin-induced autophagy was shown to play a role in tumor cell resistance to platinum-based therapy [69]. Autophagy was found to delay apoptosis in renal tubular epithelial cells, as well as in head/neck and ovarian cancers treated with cisplatin [70-72]. Pharmacologic or genetic inhibition of autophagy often resulted in increased cell death, suggesting that autophagy might increase the cell survival upon genome damage through BECN1 induction, poly (ADP-ribose) polymerase-1 (PARP1) activation or heat shock protein B1 (HMG1) release [71, 73, 74]. Autophagic flux upon cisplatin treatment was observed during tumor cell chemoresistance, nephrotoxicity and tubular cell injury [70, 72, 75-77].

As known guardians of genome integrity, tumor protein TP53, TP63 and TP73 transcription factors are often involved in autophagic process, as reviewed elsewhere [78]. Accumulating evidence clearly suggests that TP53 family members modulate expression of various genes involved in tumor cell death, and may induce the autophagic cell response [78, 79]. TP53 was found to variably affect the autophagic pathway, depending on its nuclear or cytoplasmic location. When in nucleus, TP53 could activate pro-apoptotic, cell cycle-arresting and pro-autophagic genes, as reviewed in [78-87]. However, cytoplasmic TP53 by triggering a mitochondrial mechanism could induce cell death and reduce autophagy [79, 84]. The critical autophagic modulators, DRAM1 (damage-regulated autophagy modulator) and ATG1/ULK1 (autophagy-initiation kinase) are transcriptionally activated by TP53 and subsequently induce autophagic pathways [78].

TP53 protein activates BCL-2 phosphorylation resulting in the dissociation of the BECN1-BCL-2 complex leading to a liberation of an essential autophagy inducer BECN1, as indicated in [88]. On the other hand, TP53 leads to the DRAM1 upregulation, thereby triggering accumulation of autophagosomes and autophagosome-lysosome fusion [78, 81-83]. TP53-induced autophagy may lead to cell death, which can be blocked by *DRAM1* siRNA, as described in [79]. However, TP53-mediated autophagy may also increase tumor cell survival, as blockade of autophagosomal maturation enhances TP53-mediated tumor regression and tumor-cell death [78].

Recently, AEN/ISG20L1 protein was identified as a TP53- dependent, genotoxic stress-induced modulator of autophagy [82]. TP53, TP63 and TP73 proteins were found to transcriptionally regulate *AEN* expression, while *AEN* knockdown decreases levels of autophagic vacuoles and LC3B-II protein upon genotoxic stress [82]. Pro-apoptotic genes, such as TP53-upregulated modulator of apoptosis protein (PUMA) and BCL-2-associated X protein (BAX), were shown to act as positive regulators of autophagy (e.g. mitochondrial autophagy), as reviewed elsewhere [76]. Activated TP53 may down regulate the negative regulator of autophagy mTOR through transcriptional regulation of SESN1 and 2 [83]. The key signaling molecules, 5' AMP-activated protein kinase (AMPK, a positive regulator of autophagy), and mTOR (a negative autophagic regulator), which lie upstream of the autophagy core pathway [89]. AMPK may also inhibit mTOR by activating tuberous sclerosis (TSC) 1 and 2 proteins, as indicated in [89].

TP63 and TP73 share similar structure with TP53 and have both unique and coordinate roles during tumorigenesis. The inhibition of mTOR was shown to activate TP73 resulting in TP73-dependent modulation of genes involved in mTOR-induced autophagy, as described in [90]. Endogenous TP73 protein was found to transcriptionally activate specific autophagic genes, such as *ATG5*, *ATG7*, while *TP73* knock-down increased the *UVRAG* expression levels [90].

TP53 homolog TP63 is a novel transcription factor implicated in regulation of genes involved in cell death and genome instability in head and neck squamous cell carcinomas (HNSCC) upon cisplatin exposure [76, 91]. Since *TP63* gene exhibits two promoters and its transcripts undergo several alternative spliced events, *TP63* encodes six protein isoforms with the long transactivation (TA)-domain and with the short TA-domain [76, 91]. The latter is designated as  $\Delta Np63\alpha$ , which is the longest and the most predominant isoform expressed in HNSCC cells, as indicated in [91].  $\Delta Np63\alpha$  was found to induce *ATM* transcription, thereby contributing to ATM-TSC2-mTOR complex 1-dependent autophagic pathway [76, 89]. Follow-up studies found that the exposure of HNSCC cells to cisplatin treatment led to induced expression of the *ATG1/ULK1*, *ATG3*, *ATG4A*, *ATG5*, *ATG6/BECN1*, *ATG7*, *ATG9A* and *ATG10* genes through  $\Delta Np63\alpha$ -dependent transcription, as described in [77].

Emerging evidence shows that autophagy is upregulated in tumor cells in response to various stresses, contributing to tumor cell resistance to chemotherapy, as reviewed in [51, 52, 63]. Thus, targeting autophagic signaling pathways may be an innovative strategy in prevention and combinatorial treatments of human cancers, as well as battling the tumor-derived chemoresistance, as reviewed in [92, 93].

#### 4. ANTICANCER NATURAL COMPOUNDS AND AUTOPHAGY

Besides chemotherapy, radiation, immune or genetic therapeutic strategies as well as combinatorial strategies, the natural anticancer products with favorable safety and efficacy are setting a center stage for the new venues anticancer therapies, as reviewed in [24-29, 36, 46-49, 94, 95]. Accumulating evidence shows that numerous natural compounds

act as positive anticancer regulators through adjusting oxidative stress response, inhibiting cancer cell proliferation and modulating autophagic signaling [24-29, 36, 46-49, 94, 95].

The isoquinoline quaternary alkaloid berberine, isolated from plants of genera *Berberis* and *Hydraxis*, or contained in the extract of *Rhizoma coptidis*, possesses a broad range of therapeutic uses against several diseases, as reviewed elsewhere [96-104]. Berberine was found to inhibit tumor cell proliferation and exhibited cytotoxicity towards tumor cells [96-104]. Berberine was shown inducing autophagic and apoptotic cell death in hepatocellular carcinoma HepG2, MHCC97-1, and SMMC7721 cells, as indicated in [101]. Berberine treatment led to the activation of BECN1 and inhibition of mTOR by modulating the AKT activity and upregulating p38 MAPK signaling [101]. Tumor cell death induced by berberine was diminished with the autophagy inhibitor 3-methyladenine (3-MA), or silencing of the ATG5 expression, as described in [101]. 3-MA and bafilomycin A1, as well as siRNA-mediated silencing of LC3B or BECN1 abrogated berberine-induced cytotoxicity in HepG2 cells, whereas the caspase inhibitor z-VAD-fmk reversed it [100, 101]. Interestingly, the inhibition of AMPK by RNAi abrogated berberine induced caspase-3 (CASP-3) cleavage, apoptosis, and autophagy in HepG2 cells [100]. Berberine was shown to induce autophagic cell death *in vitro* and *in vivo* when used in combination with radiotherapy in lung cancer, as indicated in [103]. Berberine enhanced radiosensitivity in nonsmall cell lung cancer (NSCLC) A549 cells through autophagy, as evidenced by increased autophagosome formation, LC3B modification, and mitochondrial disruption, as described in [103]. Berberine derivatives were shown to inhibit the proliferation of human HCT-116 and SW613-B3 colon carcinoma cells and induce autophagy, as described in [96, 97, 99, 102, 104].

Resveratrol (3,5,4'-trihydroxy-trans-stilbene, a polyphenol extracted from red grape skin, peas, nuts, blueberries, mulberries, cranberries, spinaches and lilies) exhibited potent growth-inhibitory effects against various human cancer cells *in vitro*, and in preclinical cancer models *in vivo*, as reviewed elsewhere [105-111]. Treatment with resveratrol resulted in the autophagic death of human ovarian cancer A2780 cells through modulating expression of BCL-2 and BCL-xL proteins [112-114]. Resveratrol might triggers cell death via autophagic pathway, however independent from BECN1, in human breast cancer MCF-7 cell line, which is devoid of CASP-3 activity, as described in [115, 116]. Resveratrol was found to induce autophagic cell death in chronic myelogenous leukemia cells via activation of AMPK and JNK-mediated p62/SQSTM1 expression [117]. Downregulation of the TP53-Induced Glycolysis and Apoptosis Regulator (TIGAR) protein by resveratrol reduced glutathione levels resulting in sustained ROS production, subsequently leading to apoptosis and autophagy [118]. Overexpression and silencing of TIGAR were found affecting the ROS-dependent anticancer effects of resveratrol [118].

Resveratrol induced ROS levels in human ovarian cancer cells (OVCAR-3 and Caov-3), which triggers autophagy and subsequent apoptotic tumor cell death, as described elsewhere [119]. Resveratrol induced ATG5 expression and promoted LC3B cleavage [119]. Targeting ATG5 by siRNA

also suppressed resveratrol-induced apoptotic cell death [119]. Resveratrol activates autophagic cell death in human prostate cancer PC3 and DU145 cells by downregulation of the stromal interaction molecule 1 (STIM1) expression leading to induction of endoplasmic reticulum stress, thereby, activating AMPK and inhibiting the AKT/mTOR pathway [120]. Resveratrol increased autophagy and autophagy-mediated degradation of p62 in non-small lung adenocarcinoma A549 cells [119]. Protein p62 (SQSTM1) was shown to co-localize with Fas/Cav-1 complexes, known to induce apoptosis [121]. However, silencing of p62 expression enhanced formation of Fas/Cav-1 complexes, suggesting that p62 inhibited Fas/Cav-1 complex formation [121]. Fas/Cav-1 complexes were found to trigger CASP8 activation and cleavage of BECN1, releasing a C-terminal of the latter, which subsequently translocated to the mitochondria leading to initiation of apoptosis. Inhibition of autophagy by siRNA to *BECN1* also blocked resveratrol-induced apoptosis, showing a dependence of apoptosis on autophagy [121].

Resveratrol significantly inhibits the proliferation of human breast cancer stem-like cells isolated from MCF-7 and SUM159 tumors *in vitro* and *in vivo*, as described in [122]. Various techniques (e.g. transmission electron microscopy analysis, green fluorescent protein (GFP)-LC3B-II puncta formation assay and immunoblotting analysis of LC3B-II, BECN1 and ATG7 expression) showed that resveratrol induces autophagy in breast cancer stem-like cells [122]. Moreover, resveratrol was found to suppress Wnt/ $\beta$ -catenin signaling pathway in tested cells, while the overexpression of  $\beta$ -catenin markedly reduced resveratrol-induced cytotoxicity and autophagy [122]. Resveratrol inhibited the tumor cell proliferation and induced apoptosis and autophagy in T-acute lymphoblastic leukemia cells, which was accompanied by a decreased expression of antiapoptotic proteins (MCL-1 and BCL-2) and increased expression of proapoptotic proteins (BAX, BIM, and BAD), and induced cleaved-CASP-3, as described in [123]. Significant increase in LC3B-II/LC3B-I ratio and BECN1 expression was also detected upon resveratrol exposure [123]. Furthermore, resveratrol induced significant dephosphorylation of AKT, mTOR, p70 ribosomal protein S6 kinase (p70RS6K), and 4E-BP1, but enhanced specific phosphorylation of p38 MAPK, as indicated in [123]. Resveratrol induced autophagy in human androgen-independent prostate cancer cell lines (C42B, PC3, and DU145) via activation of sirtuin 1 (SIRT1, a mammalian silent mating type information regulation 2 homolog 1), as described elsewhere [124]. Silencing of SIRT1 expression inhibited autophagy by repressing phosphorylation of p70RS6K and 4E-BP1, while the molecular events were reversed in the presence of resveratrol [124].

Resveratrol and pterostilbene (a naturally occurring structural analog of resveratrol) have been reported to exert antiproliferative and proapoptotic effects in various human cancer cells, including human bladder, breast, cervical, colon, non-small lung cancer, and prostate cancer cells, glioma cells, melanoma cells, osteosarcoma U2O cells and leukemia HL-60 cells, as described elsewhere [110, 111, 125-132]. Pterostilbene induced conversion of cytosolic LC3B-I to membrane-bound LC3B-II and accumulation of large LC3B-positive vacuolar structures, as described in [127, 128]. 3,4,4'-trihydroxy-trans-stilbene (3,4,4'-THS), an analogue of

resveratrol, increased the formation of acidic compartments, LC3B-II accumulation and GFP-LC3B labeled autophagosomes in human NSCLC A549 cells *in vitro* [125]. 3,4,4'-THS-induced apoptosis and autophagy in the cells was attenuated by NAC supporting the role for ROS in this process [125]. Pterostilbene induces tumor cell death via a mechanism involving lysosomal membrane permeabilization [128]. Human melanoma A375 cells and A549 lung cancer cells with low levels of heat shock protein (HSP)-70 showed high susceptibility to pterostilbene, whereas HT29 colon and MCF-7 breast cancer cells with higher levels of HSP70 were more resistant [128]. Silencing of HSP70 expression increased susceptibility of human colon cancer HT29 cells and breast cancer MCF-7 cells to pterostilbene [128].

Epigallocatechin-3-gallate (EGCG) is one of the major bioactive components in green tea, as reviewed elsewhere [108, 133-135]. EGCG enhanced the effect of cisplatin and oxaliplatin-induced autophagy in human colorectal cancer DLD-1 and HT-29 cells, as characterized by the accumulation of LC3B-II protein, the increase of acidic vesicular organelles, and the formation of autophagosome, as described in [136]. Exposure of squamous cell carcinoma SSC-4 cells to EGCG induced activation of apoptosis and autophagy, associated with upregulation of BAD, BAK, FAS, IGF1R, WNT11, and ZEB1 protein levels, and downregulation of CASP8, MYC, and TP53 proteins, as indicated in [137]. EGCG increases the formation of autophagosomes, increasing lysosomal acidification, and stimulating autophagic flux in hepatic cells *in vitro* and *in vivo* [138]. EGCG also increases phosphorylation of AMPK, as indicated in [138]. However, siRNA knockdown of AMPK inhibited EGCG-induced autophagy [138]. Treatment of human hepatocellular carcinoma Hep3B cells with doxorubicin (DOX) significantly increased a number of autophagic vesicles and levels of autophagic protein markers in tumor cells [139]. This effect resulted in 45% decrease in DOX-induced cell death supporting pro-survival role for autophagy in these experimental conditions [139]. However, EGCG was found to inhibit autophagic signaling, and promoted cellular growth inhibition, as indicated in [139]. The DOX-induced autophagy was blocked by the combination therapy with EGCG [139]. Rapamycin, an autophagic agonist, markedly inhibited the anticancer effect of DOX or its combination with EGCG treatment [139]. Interestingly, siRNAs targeting ATG5 and BECN1 inhibited autophagy pathways, thereby leading to an enhanced cell death in Hep3B cells [139]. On the other hand, EGCG-mediated cell death of human hepatocellular carcinoma HepG2 cells and cervical cancer HeLa cells was found to be caspase-independent and accompanied by cytosolic vacuolization [139]. Interestingly, EGCG was observed to increase non-apoptotic cell death in human hepatocellular carcinoma cells, cervical cancer cells, and mesothelioma cells via ROS-mediated lysosomal membrane permeabilization [140, 141].

Curcumin is the major bioactive component extracted from *Curcuma longa* L., *Curcuma zedoaria* (Christm) Rosc., *Curcuma amada* Roxb., and *Curcuma petiolata*, as reviewed in [24, 29, 49, 142]. Curcumin has been found to inhibit cell proliferation of chronic granulocytic leukemia, glioblastoma, breast, prostate, lung, skin, colon, and esophageal cancer through inducing autophagy [142-148]. Curcumin can inhibit

the growth of leukemia K562 cells accompanied with the upregulation of LC3B-II and BECN1 protein levels, and accumulation of autophagosomes [144]. However, the autophagy inhibitor bafilomycin A1 inhibited the tumor cell death upon curcumin exposure [144]. Curcumin inhibited growth of human lung adenocarcinoma A549 cells by inducing autophagy, evidenced by LC3B immunofluorescence and increased expression of LC3B and SQSTM1, as described in [147]. The autophagy inhibitor 3-MA partly blocked the inhibitory effect of curcumin on the growth of A549 cells [147]. Curcumin was found to induce the AMPK phosphorylation in A549 cells, while the inactivation of the AMPK impaired the autophagy-inducing effect of curcumin [147]. Curcumin induced the expression of BECN1 and TP53, and ROS production, thereby activating autophagic pathway leading to the death in human colon cancer cells [148]. Curcumin markedly induced the LC3B-I to LC3B-II conversion and degradation of SQSTM1, as well as caused GFP-LC3B puncta formation in human colon colorectal carcinoma HCT-116 cells [148]. Antioxidant N-acetyl-L-cysteine (NAC) blocked these curcumin-induced molecular effects, suggesting that curcumin-induced ROS implicated in autophagosome development [148]. NAC also abolished curcumin-induced activation of ERK1/2 and p38MAPK, as indicated in [148].

In human glioblastoma cells (U87-MG and U373-MG) curcumin induced autophagy *in vitro* and *in vivo* through inhibiting the AKT/mTOR/p70RS6K pathway and activating the extracellular signal-regulated kinase (ERK)-1/2 pathway, as described elsewhere [143, 149]. Moreover, curcumin treatment resulted in the mitochondrial fission in human hepatocellular carcinoma HepG2 cells, reduced mitochondrial membrane potential and activated the mitochondria-mediated autophagy [150]. Forced overexpression of BCL-2 also blocked curcumin-induced autophagy in human breast cancer MCF-7 cells, through its inhibitory interactions with BECN1, as described in [146]. Pre-treatment of cells with PI3K inhibitor LY294002 enhanced curcumin-induced autophagy via modulating of autophagosome formation in MCF-7 cells [146]. ATG7 silencing further increased apoptotic potential of curcumin in wild type and *BCL-2*<sup>+</sup> MCF-7 cells, as indicated in [146]. Curcumin could induce both apoptosis and autophagy in A431 squamous cell carcinoma cells expressing the p53R273H mutant, as shown in [151]. Rapamycin along with curcumin induced p53 degradation, and increased the autophagosome formation [151]. Silencing of BECN1 or ATG7 blocked the induction of autophagy leading to increasing p53 stability in curcumin-treated cells [151]. Curcumin inhibited the proliferation of human uterine leiomyosarcoma SKN and SK-UT-1 cells [152]. Curcumin induced autophagy and apoptosis in SKN and SK-UT-1 cells [152]. Curcumin increased ERK 1/2 activity in both SKN and SK-UT-1 cells, whereas PD98059, an MEK1 inhibitor, inhibited both the ERK1/2 pathway and curcumin-induced autophagy, as indicated in [152].

Curcumin exhibited anticancer activity against oral squamous cell carcinoma cells via induction of autophagy, marked by autophagic vacuoles formation, and evidenced the LC3B-I to LC3B-II conversion [153]. The curcumin-induced autophagy was shown to be ROS-dependent [153]. Curcumin reduced viability of human malignant pleural mesothe-

glioma ACC-MESO-1 cells [154]. Curcumin increased LC3B-I-to -LC3B-II conversion, and induced the formation of autophagosomes, while silencing of ATG5 attenuated these changes, as described in [154]. Curcumin induced differentiation of glioma-initiating cells that are responsible for the initiation and recurrence of glioblastoma [155]. Curcumin was found to induce autophagy in these cells *in vitro* and *in vivo* [155]. Moreover, curcumin also suppressed tumor formation on intracranial implantation of glioma-initiating cells into mice [155]. Tetrahydrocurcumin, a major metabolite of curcumin, has been exhibited the antiproliferative effects on human promyelocytic leukemia HL-60 cells by increasing acidic vesicular organelle formation, specific for autophagy [156]. Tetrahydrocurcumin significantly downregulated phosphatidylinositol 3-kinase/protein kinase B and mitogen-activated protein kinase pathways, including decreasing the phosphorylation of mTOR, glycogen synthase kinase 3 $\beta$  and p70RS6K, as indicated in [156].

Some of the Chinese medicinal herbs induce autophagy via downregulation of mTOR and upregulation of BECN1 [24, 43, 45]. Fangchinoline (isolated from Fangji, *Stephania tetrandra* S. Moore) triggered autophagy in human hepatocellular carcinoma HepG2 and PLC/PRF/5 cells, as described in [157]. Blocking fangchinoline-induced autophagy process markedly modulated the apoptotic pathway [157]. Ginsenosides, major pharmacological active ingredients in Ginseng, induced cell death of tumor cells, thereby improving sensitivity of tumor cells to chemotherapy [24, 158-162]. Ginsenosides Rg3 and Rh2 can inhibit the tumor cell growth, while Rg3 is instrumental in combating tumor cell resistance to cancer chemotherapy, as reviewed in [24, 163]. Combination of Rg3 with docetaxel, paclitaxel, cisplatin or DOX increased the sensitivity of human colon and prostate cancer cells to chemotherapy [163]. The anticancer function of ginsenosides is associated with its ability to regulate autophagy in various human cancer cells, including hepatocellular carcinoma cells, as reviewed in [24, 164-166]. Rk1 can induce autophagy and increase expression of autophagy marker LC3B-II, as indicated in [165]. Ginsenoside K activated an autophagy pathway evidenced characterized by accumulation of vesicles and LC3B-II, and the increased autophagic flux [166]. Ginsenoside K induced the c-Jun NH2-terminal Kinase (JNK) signaling pathway, as described in [166]. Whereas silencing of JNK attenuated autophagy-mediated cell death in response to ginsenoside K, as indicated in [166]. Notably, ginsenoside K disrupted the interaction between ATG6 and BCL-2 leading to autophagic signaling [166]. Ginsenoside F2 was also found to induce the formation of GFP-LC3B-labeled autophagosomes and upregulate of ATG7 expression in human breast cancer cells [167].

Terpenoids are the largest class of natural compounds exhibited multiple anticancer properties, especially due to their selectivity toward tumor and cancer stem cells (CSC), as reviewed in [29, 168, 169]. Sesquiterpene lactones are 15-C terpenoids, such as parthenolide, artemisinin, and thapsigargin were shown to be beneficial in cancer clinical trials, as reviewed [169-172]. The sesquiterpene lactone parthenolide (4a, 5b-epoxy-germacra-1-(10), 11-(13)-dien-12, 6a-olide from the shoots of feverfew *Tanacetum parthenium*) was found to be selective against CSCs by targeting specific signaling pathways and epigenetic events [173, 174]. Parthe-

nolide was found to induce autophagy in the triple-negative breast cancer MDA-MB231 cells, as shown by increased expression of BECN1, and the formation of LC3B-II [175]. Parthenolide treatment of human hepatocellular carcinoma HepG2 cells resulted in autophagic cell death, as indicated in [176]. Recently, the translation initiation factor eIF4E binding protein 1 (4E-BP1) was shown to be involved in parthenolide-mediated autophagic cell death in human promyelocytic leukemia HL-60 cells and cervical cancer HeLa cells which was independent of its role in protein translation [177].

Triptolide is a diterpenoid from the roots of *Tripterygium wilfordii* was found to inhibit the proliferation of 60 US National Cancer Institute cancer cell lines, as reviewed elsewhere [178, 179]. Furthermore, its anticancer activities were confirmed in various animal models grafted with human tumors resulting in the development of several more water-soluble and less toxic derivatives such as PG490-88 or F60008 that entered clinical trials [179]. Triptolide was shown to inhibit the growth of human pancreatic cancer cells *in vitro* and *in vivo*, including pancreatic adenocarcinomas [180, 181]. Triptolide may induce caspase-independent autophagic cell death in pancreatic cancer S2-013, S2-VP10, and Hs766T cells [181]. Triptolide treatment was reversed by 3-MA, or silencing of ATG5 and BECN1 [173]. A triptolide was shown to suppress the tumor cell growth and induce autophagic cell death in human lung cancer A549 cells, as well as in human neuroblastoma SH-SY5Y cells with no observed signs of apoptosis [179, 182, 183]. Betulinic acid is a triterpenoid isolated from the bark of the white birch tree, exhibited anticancer properties against several tumor cells *in vitro* and *in vivo* [184, 185]. Betulinic acid and its analogues were found to decrease the phosphorylation of AKT and induce autophagic cell death in human glioblastoma cells, as described in [186]. However, in human multiple myeloma KM3 cells, betulinic acid treatment inhibited autophagy and induced apoptosis, associated with decreased BECN1 level, but increased CASP-3 level, as indicated [187]. Betulinic acid was recently found to induce the death in human cervical cancer HeLa cells, while caspase inhibitors and necrostatin-1 (NEC-1) blocked apoptosis and necroptosis, but not cell death in HeLa cells, implicating caspase-independent mechanisms of cell death in these cells [188].

Oridonin, a diterpenoid extracted from *Rabdosia rubescens*, reduced a proliferation of melanoma cells and cervical cancer cells *in vitro* and *in vivo* through regulating apoptosis and autophagy transcription factors [189]. Oridonin promoted autophagy in L929 cells through p38 MAPK and nuclear factor kappa B (NF- $\kappa$ B) pathways [190-193]. Terpinen-4-ol was shown to induce autophagic and apoptotic cell death in human promyelocytic leukemic HL-60 cells through inducing the accumulation of LC3B-I/-II, ATG5 and BECN1 proteins cytochrome C release from mitochondria, and decreasing BCL-xL expression [194]. Celastrol, an active compound extracted from the root bark of *Tripterygium wilfordii* Hook F., exhibiting a 20S proteasome inhibitor activity, while inducing apoptosis and autophagy in cancer cells [195-201]. Both apoptotic and autophagic pathways were found intertwined upon celastrol treatment, since inhibition of apoptosis enhanced autophagy, while suppression of auto-

phagy diminished apoptosis via the ROS/JNK signaling pathway in human osteosarcoma cells [197]. Celastrol could induce hypoxia-inducible factor (HIF)-1 $\alpha$  protein accumulation leading to transcriptional activation of HIF-1 target genes [198, 199]. Moreover, the celastrol-induced accumulation of HIF-1 $\alpha$  increased the expression of BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3), which induced autophagy in hepatocellular carcinoma HepG2 cells [198, 199]. Celastrol was found to exhibit potent anti-tumor activity against gliomas in xenografted mouse models.

Celastrol was observed to promote protein instability by accumulation of polyubiquitinated protein aggregates, p62 (SQSTM1), and heat-shock proteins, HSP72 and HSP90, as indicated in [200]. Celastrol induced autophagy in human gastric cancer AGS and YCC-2 cells accompanied with an increase in phosphorylated AMPK, and a decrease in phosphorylated AKT, mTOR and p70RS6K proteins [201]. Moreover, gastric tumor burdens were reduced by celastrol administration in a mouse model with grafted human gastric tumor [201]. Celastrol was found to promote paraptosis-like cytoplasmic vacuolization in human cervix cancer HeLa, lung cancer A549 and prostate cancer PC-3 cells, as indicated in [202].

Sulforaphane (1-isothiocyanato-4-(methylsulfinyl)butane) is found in cruciferous vegetables, such as broccoli, cabbage, cauliflower and hoary weed, as reviewed elsewhere [203]. Sulforaphane exhibited antiproliferative properties toward various human tumor cells via multiple molecular mechanisms, as reviewed elsewhere [204-209]. Sulforaphane was shown to induce formation of autophagosome-like structures, as well as acidic vesicular organelles in human prostate cancer PC-3 cells, as described in [204]. Sulforaphane increased the LC3B-I protein levels, and promoted a LC3B-I to LC3B-II processing, as indicated in [202]. Upon sulforaphane exposure, tumor cells showed LC3B-II puncta associated with autophagosomes [204]. Sulforaphane was also shown to disrupt the BCL-2/BECN1 interaction leading to autophagic pathway initiated by liberated BECN1 [204]. Sulforaphane decreased the phosphorylated AKT-Ser473 level, and simultaneous treatment of sulforaphane with autophagy inhibitors, 3-MA or chloroquine enhanced drug cytotoxicity and inhibited tumor cell proliferation [204, 209].

Pyrrole colchicine mimetic, JG-03-14, that binds to the tubulin colchicine site was shown to promote cell death through autophagy in human breast cancer MCF-7 cells expressing wild type TP53 and MDA-MB-231 cells expressing mutant TP53 protein and in B16/F10 melanoma and the HCT-116 colon cancer cells, as described elsewhere [210, 211]. A novel derivative of allicolchicine (S)-3,8,9,10-tetramethoxyallicolchicine (also known as Green 1) was observed to promote autophagy and necroptosis in human pancreatic cancer PANC-1 cells and acute T cell leukemia cells (E6-1 or Jurkat), as indicated in [212]. Allicin, an organic sulfide from garlic *Allium sativum*, was found to exhibit antiproliferative effects on colon cancer, glioma and hepatocellular carcinoma cells, as reviewed in [213, 214]. Allicin can induce death of human hepatocellular carcinoma HepG2 cells through the reduced TP53 expression in the cytoplasm, inhibited PI3K/mTOR signaling pathway, reduced BCL-2 expression and enhanced AMPK/TSC2 and BECN1 pathways, as indicated in [215, 216].

Citreoviridin (CIT), a mycotoxin derived from fungal species (*Penicillium citreoviride*), was found to expression of LC3B-II protein in human hepatocellular carcinoma HepG2 cells [217, 218]. Inhibition of autophagosome formation with ATG5 siRNA attenuated CIT-induced lysosomal membrane permeabilization and tumor cell death, as indicated in [217]. Decrease in p62 (SQSTM1) levels and increase in LC3B turnover indicated that the accumulation of autophagosomes in the CIT-treated HepG2 cells [217, 218]. 7-hydroxydehydro-nuciferine (7-HDNF) isolated from the leaves of *Nelumbo nucifera Gaertn cv. Rosa-plena* is an effective inhibitor of melanoma tumor growth in a mouse xenografted model *in vivo* [219]. 7-HDNF induced an increased autophagic pathway in A375.S2 melanoma cells through the enhanced expression of BECN1 (also known as ATG6), ATG3, ATG12, ATG7, ATG10, ATG16 and ATG5 protein in a dose-dependent manner, as indicated in [219].

Monanchocidin A (MonA) is a novel alkaloid recently isolated from the marine sponge *Monanchora pulchra* [220]. MonA exhibited cytotoxic activity towards human genitourinary cancer cells, including cisplatin-sensitive and -resistant germ cell tumor cell lines, hormone-sensitive and castration-resistant prostate carcinoma cell lines and different bladder carcinoma cell lines, as described in [220]. In contrast, non-malignant cells were significantly less sensitive [220]. MonA was found to induce autophagy and lysosomal membrane permeabilization in tumor cells, while cytotoxicity and protein degradation could be inhibited by 3-MA, as indicated in [220]. Cryptotanshinone and dihydrotanshinone, two lipophilic tanshinones from a traditional Chinese medicine *Salvia miltiorrhiza*, were shown to induce autophagic flux and LC3B-II accumulation in multidrug-resistant colon cancer cells SW620 Ad300 cells [221]. Cardamonin (2', 4'-dihydroxy-6'-methoxychalcone) is derived from *Alpinia katsumadai Hayata* (Zingiberaceae), as described in [221]. Cardamonin inhibited cell proliferation, and enhanced autophagy in human colon colorectal carcinoma HCT-116 cells [222]. Peiminine enhances autophagic flux in HCT-116 cells though repressing the phosphorylation of mTOR, as described in [223]. Silencing ATG5 greatly reduced the peiminine-induced cell death in wild type HCT-116 cells, while treating BAX/BAK-deficient cells with peiminine resulted in significant cell death, as indicated [223].

Cannabinoids promote autophagy-dependent apoptosis in melanoma cells, as reviewed in [224]. Treatment with  $\Delta$  (9)-Tetrahydrocannabinol (THC) activated autophagy, loss of cell viability, and apoptosis, whereas co-treatment with chloroquine or knockdown of ATG7, but not BECN1 or AMBRA1, prevented THC-induced autophagy and cell death *in vitro*, as described elsewhere [224]. Similarly, THC inhibited tumor growth of glioma cells *in vitro* and in animal models *in vivo* [225]. Moreover, the combined administration of THC and TMZ was more effective for inhibiting glioma growth, than the individual administration of any of these two agents [225]. Natural compounds from the plant *Casimiroa edulis*, Zapotidine (Zap) and Oxo-Zapotidine (Oxo-Zap) alone, or in a combination with THC were found to dramatically reduce in the phosphorylated AKT levels in U87MG glioma cells [225]. Both drugs enhanced autophagic process by increasing LC3B-II/LC3B-I ratio [225].



Glycyrrhetic acid (GA), one of the main constituents of the *Glycyrrhiza uralensis* Fisch, exerts potential anticancer effects toward human hepatocellular HepG2 cells [226]. GA reduced the cell viability, and enhanced the expression of LC3B-II in tumor cells, while chloroquine or bafilomycin A1 inhibited these processes [226]. Dihydromyricetin is a natural flavonol, was found to induce the expression of LC3B protein, the degradation of SQSTM1, and the formation of autophagosomes, as described in [227]. An aqueous extract of *Hibiscus sabdariffa* was shown to increase the expressions of autophagy-related proteins, ATG5, BECN1, and LC3B-I/-II conversion, and induce autophagic cell death in human skin malignant melanoma A375 cells, as indicated in [228]. Sann-Joong-Kuey-Jian-Tang (SJKJT), a Traditional Chinese Medicine, was found to induce autophagy in human BxPC-3 pancreatic adenocarcinoma cells [229]. SJKJT was shown to increase expression of mTOR, LC3B-II, BECN1, ATG3, ATG7 and ATG5, ATG12 proteins in BxPC-3 cells *in vitro* [229].

Seriniquinone, isolated from a marine bacterium of the genus *Serinicoccus*, demonstrated potent anti-proliferative activity toward melanoma cell lines by activation of autophagocytosis, while targeting small protein, dermcidin [230]. The cardiostonic steroid UNBS1450 0 from *Calotropis procera* was shown to autophagy-related cell death, by repressing NF- $\kappa$ B activation, as well as by downregulating c-MYC in cancer cells [231]. Oblongifolin C (OC), a natural small molecule compound extracted from *Garcinia yunnanensis* Hu, is a potent autophagic flux inhibitor, as described elsewhere [232-234]. Exposure to OC results in an increased number of autophagosomes and impaired degradation of SQSTM1/p62, as described in [233]. Follow-up studies in xenografted mice *in vivo* showed that OC has anticancer potency as revealed by increased staining of cleaved CASP-3, LC3 puncta, and SQSTM1, as well as reduced expression of lysosomal cathepsins [233]. Furthermore, OC was found to inhibit metastasis in human esophageal squamous carcinoma Eca109 cells and hepatocellular carcinoma HepG2 cells, as indicated in [235].

Plant lectins have been considered as possible anti-tumor drugs because of their ability to induce autophagic cell death, as reviewed elsewhere [236-243]. Polygonatum odoratum lectin (POL), a mannose-binding GNA-related lectin from traditional Chinese medicine herb, was shown to exhibit anti-proliferative and apoptosis-inducing activities toward a variety of cancer cells, as reviewed in [236]. POL could induce both apoptosis and autophagy in human breast cancer MCF-7 cells and NSCLC A549 cells [236, 237]. POL promoted apoptosis through inhibiting AKT/NF- $\kappa$ B pathway, while induced autophagy via suppressing AKT-mTOR pathway [236, 237]. Polygonatum cyrtonema lectin (PCL), a mannose/sialic acid-binding plant lectin, was shown to induce cancer cell autophagic death via activating mitochondrial ROS-p38-p53 pathway, as well as via blocking RAS-RAF and PI3K-AKT pathways [238-240]. PCL was shown to markedly inhibit the growth of human melanoma A375 cells while normal melanocytes were not affected [238-240]. PCL was found to induce both apoptosis and autophagy in A375 cells [239].

Experimental data confirmed that the ROS-p38MAPK-p53 pathway could be involved in the stimulation of auto-

phagy, suggesting that autophagy may play a death-promoting role via the above-mentioned apoptotic pathway, as indicated in [238, 239]. ArtinM, a D-mannose-binding lectin from *Artocarpus heterophyllus*, interacts with N-glycosylated receptors on the surface of human myelocytic leukemia NB4 cells [241]. ArtinM was found to suppress tumor growth via induction of ROS generation and autophagy in NB4 cells [241]. Momordica charantia lectin (MCL) induced autophagy, and subsequently apoptosis in HCC cells, as indicated in [242]. Concanavalin-A (ConA) lectin was found to regulate expression of the autophagy biomarker BNIP3 in human U87 glioblastoma cells [243].

Thymoquinone exposure resulted in caspase-independent, autophagic cell death via mitochondrial outer membrane permeabilization and activation of JNK and p38 MAPK in human LoVo colon cancer cells [244]. Honokiol (HNK), purified from the *Magnolia officinalis* bark, is a promising anticancer agent against prostate cancer cells (PC-3 and LNCaP cells) *in vitro* and (PC-3 xenografts) *in vivo* [245]. The PC-3 tumor xenografts from HNK-treated mice contained higher levels of LC3B-II protein compared to control tumors [245]. Both cell viability inhibition and apoptosis induced by HNK was significantly decreased with 3-MA, as well as ATG5 RNAi, as indicated in [245]. Mollugin, a bioactive phytochemical isolated from *Rubia cordifolia* L., exhibited anticancer activity against various cancer cells [246]. Further experiments demonstrated that PI3K/AKT/mTOR/p70RS6K and ERK signaling pathways participated in mollugin-induced autophagy and apoptosis [247]. Cyclovirobuxine D (CVB-D) could induce autophagy in the MCF-7 human breast cancer cell line evidenced by accumulation of autophagosomes and elevated LC3B fluorescent puncta, as well as increased LC3B-I-to-LC3B-II conversion, and the expression of ATG5, as described in [247]. CVB-D-induced autophagy and decrease in cell viability could be blocked by 3-MA [247].

Jujuboside B, a saponin from the seeds of *Zizyphus jujuba* var. *spinosa*, induced apoptosis and autophagy in human AGS and HCT-116 gastric adenocarcinoma cells *in vitro* and effectively suppressed tumor growth in a nude mouse xenograft model bearing HCT-116 cells *in vivo* [248]. Moreover, jujuboside B activated p38/c-Jun N-terminal kinase (JNK), and induced autophagy indicated by the formation of cytoplasmic vacuoles and LC3B-I/II conversion [248]. The autophagy inhibitor bafilomycin A1 decreased jujuboside B-induced cell viability, as indicated [248]. Feroniellin A (FERO), a novel furanocoumarin, was shown to induce autophagy, associated with LC3B-I to LC3B-II conversion, induction of GFP-LC3B puncta, enhanced expression of BECN1 and ATG5, and inactivation of mTOR in etoposide-resistant human lung carcinoma A549RT-eto cells [249]. Silencing of BECN1 by siRNA reduced FERO-induced apoptosis in A549RT-eto cells and activation of autophagy by rapamycin accelerated FERO-induced apoptosis [249].

## 5. NECROPTOSIS SIGNALING PATHWAYS, CANCER AND NATURAL COMPOUNDS

Necroptosis is classified as a programmed cell death in the absence of morphological traits of apoptosis or auto-

phagy [15, 18, 20, 23, 34-36]. Upon necroptosis induced by the tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) receptor ligand/TNF $\alpha$  receptor 1 (TNFR1), the latter recruits a receptor-interacting protein kinase (RIPK)-1- and -3, as reviewed elsewhere [35, 250-258]. Similarly, other death domain receptors trigger a non-apoptotic cell death resembling necroptosis, as indicated in [35, 250-258]. Upon death receptor oligomerization, they recruit various proteins, including TNFR-associated death domain (TRADD), cellular inhibitor of apoptosis proteins (cIAP), TNF receptor-associated factor (TRAF)-2, and -5, as well as RIPK-1 and -3 into a multimeric protein complex called TNFR1 complex I, as reviewed in [35, 250-258]. Within this complex, RIPK-1 is polyubiquitinated with lysine-63 (K63)-linked ubiquitin chains by cIAPs leading to the activation of the NF- $\kappa$ B signaling, as reviewed elsewhere [250-258]. After TNFR is rapidly internalized upon ligand binding, RIPK-1 becomes deubiquitinated by the cylindromatosis deubiquitinase (CYLD), as indicated [35, 259-262].

When CASP8 is inhibited or inactivated, RIPK-1 associates with RIPK-3, thereby triggering the necroptotic signaling pathway, as reviewed in [35, 250, 255]. On the other hand, activation of CASP8 leads to RIPK-1 cleavage and inactivation of necroptotic pathway [35, 250, 255]. This RIPK-1/RIPK-3 cytoplasmic protein complex called necrosome constitutes a key molecular platform of necroptosis, which involves the reciprocal phosphorylation of RIPK-1 and RIPK-3, as indicated in [35, 250, 256]. RIPK-3 subsequently phosphorylates the mixed-lineage kinase domain-like (MLKL) protein finalizing the necroptotic choice for cell death, as reviewed in [35, 262-264]. MLKL forms a homotrimer through its amino-terminal coiled-coil domain and is localized in the cell plasma membrane during TNF-induced necroptosis [263, 264]. TRPM7 (transient receptor potential melastatin related 7) was shown to act as MLKL downstream target for the mediation of calcium influx and TNF-induced necroptosis [264]. Notably, the final consequences of necroptotic cell death can be distinguished from apoptotic cell death, as the plasma membrane typically ruptures, resulting in the release of the intracellular content into the microenvironment, known as danger-associated molecular patterns (DAMPs), as reviewed in [265-267].

Emerging evidence shows that necroptosis can be disturbed in human cancers, including cervical and pancreatic cancers, leukemia, glioma, glioblastoma, fibroblastoma, neuroblastoma, as reviewed in [252, 268-282]. For example, RIPK-3 and CYLD were found to be deregulated in chronic lymphocytic leukemia (CLL) cells [273, 275]. Several natural compounds were shown to induce necroptosis in human tumor cells. For example, shikonin, a naphthoquinone derived from *Lithospermum erythrorhizon Siebold & Zucc.* (Zicao), was found to be the first natural product capable to induce both apoptosis and necroptosis in human several cancer cell lines, including human breast cancer MCF-7 cells, osteosarcoma cells, glioma/glioblastoma cells, multiple myeloma and leukemia cells, as reviewed elsewhere [282-295]. Shikonin-treated cells were showing morphological alterations distinct from those occurring in apoptosis or autophagic cell death [282-295]. The loss of plasma membrane integrity was one of the morphologic characteristics of necrotic cell death, as indicated in [282-295]. Shikonin exerts a dramatic anticancer effect on both primary and metastatic osteosar-

coma by inducing RIPK-1 and 3- dependent necroptosis [282, 284]. Induction of cell death pathway by shikonin could be blocked a specific necroptosis inhibitor NEC-1, but not by general caspase inhibitor Z-VAD-fmk could block shikonin-induced of cell death pathway, suggesting the necroptotic pathway rather than apoptotic pathway is a signaling of choice in these experimental conditions [268, 282-295]. The number of K7 osteosarcoma necrotic cells caused by shikonin was decreased after being pretreated with NEC-1, as indicated in [282, 284]. Treatment with shikonin led to an increased expression of RIPK-1 and RIPK-3, while CASP-3, -6 and PARP were not activated in K7 and U2OS cells [282, 284]. Size of primary osteosarcoma tumors and lung metastases were significantly reduced by shikonin treatment accompanied the elevated levels for RIPK-1 and RIPK-3 proteins [282, 284]. Shikonin was observed to induce necroptotic cell death in cancer cells including drug- and apoptosis-resistant cancer cells that overexpress P-glycoprotein, multidrug resistance protein-1 (MRP1), breast cancer resistance protein-1 (BCRP1), BCL-2, or BCL-xL [282]. Shikonin-induced necroptosis can be reverted to apoptosis in the presence of necrostatin-1 (NEC-1), due to the conversion from mitochondrial inner to outer membrane permeability, which was associated with BAX translocation [268].

The combination of erlotinib (Tarceva, known inhibitor of EGFR kinase) and shikonin or its derivatives (e.g. deoxyshikonin, isobutyrylshikonin, acetylshikonin,  $\beta$ ,  $\beta$ -dimethylacrylshikonin and acetylalkannin) showed synergistic cytotoxicity toward human glioblastoma U87MG<sup>ΔEGFR</sup> cells (expressing kinase defective mutant of epidermal growth factor receptor, EGFR), as well as in EGFR-expressing cell lines, glioblastoma BS153 cells (wild type EGFR amplified), epidermoid skin cancer A431 cells (wild type EGFR) and glioblastoma DK-MG cells (mutated EGFR), as described elsewhere [285]. Shikonin inhibited EGFR phosphorylation and decreased phosphorylation of EGFR downstream molecules, including AKT, P44/42 MAPK and phospholipase C (PLC)- $\gamma$ 1, but also synergistically (along with erlotinib) inhibited  $\Delta$ EGFR phosphorylation in U87MG<sup>ΔEGFR</sup> cells [285]. Shikonin exerted potent cytotoxic effects on human multiple myeloma bortezomib-resistant KMS11/BTZ cells, as described in [286]. Shikonin (10-20  $\mu$ M) induced cell death, which was inhibited by NEC-1, while its activity was unaffected by Z-VAD-fmk, suggesting the necroptotic nature of cell death in these cells [286]. Shikonin induced cell death in rat C6 and human U87 glioma cells, which was inhibited by NEC-1, not by pan-caspase inhibitor z-VAD-fmk [287]. The increased level of reactive oxygen species (ROS) caused by shikonin was attenuated by NEC-1 and blocking ROS by NAC rescued shikonin-induced cell death in both C6 and U87 glioma cells [287]. Moreover, shikonin upregulated the RIPK-1 protein level, but NAC suppressed RIPK-1 expression, suggesting a role for ROS in regulation of RIPK-1 expression [287]. The allosteric inhibitor of RIPK-1, NEC-1, was found to increase nuclear condensation and caspase activation induced by shikonin in human promyelocytic HL60 cells, bone marrow CLL K562 cells and primary leukemia cells [288]. Small interfering RNA (siRNA)-mediated knockdown of RIPK-1 significantly enhanced shikonin-induced cell death in K562

and HL60 cells [288]. Shikonin could circumvent drug resistance, displayed by tumor cells and mediated by P-glycoprotein, BCL-2 and BCL-xL, by induction of necroptosis [289-293]. Naturally-occurring shikonin analogues (deoxyshikonin, acetylshikonin, isobutyrylshikonin, beta, beta-dimethylacrylshikonin, isovalerylshikonin, alpha-methyl-n-butylshikonin) were found to induce necroptosis in resistant tumor cells overexpressing MDR1 and BCRP1, as indicated in [285-292]. Shikonin induced a cell death in human breast cancer MCF-7 cells distinct from apoptosis, and that the cell death was prevented by NEC-1, as described in [292-295].

Staurosporine, an inhibitor of protein kinases, was found to induce necroptosis in leukemia cells, when caspase activation is inhibited [296]. TNF-related apoptosis-inducing ligand (TRAIL) was recently described to induce necroptosis via RIPK-1/RIPK-3-dependent PARP1 activation, thereby placing PARP1 activation as an effector mechanism downstream of RIPK-1 [297, 298]. Obatoclax (GX15-070), a small-molecule inhibitor of antiapoptotic BCL-2 proteins, was shown to induce autophagy-dependent necroptosis in glucocorticoid-resistant childhood acute lymphoblastic leukemia, as described elsewhere [299-301]. Obatoclax was found to induce assembly of necrosome on autophagosomal membranes [299]. Obatoclax increased the physical association of ATG5 with RIPK-1 and 3, as indicated in [299]. Furthermore, photodynamic therapy using the 5-aminolevulinic acid was found to trigger a RIPK-3-mediated necrosis in glioblastoma cells [302].

Piperlongumine (a natural product constituent of the fruit of the *Piper longum*), and Taurolidine (derivative of natural product taurine) were found to inhibit tumor cells growth *in vitro* and *in vivo* [303]. Piperlongumine may selectively kill some types cancer cells over normal cells [303]. Piperlongumine inhibits the growth of xenografted human malignant breast tumors *in vivo* [303]. Taurolidine induces cytotoxicity for various tumor cells *in vitro* and *in vivo*, including cancer stem cells [303]. The effect of Piperlongumine and Taurolidine is based on the induction of programmed cell death, largely via apoptosis but also necroptosis and autophagy via a redox-directed mechanism, as indicated in [303]. Annonaceous acetogenin mimic AA005 cell death in human colorectal adenocarcinoma SW620 cells, characterized by lack of CASP-3 activation or apoptotic body formation [304]. Decrease in ROS levels markedly reduced the AA005-mediated cell death in SW620 cells [304]. Moreover, repression of RIPK-1 by NEC-1 inhibited translocation of apoptosis-inducing factor and partially suppressed AA005-induced cell death in SW620 cells, suggesting the role for necroptotic pathway [304].

Eupomatenoid-5 (Eup-5), a neolignan isolated from *Piper regnellii* (Miq.) C. DC. var. *regnellii* leaves, was found to induce cell death in human breast cancer MCF-7 cells and kidney cancer 786-0 cells, as described in [305]. In MCF-7 cells, Eup-5 led to phosphatidylserine externalization and caspase activation, whereas Eup-5-treated 786-0 cells exhibited characteristics of programmed necroptosis process [305]. Green tea polyphenol was shown to induce BAX and BAK activation, cytochrome c release, caspase activation, and necroptosis of human hepatocellular carcinoma Hep3B cells [304]. Intriguingly, cytochrome c release and necropto-

sis were diminished in Hep3B cells lacking expression of BAX (*BAX*<sup>-/-</sup>), or BAK (*BAK*<sup>-/-</sup>), as indicated in [306].

Parthenolide was shown to induce necrosis and apoptosis simultaneously in human acute promyelocytic HL-60 cells and Jurkat T lymphoma cells [307]. The interaction of parthenolide with the plasma membrane led to membrane rupture and resulted in rapid necrotic cell death [308]. Intriguingly, parthenolide-mediated necrosis in human breast cancer MDA-MB231 cells was reduced by NAC and NEC-1, implying the role for activation of ROS and RIPK-1 in these processes [309]. Furthermore, parthenolide was found to inhibit the NF- $\kappa$ B activity associated with necrosis in multiple myeloma via targeting TNF receptor associated factor (TRAF)-6, as indicated in [310].

## 6. NATURAL COMPOUNDS AND OTHER CELL DEATH PATHWAYS

Under extreme stress conditions, cells undergo cell death, while employing multiple pathways, which are not limited to apoptosis, autophagy or necroptosis, as reviewed elsewhere [311, 312]. Some anticancer chemotherapies trigger multiple oncosuppressive mechanisms, including paraptosis, parthanatos, and mitotic catastrophe [311, 312]. A few natural compounds were shown to affect some of these pathways, as described below.

Paraptosis is morphologically distinct from apoptosis, autophagy and necrosis and characterized by cytoplasmic vacuole formation and late mitochondrial swelling and clumping, which is independent of caspase activation and inhibition, as reviewed in [313, 314]. In contrast to apoptosis, in which HMGB1 is localized to the nucleus, HMGB1 is released from the nucleus during paraptosis [313, 314]. Autophagic cell death inhibitor 3-MA is ineffective at inhibiting paraptosis [313, 314]. Many anticancer drugs, including natural compounds, have been shown to cause paraptosis in various human cancer cells. Paclitaxel (70 $\mu$ M) was found to induce a paraptosis-like cell death, suggesting that this pathway could be beneficial in treating apoptosis-resistant cancers [315].  $\gamma$ -Tocotrienol, a vitamin E derived from palm oil, induced paraptosis-like cell death, while suppressing the Wnt signaling pathway in colon cancer cells [316]. Protopanaxadiols Rg3 and Rh2 were shown to induce cytosolic vacuolization in human colorectal cancer HCT116 cells [317]. Rh2-induced vacuolization was decreased by a MEK1/2 specific inhibitor U0126, thus supporting the MAPK-dependent mechanism underlying paraptosis [317]. Silencing of p53 reduced the ability of Rh2 to induce vacuole formation characteristic for paraptosis [317]. Honokiol from *Magnolia officinalis* can induce paraptosis in human leukemia NB4 cells [318]. Hesperidin, a flavanone glycoside found in citrus fruits, induced paraptotic cell death in human hepatocellular carcinoma HepG2 cells [319]. Celastrol, a triterpene extracted from *Tripterygium wilfordii*, was found to induce paraptosis in several human breast and colon cancer cell lines, which was characterized by extensive vacuolization in the endoplasmic reticulum and mitochondria [202, 320].

Excessive PARP-1 activation triggers a parthanatos, in which poly (ADP)-ribose (PAR) induces the mitochondrial release and nuclear translocation of apoptosis-inducing

Table 1. Effect of natural compounds on the autophagy in tumor cells.

Compound Name	Compound Source	Tumor Cells	Mode of Action	Refs.
Berberine	<i>Rhizoma coptidis</i>	nonsmall cell lung cancer A549 cells; hepatocellular carcinoma HepG2, MHCC97-1, and SMMC7721 cells; colon carcinoma HCT116 and SW613-B3 cells	Activation of autophagic intermediates; BECN1, ATG5, LC3B-I/-II conversion	[94-102]
Resveratrol	red grape skin, blueberries, mulberries, cranberries	ovarian cancer A2780 cells; breast cancer MCF-7 cells; ovarian cancer cells (OVCAR-3 and Caov-3); prostate cancer PC3 and DU145 cells; non-small lung adenocarcinoma A549 cells; in T-acute lymphoblastic leukemia cells	Activation of AMPK and JNK-mediated p62/SQSTM1 expression; ROS generation, induction of ATG5; increase in LC3B-I/LC3B-II conversion and BECN1 expression	[110-115, 117-119, 121]
Epigallocatechin-3-gallate	Green tea	colorectal cancer DLD-1 and HT-29 cells; hepatocellular carcinoma HepG2 cells; cervical cancer cells, and mesothelioma cells	Inducing accumulation of LC3B-II protein; ROS-mediated lysosomal membrane permeabilization	[134, 137-139]
Curcumin	<i>Curcuma longa L.</i> , <i>Curcuma zedoaria (Christm) Rosc.</i> , <i>Curcuma amada Roxb.</i> , and <i>Curcuma petiolarata</i> ,	leukemia K562 cells; colon cancer cells; glioblastoma cells; colorectal carcinoma HCT116 cells, breast cancer MCF-7 cells; lung adenocarcinoma A549 cells; oral squamous cell carcinoma cells; malignant pleural mesothelioma ACC-MESO-1 cells	Induced the expression of BECN1 and TP53, and ROS production; induced LC3B-I/-II conversion; ATG5 expression; autophagosome formation; activation of AMPK signaling	[142, 144-147, 151, 152]
Ginsenosides	<i>Ginkgo biloba</i>	hepatocellular carcinoma cells; breast cancer cells	induced LC3B-I/-II conversion; disrupted the interaction between ATG6 and BCL-2; upregulate of ATG7 expression	[163-165]
Parthenolide	<i>Tanacetum parthenium</i>	breast cancer MDA-MB231 cells; hepatocellular carcinoma HepG2 cells; promyelocytic leukemia HL-60 cells and cervical cancer HeLa cells	Increased expression of BECN1, and LC3B-I/-II conversion	[173-175]
Triptolide	<i>Tripterygium wilfordii</i>	pancreatic cancer S2-013, S2-VP10, and Hs766T cells; lung cancer A549 cells; neuroblastoma SH-SY5Y cells	Activation of BECN1, ATG5, and LC3B-I/-II conversion	[177, 179, 181]
Terpinen-4-ol	Tea tree oil	promyelocytic leukemic HL-60 cells	Activation of BECN1, ATG5, and LC3B-I/-II conversion	[192]
Celastrol	<i>Tripterygium wilfordii Hook F</i>	hepatocellular carcinoma HepG2 cells; gastric cancer AGS and YCC-2 cells	Increased BNIP3 expression	[196]
Sulforaphane	<i>Brassicaceae</i>	prostate cancer PC-3 cells	Increased LC3B-I/-II conversion; disrupts the BCL-2/BECN1 interaction	[197, 201]
Allicin	<i>Allium sativum</i>	hepatocellular carcinoma HepG2 cells	Enhanced AMPK/TSC2 and BECN1 pathways	[212, 213]
Citreoviridin	<i>Penicillium citreoviride</i>	hepatocellular carcinoma HepG2 cells	Increased LC3B-I/-II conversion; activation of ATG5	[214, 215]

(Table 1) contd....

Compound Name	Compound Source	Tumor Cells	Mode of Action	Refs.
7-hydroxydehydronuciferine	<i>Nelumbo nucifera Gaertn</i> <i>cv. Rosa-plena</i>	melanoma A375.S2 cells	Enhanced expression of BECN1 (also known as ATG6), ATG3, ATG12, ATG7, ATG10, ATG16 and ATG5 protein	[216]
Glycyrrhetic acid	<i>Glycyrrhiza uralensis Fisch</i>	hepatocellular HepG2 cells	Increased LC3B-I/-II conversion	[223]
Honokiol	<i>Magnolia officinalis</i>	prostate cancer PC-3 and LNCaP cells	Increased LC3B-I/-II conversion, ATG5 expression	[242]
Jujuboside B	<i>Zizyphus jujuba var. spinosa</i>	gastric adenocarcinoma AGS cells; colon adenocarcinoma HCT116 cells	Increased LC3B-I/-II conversion	[245]

Table 2. Effect of natural compounds on the necroptotic, paraptotic, parthanatos, and mitotic catastrophe pathways in tumor cells.

Compound Name	Compound Source	Tumor Cells	Mode of Action	Refs.
Shikonin	<i>Lithospermum erythrorhizon Siebold &amp; Zucc.</i>	breast cancer MCF-7 cells, osteosarcoma cells, glioma cells, multiple myeloma and leukemia cells	Induced RIPK-1 and RIPK-3	[279, 280, 279, 287-299]
Piperlongumine	<i>Piper longum</i>	malignant breast tumors in xenografted mice <i>in vivo</i>	ROS production	[300]
Acetogenin mimic AA005	<i>Annonaceae</i>	colorectal adenocarcinoma SW620 cells	ROS production; induced RIPK-1	[301]
Eupomatenoid-5	<i>Piper regnellii (Miq.) C. DC. var. regnellii</i>	kidney cancer 786-0 cells	necrosis morphology	[302]
Parthenolide	<i>Tanacetum parthenium</i>	acute promyelocytic HL-60 cells; Jurkat T lymphoma cells; breast cancer MDA-MB231 cells	Activation of ROS and RIPK-1	[304-307]
$\gamma$ -Tocotrienol,	vitamin E derived from palm oil	colon cancer cells	Paraptosis	[314]
Ginsenoside Rh2	<i>Ginseng biloba</i>	colorectal cancer cells	Paraptosis	[315]
Honokiol	<i>Magnolia officinalis,</i>	leukemia NB4 cells	Paraptosis	[316]
Hesperidin	citrus fruits	hepatocellular carcinoma HepG2 cells	Paraptosis	[317]
Celastrol	<i>Tripterygium wilfordii</i>	breast and colon cancer cells	Paraptosis	[200, 318]
Moscatilin	<i>Dendrobium loddigesii</i>	squamous cell carcinoma and adenocarcinoma cells	Mitotic catastrophe	[328]
2-deprenyl-rheediaxanthone B	<i>Metaxya rostrata C. Presl</i>	colorectal cancer cells	Mitotic catastrophe	[329]
Flavone eupatorin	<i>Orthosiphon stamineus</i>	various cancer cells	Mitotic catastrophe	[330]
MMH01	<i>Antrodia cinnamomea</i>	leukemia U937 cells	Mitotic catastrophe	[331]
Ruta	<i>Ruta graveolens</i>	brain cancer and HL-60 leukemia cells	Mitotic catastrophe	[332]
Ethanol extract	<i>Derris scandens Benth</i>	colon cancer HT29 cells	Mitotic catastrophe	[333]

factor (AIF) to initiate a chromatin destruction and subsequent cell death, as indicated [284, 321-325]. In contrast to

apoptosis, parthanatos does not require activated caspases for its execution [321-325]. AIF binding to PAR is required for

parthanatos both *in vitro* and *in vivo*, as reviewed in [321-325]. This interaction triggered AIF release from the cytosolic side of the mitochondrial outer membrane [321-325]. Sepantronium bromide (YM155), a survivin suppressant, inhibited growth of esophageal squamous-cell carcinoma xenografts in mice [326]. YM155 decreased survivin levels and caused PARP-1 activation, poly-ADP polymer formation, and AIF translocation from the cytosol to the nucleus [326]. Genetic knockdown of PARP-1 or AIF abrogated YM155-induced parthanatos cell death. PARP-1-stimulated expression of FOS, JUN and c-MYC transcription factors was also increased upon YM155 treatment [326].

Mitotic catastrophe is a cell death resulted from an aberrant chromosomal segregation, or DNA damage, as reviewed elsewhere [327-329]. It can be triggered by instability of microtubule, various anticancer drugs, as well as induced by ionizing radiation [327-329]. Altered cells resisting a mitotic catastrophe are likely to undergo oncogenesis, potentially leading to cancer [327-329]. Mitotic catastrophe is an intrinsic oncosuppressive mechanism that senses mitotic failure and responds by driving a cell to an irreversible antiproliferative death, as reviewed in [330]. Natural compounds were recently found to induce this type of cell death. For example, moscatilin from the orchid *Dendrobium loddigesii*, was found to exhibit anticancer activity and induce multipolar mitosis and subsequent multinucleation in moscatilin-treated cells, indicating the development of mitotic catastrophe in human SCC cells and adenocarcinoma cells [331]. 2-deprenyl-rheediaxanthone B (XB) isolated from the *Metaxya rostrata* C. Presl. (Metaxyaceae) induced loss of cell viability in human colorectal cancer cell lines [332]. Tumor cells exposed to the compound XB were incapable of undergoing regular mitosis due to downregulation of FoxM1 transcription factor and absence of chromosome condensation [332]. Intriguingly, the anti-apoptotic proteins BCL-2 and BCL-xL were upregulated; therefore caspase-3 was not activated upon exposure to the compound XB [332]. However, XB triggered Ataxia telangiectasia and Rad3 related (ATR) kinase damage pathway and activated caspase-2 causing tumor cell death by a mitotic catastrophe mechanism, as indicated in [332]. Flavone eupatorin isolated from *Orthosiphon stamineus* was found to reduce viability of various cancer cells through induction of mitotic catastrophe, accompanied by key molecular events defining apoptosis, as described in [333]. MMH01 from *Antrodia cinnamomea* was shown to decrease growth of human leukemia U937 and pancreatic cancer BxPC3 cells [334]. MMH01 was found to induce apoptosis and mitotic catastrophe in U937 cells, while trigger apoptosis or necrosis in BxPC3 cells [334]. A homeopathic medicine, Ruta isolated from *Ruta graveolens* was found to induce telomere erosion and mitotic catastrophe in human brain cancer and HL-60 leukemia cells *in vitro* and *in vivo* [335]. Ethanolic extract of *Derris scandens* Benth is a potent radiosensitizer of human colon cancer HT29 cells, as described in [336]. Treatment of HT29 cells with *D. scandens* extract in combination with gamma irradiation synergistically sensitizes HT29 cells to mitotic catastrophe by decreasing ERK1/2 activation [336].

## CONCLUSION AND FUTURE PERSPECTIVES

Evasion from programmed cell death mechanisms is a hallmark of cancer contributing to tumor initiation, progres-

sion and tumor resistance to chemotherapy [1, 2, 4]. Thus, novel anticancer therapeutic solutions to reactivate cell death programs in human malignancies are welcomed. Accumulating evidence shows that natural compounds exert damaging effects on cancer cells with minimal adverse effects on the normal cells, therefore they hold a great promise for the future anticancer therapeutics [29]. More than 3000 plant species have been reported to treat cancer and about thirty plant-derived compounds have been isolated and tested in cancer clinical trials so far, as indicated in [29]. The molecular mechanisms of action for plant-derived anticancer drugs are often associated with cell death pathways, especially with intrinsic or extrinsic caspase-dependent apoptosis [20, 29, 42, 45, 65, 96, 108, 111, 156, 337-343]. A number of natural compounds reviewed in this work have shown to play a significant role in non-apoptotic pathways leading to tumor cell death, namely autophagy, necroptosis, paraptosis, parthanatos, and mitotic catastrophe [20, 29, 42, 45, 65, 96, 108, 111, 158, 284, 311-313, 321, 337-343]. The tumor suppressive action of natural compounds-induced autophagy may provoke apoptosis-independent cell death, and complement apoptotic cell death by robust or target-specific mechanisms [20, 29, 42, 45, 65, 96, 108, 111, 158, 337-343]. (Tables 1 and 2) summarize the ability of natural compounds to induce autophagy and other pathways leading to tumor cell death.

The understanding of molecular pathways involved in non-apoptotic cell death induced by these natural anticancer drugs would assist in exploiting novel molecular targets of plant-derived compounds necessary to advance more safe and effective anticancer therapeutics allowing to circumvent cancer drug resistance [20, 29, 42, 45, 65, 96, 108, 111, 158, 337-343]. The success with natural product shikonin, which able to induce multiple cell death mechanisms, supports the notion that natural compounds could bypass specific drug resistance developed by tumor cells using simultaneous activation of multiple death pathways (apoptosis, autophagy, necroptosis), as reviewed elsewhere [20, 29, 42, 45, 65, 96, 108, 111, 158, 337-343]. Thus, a rationalized combination of several cell death inducers that complement each other would maximize their efficacy while minimizing their side effects [20, 29, 42, 45, 65, 96, 108, 111, 158, 337-343]. While *in vitro* studies showed the strong ability of natural compounds to induce non-apoptotic death of tumor cells, more *in vivo* investigations needed to strengthen this notion before making a leap to clinical application [339-343].

## LIST OF ABBREVIATIONS

AMPK	=	AMP-activated Protein Kinase
ATG	=	Autophagy-related Gene
ATR	=	Ataxia Telangiectasia and Rad3 Related
BCL	=	B-cell Lymphoma
BAX	=	BCL-2-associated X Protein
cIAP	=	Cellular Inhibitor of Apoptosis Protein
CIT	=	Citreoviridin
CYLD	=	Cylindromatosis Deubiquitinase
CSC	=	Cancer Stem Cells
DRAM1	=	Damage-regulated Autophagy Modulator

DAMP	=	Danger-associated Molecular Patterns
DOX	=	Doxorubicin
4E-BP	=	eIF4E Binding Protein
EGFR	=	Epidermal Growth Factor Receptor
EGCG	=	Epigallocatechin-3-gallate
ERK	=	Extracellular Signal-regulated Kinases
GA	=	Glycyrrhetic Acid
HSP	=	Heat Shock Protein
HDNF	=	Hydroxydehydronuciferine
LAMP2	=	Lysosomal-associated Membrane Protein 2
mTOR	=	Mammalian Target of Rapamycin
3-MA	=	Methyladenine
MAP1LC3B	=	Microtubule-associated Protein 1 light chain 3-beta
MLKL	=	Mixed-lineage Kinase Domain-like
MonA	=	Monanchocidin A
MCL	=	Momordica Charantia Lectin
NAC	=	N-acetyl Cysteine
NSCLC	=	Necrostatin, NEC, Non-small Cell Lung Cancer
NF-κB	=	Nuclear Factor-kappa B
Oxo-Zap	=	Oxo-Zapotidine
PARP	=	Poly (ADP-ribose) Polymerase
POL	=	Polygonatum Odoratum Lectin
p70RS6K	=	p70 ribosomal Protein S6 Kinase
PKB	=	Protein Kinase B
PCL	=	Polygonatum Cyrtoneum Lectin
RIPK	=	Receptor-interacting Protein Kinase
ROS	=	Reactive Oxygen Species
SJKJT	=	Sann-Joong-Kuey-Jian-Tang
SCC	=	Squamous Cell Carcinoma
STIM1	=	Stromal Interaction Molecule 1
TMZ	=	Temozolomide
THC	=	Δ(9)-tetrahydrocannabinol
TSC	=	Tuberous Sclerosis
TNFα	=	Tumor Necrosis Factor α
TRAIL	=	TNF-related Apoptosis-inducing Ligand
TP	=	Tumor Protein
PUMA	=	TP53-upregulated Modulator of Apoptosis Protein
ULK	=	unc51-like Kinase
Zap	=	Zapotidine

#### CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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