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REVIEW

Terpenoids' anti-cancer effects: focus on autophagy

Chirine El-Baba[1] · Amro Baassiri[2] · Georges Kiriako[3] · Batoul Dia[2] · Sukayna Fadlallah[2] · Sara Moodad[2] · Nadine Darwiche[1]

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Abstract
Terpenoids are the largest class of natural products, most of which are derived from plants. Amongst their numerous biological properties, their anti-tumor effects are of interest for they are extremely diverse which include anti-proliferative, apoptotic, anti-angiogenic, and anti-metastatic activities. Recently, several in vitro and in vivo studies have been dedicated to understanding the 'terpenoid induced autophagy' phenomenon in cancer cells. Light has already been shed on the intricacy of apoptosis and autophagy relationship. This latter crosstalk is driven by the delicate balance between activating or silencing of certain proteins whereby the outcome is expressed via interrelated signaling pathways. In this review, we focus on nine of the most studied terpenoids and on their cell death and autophagic activity. These terpenoids are grouped in three classes: sesquiterpenoid (artemisinin, parthenolide), diterpenoids (oridonin, triptolide), and triterpenoids (alisol, betulinic acid, oleanolic acid, platycodin D, and ursolic acid). We have selected these nine terpenoids among others as they belong to the different major classes of terpenoids and our extensive search of the literature indicated that they were the most studied in terms of autophagy in cancer. These terpenoids alone demonstrate the complexity by which these secondary metabolites induce autophagy via complex signaling pathways such as MAPK/ERK/JNK, PI3K/AKT/mTOR, AMPK, NF-kB, and reactive oxygen species. Moreover, induction of autophagy can be either destructive or protective in tumor cells. Nevertheless, should this phenomenon be well understood, we ought to be able to exploit it to create novel therapies and design more effective regimens in the management and treatment of cancer.

Keywords Terpenoids · Autophagy · Cancer · Cell death

Introduction

Cancer is the leading cause of mortality worldwide and is considered as one of the major obstacles hindering the increase in life expectancy [1, 2]. The rapid identification of numerous potential therapeutic targets for different cancer types is setting a high demand for the development of new drugs. Due to the side effects of chemotherapy, the need for alternative anticancer agents from natural sources is increasing.

✉ Nadine Darwiche
nd03@aub.edu.lb

1 Department of Biochemistry and Molecular Genetics, American University of Beirut, Beirut, Lebanon

2 Department of Biomedical Sciences, American University of Beirut, Beirut, Lebanon

3 Department of Biomedical Engineering, American University of Beirut, Beirut, Lebanon

The unparalleled chemical diversity of compounds harbored within millions of plant species is the epitome of nature's ingenuity [3]. Structural variety complemented with multifunctional activity makes plant-extracted natural products auspicious [4–8]. Currently, these plant products account for more than 60% of the Food and Drug Administration (FDA; USA) approved commercially available drugs that target cancer [9]. Terpenoids, the largest class of natural products, includes more than 40,000 structures that are used in flavor, fragrances, chemical, and pharmaceutical industries [10–14]. Terpenoids, composed of five carbon isoprene units, are divided into subclasses based on their structures and include hemiterpenoids, monoterpenoids, sesquiterpenoids, diterpenoids, sesterterpenoids, triterpenoids, tetraterpenoids, and polyterpenoids [15]. Each terpenoids' subclass has its own set of diverse biological properties. Terpenoids have anticancer activities as they target several stages of cancer development such as cell proliferation, cell death, angiogenesis, and metastasis [8]. Many terpenoids affect

epigenetic and cellular death mechanisms through targeting nuclear factor kB (NF-kB), Janus kinases-signal transducer and activated of transcription proteins (JAK-STAT), activator protein-1 (AP-1), metalloproteinases (MMPs), DNA topoisomerase I and II, blocking the endoplasmic reticulum (ER) calcium ATPase pump, inhibiting proteasome, activating p53, and modulating DNA minor grooves [14–16].

The major mechanism of cell death induced by terpenoids is apoptosis [17, 18]. However, recent studies indicate that terpenoids can result in other forms of cell death, specifically autophagy, as highlighted in this review. Autophagy is a self-eating process that involves the formation of double-membrane vacuoles, autophagosomes, which then merge with lysosomes [19, 20]. Autophagy is regulated by numerous players, namely the autophagy genes (*ATG*) [21]. This leads to the degradation and recycling of large protein molecules and dysfunctional organelles [22, 23]. In eukaryotes, autophagy is important in preventing cellular damage and aging, maintaining homeostasis, and enhancing cell survival during stressful conditions [24]. On the other hand, autophagy can play a role in pathological conditions including neurodegenerative diseases, infection, and cancer [23, 25–29]. The emerging role of autophagy in cancer is one of a double-edged sword [30–32]. In fact, autophagy enables cancer cell survival during stressful events such as starvation and hypoxic conditions or may lead to apoptotic or non-apoptotic cell death.

This review summarizes nine different terpenoids among the various subclasses (Fig. 1) and their cell death mechanisms of action with an emphasis on autophagy (Fig. 2). These latter plant terpenoids were selected as they present with several antitumor mechanism involving autophagy. In addition, we have chosen these nine terpenoids among others as they belong to the different major classes of terpenoids and our extensive search of the literature indicated that they were the most studied in terms of autophagy in cancer. Furthermore, the cross-talk between apoptosis and autophagy will be addressed since they share several signaling pathways [23, 33–35]. We will first cover the different mechanisms of cell death and autophagy of the representative sesquiterpenoids (artemisinin, parthenolide) followed by the diterpenoids (oridonin, triptolide) and will end up with the triterpenoids (alisol, betulinic acid, oleanolic acid, platycodin D, ursolic acid) as summarized in Tables 1 and 2.

Artemisinin and its derivatives and anticancer activities

Artemisinin, a sesquiterpene lactone, was first isolated from the sweet wormwood *Artemisia annua L.* by the Nobel Prize winner Youyou Tu [36, 37]. Artemisinin is mostly used in antimalarial treatments and along its derivatives such as dihydroartemisinin (DHA), and artesunate (ARS) have proven to harbor antitumor properties [38]. Artemisinin activity was established in vitro and in vivo and induces caspase 3-dependent apoptosis in tumor cells while exhibiting low toxicity to normal cells [16, 39]. Artemisinin was shown to induce ferroptosis in several

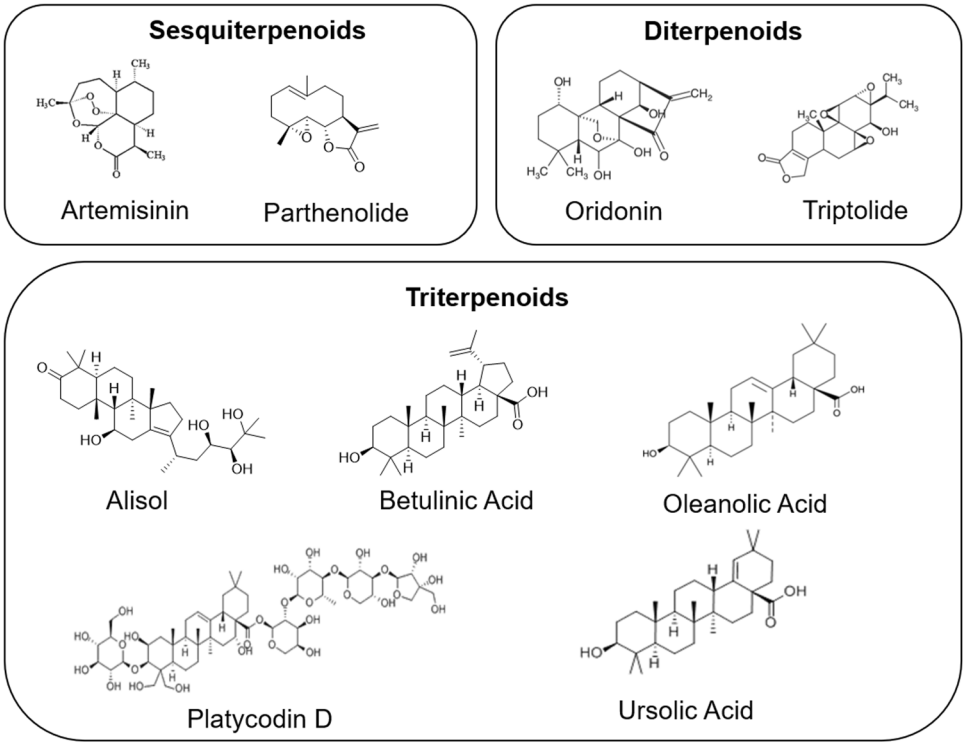

Fig. 1 Chemical structures of selected terpenoids divided into three subclasses: sesquiterpenoids (artemisinin, parthenolide), diterpenoids (oridonin, triptolide), and triterpenoids (alisol, betulinic acid, oleanolic acid, platycodin D, and ursolic acid)

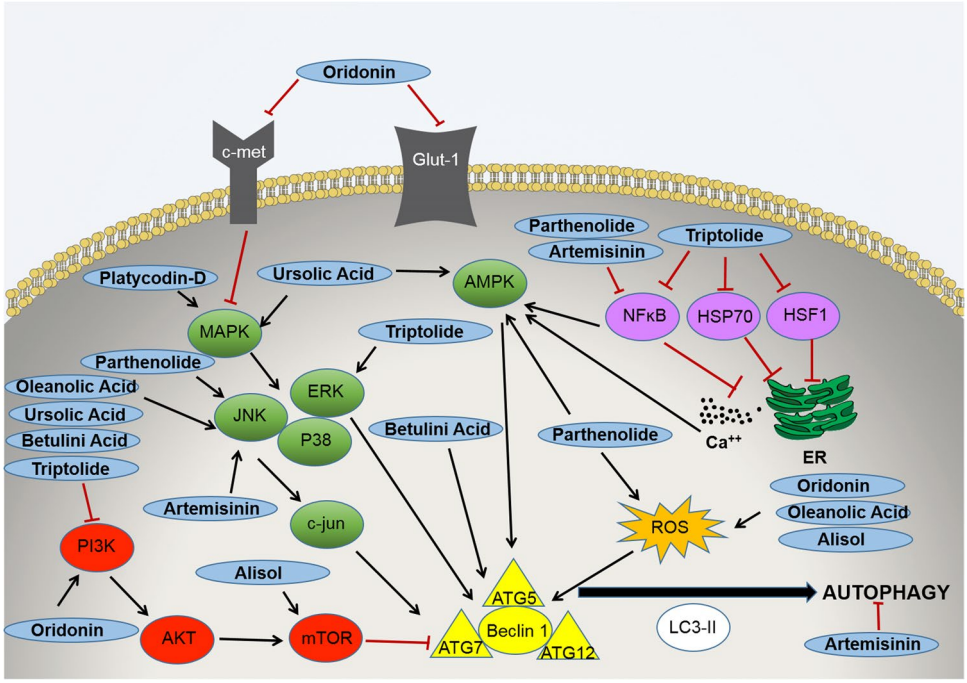

Fig. 2 The effect of terpenoids on the autophagic signaling pathways. These terpenoids alone (blue oval) demonstrate the complexity by which these secondary metabolites induce autophagy via complex signaling pathways such as MAPK/ERK/JNK, PI3K/AKT/mTOR, AMPK, NF-kB, and reactive oxygen species. *AKT* protein kinase B; *AMPK* AMP-activated kinase; *ATG* autophagy-related gene; *c-met* hepatocyte growth factor receptor. *ER* sarcoplasmic/endoplasmic reticulum; *ERK* extracellular signal-regulated kinase; *Glut-1* glucose transporter 1; *HSF1* heat shock factor 1; *HSP70* heat shock protein 70; *JNK* c-jun N-terminal kinase; *LC3* microtubule-associated protein light chain 3; *MAPK* mitogen-activated protein kinase; *mTOR* mechanistic target of rapamycin; *NF-kB* nuclear factor-kB; *PI3K* phosphoinositide 3-kinase; *ROS* reactive oxygen species

cancer cells by increasing intracellular ROS activity and triggering degradation of lysosomes [40]. ARS is water soluble, inhibits cell growth through inducing cell cycle arrest [41, 42] and causes tumor cell death through apoptosis, ferroptosis, and autophagy [43, 44]. Recently, ARS was reported to induce G1 arrest without DNA damage induction in 2 dimensional (2D) and 3D breast cancer models [45].

DHA is the most potent derivative of artemisinin and has been emerging as an anticancer agent with a cytotoxic effect on a wide range of human cancer cell lines [8, 39, 46–56]. In addition, DHA has a significantly lower cytotoxicity on normal cells which makes it an ideal chemotherapeutic agent [8].

DHA has a diverse set of cell death mechanisms which include apoptosis, autophagy, cell cycle arrest, reactive oxygen species (ROS) generation, iron involvement, and T-helper type 1 (Th1) immune response shift [41, 47, 49, 57–63].

Artemisinin and its derivatives in autophagy

The past few years have witnessed great interest in studying autophagy on artemisinin and its derivatives and have been shown to induce autophagic cell death in tumors [64, 65]. Artemisinin and ARS induce G2/M cell cycle arrest, increase in cyclins B1, D1, and E and apoptosis in breast cancer cells, and result in autophagic cell death via Beclin1 upregulation, LC3 aggregation, and LC3-II conversion [42, 66]. A hallmark of autophagy induction was measured, namely the conversion of LC3-I to LC3-II [67]. It is worth noting that there is a close correlation between the amount of LC3-II and the number of autophagosomes [68]. Inhibiting autophagy by 3-methyladenine (3-MA) abrogated the latter observed cell death. ARS treatment of human bladder cancer cells (T24 and EJ) resulted in autophagy-dependent apoptosis, ROS increase, and activation of AMPK-mTOR-ULK1 [69]. On the other hand, artemisinin in combination with chemotherapeutic drugs synergize to induce caspase 3-dependent apoptosis by inhibiting autophagy [39, 70]. Studies have shown that DHA can induce autophagy in a number of human cancer cell lines, namely ovarian (SKOV3/DDP) [61, 71], multiple myeloma (RPMI 8226), promyelocytic leukemia (NB4), colorectal (HCT116), cervical (HeLa) [63, 67, 72, 73], esophageal (Eca109 and Ec9706) [62, 74], pancreatic (BxPC-3 and PANC-1) [75], hepatic (HepG2, HepG2215) [73, 76, 77], chronic myelogenous leukemia (K562) [59], glioma (SKMG-4) [78], LN-Z308, T98G and LN-229 [79], and tongue squamous cell carcinoma

Table 1 Sesquiterpenoids and diterpenoids anticancer compounds as autophagic regulators

Terpenoids	Cancer model	Autophagy mechanism and effects	Reference
Sesquiterpenoids			
Artemisinin	MCF-7 and MDA-MB-231 human breast cancer cells	↑Beclin 1 LC3-I to LC3-II conversion → LC3 aggregation → Autophagic cell death	[42]
	T24 and EJ human bladder cancer cells	↑ROS ↑AMPK/mTOR/ULK1 → Autophagic cell death	[69]
	SKOV3 and SKOV3/DDP human ovarian cancer cells	↑pmTOR	[71]
	SKOV3 and primary EOC human ovarian cancer cells	↓NFkB → Autophagic cell death	[61]
	RPMI 8226 human multiple myeloma, NB4 promyelocytic leukemia, HCT116 colorectal, and HeLa cervical cancer cells	↓NFkB, ↑ ROS, ↓p62 LC3-I to LC3-II conversion → LC3 aggregation → Autophagic cell death	[72]
	HeLa, HCT116, HepG2 and SKOV3 in vitro and in vivo	↑Stress-regulated protein p8, ↑ATF4, ↑CHOP → Autophagic cell survival	[73]
	HL60 human acute promyelocytic leukemia, KG1 acute myeloid leukemia, and THP-1 acute monocytic leukemia cell lines	↑AMPK/mTOR/p70S6K, ↑ROS, ↓ferritin → Autophagic cell death	[63]
	HeLa cervical cancer cells	LC3-I to LC3-II conversion → LC3 aggregation ↑ROS, ↑p-Bcl-2, ↑p-JNK1/2, ↑Beclin 1, ↓pmTOR → Autophagic cell death	[67]
	Eca109 and Ec9706 human esophageal cancer cells	LC3-I to LC3-II conversion	[74]
	Eca109 human esophageal cancer in vitro and in vivo	↑ROS, ↓TRF2→ DNA damage response → Autophagic cell death	[62]
	BxPC-3 and PANC-1 pancreatic cancer	↑LC3-II, ↑ROS, ↑Beclin 1, ↑MAPK/JNK →Autophagic cell survival	[75]
	HepG2215 hepatic	↑ ROS → DNA damage response, ↑autophagosomes, ↑AIM2/caspase-1 inflammasome, ↑Beclin 1, ↓p62 LC3-I to LC3-II conversion	[76]
	HepG2.2.15 HBV positive hepatocellular carcinoma cells in vitro and in vivo	LC3-I to LC3-II conversion, ↓AKT/mTOR →Autophagic cell survival	[77]
	K562 chronic myelogenous leukemia	↑ROS, ↑LC3-II → Autophagic cell death	[59]
	MGR1, MGR3, SF295, SKMG-1, SKMG-4, T98G, U251, U251/CP2, U373 and U87 human glioma cell lines in vitro and in vivo	↑Beclin 1, ↑LC3-II → Autophagic cell death	[78]
	T29 primary human glioblastoma cell line, LN-Z308, T98G and LN-229 human glioma cell lines in vitro and in vivo	↑ROS, ↑LC3-II	[79]
	Cal-27 tongue squamous cell carcinoma cells	↑LC3-II, ↑Beclin 1, ↑autophagosomes ↑ ROS→ DNA double strand breaks → Autophagic cell death	[80]
	A549 human adenocarcinoma epithelial cells in vitro and in vivo	LC3-I to LC3-II conversion, ↑MAPK ↓PI3K/AKT/mTOR → Autophagic cell death	[81]
	HUVEC Human umbilical vein endothelial cells	↑autophagosomes, ↑ROS, ↑LC3-II ↓AKT/mTOR	[82]
Parthenolide	Saos-2 and MG-63 Osteosarcoma cells	↑PINK1, mitochondrial translocation of Parkin → mitophagy, ↑ROS → Autophagic cell death	[98]
	MDA-MB231 breast cancer in vitro and in vivo	↑ROS, ↑JNK, ↓NFkB, ↑Beclin 1, LC3-I to LC3-II conversion → Autophagic cell death	[99]
	MCF-7 and MCF-10A breast cancer cells	↑ROS, ↑AMPK pathway →Autophagic cell survival	[101]

Table 1 (continued)

Terpenoids	Cancer model	Autophagy mechanism and effects	Reference
	MCF7 and MDA-MB231 breast cancer cells	↓p62/SQSTM1, ↑Beclin 1, ↑ATG13, ↑ATG14 ↓PI3K/AKT/mTOR →Autophagic cell survival	[103]
	Panc-1 and BxPC3 pancreatic cancer cells	↑autophagosomes, ↑LC3-II, ↑p62/SQSTM1, ↑Beclin 1, → Autophagic cell death	[100]
	HeLa cervical cancer	↑Beclin 1, ↑ATG5, ↑ATG3, ↓PI3K/AKT/mTOR, ↑ ROS → mitochondrial membrane potential loss → Autophagic cell death	[92]
	HepG2 human hepatocellular carcinoma cells	↑MSD uptake, acidic vesicular organelle cytoplasmic accumulation → Autophagic cell death	[102]
	MDA-T32 human papillary thyroid carcinoma cells in vitro and in vivo	↑LC3-II, ↑Beclin 1, ↓PI3K/AKT/mTOR → Autophagic cell death	[93]
	HL-60 human promyelocytic leukemia cell line, HeLa human epithelial carcinoma cell line, and HEK293T primary embryonic human kidney cells	↑ROS, ↓translation initiation factor eIF4E binding protein 1 (4E-BP1) → Autophagic cell death	[106]
Diterpenoids			
Oridonin	SW480, HCT-15 colorectal cancer cells in vitro and in vivo	↓GLUT1, ↓MCT1, ↑LC3-II, ↓p-AMPK, ↑Beclin 1, ↑ATG5 →Autophagic cell death	[108]
	MDA-MB-436 and MDA-MB-231 breast cancer	↑LC3-II, ↑Beclin 1 →Autophagic cell death	[112]
	cervical cancer Hela cells	↑ROS, ↑Beclin 1, LC3-I to LC3-II conversion →Autophagic cell survival	[306]
	A549 lung cancer	LC3-I to LC3-II conversion, ↑ Beclin1 ↓c-met → ↑ERK pathway → Autophagic cell death	[130]
	PC3 and LNCaP prostate cancer	↑autophagosomes, acidic vesicular organelle cytoplasmic accumulation, LC3-I to LC3-II conversion →Autophagic cell survival	[131]
	RPMI8266 human multiple myeloma	↑Beclin 1, ↑ROS, ↓sirtuin 1 →Autophagic cell survival	[138]
	U937 human histiocytic lymphoma	↑p-ERK, ↑pro IL-1β ↑ Beclin1, ↑LC3-II, ↑ATG4B	[139]
Triptolide	WEHI-3 murine leukemia cells in vitro and in vivo	↑ROS, ↑mitochondrial membrane potential, ↑intracellular calcium,↑acidic vacuoles, ↑MSD uptake, ↑ATG5, ↑ATG7, and ↑ATG12, →autophagic cell death	[158]
	MCF-7 human breast cancer	↓p62, ↑p38/ERK/mTOR pathway →autophagic cell death	[156]
	S2-013, S2-VP10, and Hs766T metastatic pancreatic cancer cells	↑ATG5, ↑Beclin 1, ↓AKT/mTOR/p70S6K, ↑ERK pathway →Autophagic cell death	[164]
	MIA, PaCa-2, and PANC pancreatic cancer cells in vitro and in vivo	↑autophagosomes, ↑LC3-II, ↑ATG5, ↑ULK1, ↑VPS34, ↓mTOR, ↓PUMA →Autophagic cell death	[163]
	MG-6 human osteosarcoma cells	↑Beclin 1, ↑LC3-II, ↓p62, ↓VEGF, ↓HIF-1α, ↓Wnt/β catenin →Autophagic cell death	[157]
	SiHa Cervical cancer	↑p38, ↑MAPK, ↓PI3k/AKT/mTOR →Autophagic cell survival	[165]
	SKOV3/DDP ovarian cancer cells in vitro and in vivo	↑ROS, ↓ JAK2/STAT3 → Autophagic cell death	[166]
	SH-SY5Y and IMR-32 neuroblastoma cells	↑intracellular calcium, ↑LC3-II, ↓NFkB, ↓HSF1, ↓HSP70	[167]

Table 1 (continued)

Terpenoids	Cancer model	Autophagy mechanism and effects	Reference
	PC-3, LNCaP and C4-2 pancreatic cancer cells	↑intracellular calcium → ER stress, ↓mTOR, ↑ULK1, ↑Beclin 1, ↑CaMKKβ/AMPK →Autophagic cell survival	[160]

AIM2 absent in melanoma 2; *AKT* protein kinase B; *AMPK* AMP-activated kinase; *ATF4* Activating transcription factor 4; *ATG* autophagy-related gene; *Bcl-2* B-cell lymphoma 2; *CaMKKβ* Ca2+/CaM-dependent protein kinase kinase β; *CHOP* Cytoxan, Hydroxyrubicin,, Oncovin, Prednisone); *ERK* extracellular signal-regulated kinase; *JAK2* Janus Kinase 2 gene; *JNK* c-jun N-terminal kinase; HIF-1α, hypoxia-inducible factor 1-alpha; *HSF1* heat shock factor 1; *HSP70* heat shock protein 70; *IL-1β* Interleukin 1 beta; *LC3* microtubule-associated protein light chain 3; *MCT1* monocarboxylate transporter 1; *mTOR* mechanistic target of rapamycin; *NFkB* nuclear factor-kB; *p-* phosphorylated; *p70S6K* ribosomal protein S6 kinase beta-1; *PINK1* PTEN-induced kinase 1; *PI3K* phosphoinositide 3-kinase; *PUMA* p53 upregulated modulator of apoptosis; *ROS* reactive oxygen species; *STAT3* signal transducer and activator of transcription 3; *TRF2* telomeric repeat binding factor 2; *ULK1* Unc-51 like autophagy activating kinase; *VEGF* vascular endothelial growth factor; *VPS34* phosphatidylinositol 3-kinase

(Cal-27) cells [80]. DHA-treated cells presented with acidic vesicular organelles (autophagosomes and autolysosomes), increased expression of LC3-II protein, decreased p62 protein aggregation, and increased Beclin1 levels compared to control cells [59, 71–75, 78–80]. Furthermore, the MAPK/JNK signaling pathway was studied whereby it showed an increase in JNK phosphorylation that was dose- and time-dependent. JNK activation was decreased in cells that were pretreated with N-acetyl-L-cysteine (NAC, a ROS inhibitor) which suggests this process is ROS-dependent [67, 75, 81]. DHA promoted autophagy in tumor cells by suppressing the phosphorylation and activation of AKT/mTOR pathway [82]. On the other hand, NF-kB activation was suppressed in DHA-treated myeloma and ovarian cells in a dose-dependent manner and induced autophagic cell death [61, 72]. DHA-induced autophagy in cancer cells was ROS-dependent [62, 76]. Finally, Zhang et al. have demonstrated that co-treatment of glioma SKMG-4 cells with DHA and Temozolomide induced autophagy and was more effective at tumor inhibition efficacy in vitro and in vivo than in cells treated with Temozolomide alone [78].

Parthenolide and anticancer activities

Parthenolide**,** a 15-C terpenoids known as sesquiterpene lactone, is found in the feverfew tree (*Tanacetum parthenium*). It has many pharmacological effects such as anti-inflammatory, anti-bacterial, and anticancer and it is widely used for the treatment of headache, fever, and arthritis [83–85]. Parthenolide was found to target cancer stem cell (CSC) which drove the development of an analogue with more favorable pharmacological properties, the dimethylaminoparthenolide (DMAPT) [86, 87]. Parthenolide displays anticancer activities against many tumor types such as colorectal, melanoma, pancreatic, breast, prostate, cervical, renal, and thyroid [88–94]. It usually induces apoptosis through increasing oxidative stress, mitochondrial dysfunction, inhibiting NF-kB and mTOR/PI3K/AKT pathways, stimulating p53 signaling, regulating MAPK and JNK, interfering with STAT3, and controlling Bcl-2 family members [86, 93, 95–97].

Parthenolide and autophagy

Parthenolide administration in osteosarcoma cells resulted in ROS generation followed by autophagic cell death, suggesting a role of parthenolide in inducing autophagy and not apoptosis [98]. Similarly, treatment of MDA-MB231 breast cancer cells with parthenolide and DMAPT resulted in ROS generation, activation of JNK, downregulation of NF-kB, and autophagic cell death as indicated by enhanced Beclin1 expression and the conversion of LC3-I to LC3-II [99]. At a more advanced stage, ROS resulted in dissolution of the mitochondrial membrane and necrotic cell death. In a study done on pancreatic cancer cells, it was demonstrated that parthenolide induced autophagy as manifested by autophagosomes production and increase in LC3-II levels [100]. Additionally, blocking autophagy inhibited parthenolide-induced apoptosis, indicating that this drug inhibited proliferation of cancer cells by prompting autophagy-mediated apoptosis. On the other hand, parthenolide treatment of MCF-7 breast cancer cells resulted in activation of apoptosis pathway and ROS production leading to AMPK-autophagy pathway; a protective-survival mechanism rather than a cell death mechanism [92, 101]. In another study, parthenolide induced apoptosis as well as autophagy and inhibited proliferation of HepG2 human hepatocellular carcinoma cells [102] and breast cancer cells through inhibition of PI3K/AKT/mTOR pathway [103]. Treatment of human leukemic HL-60 and Jurkat cells with parthenolide resulted in atypical apoptosis briefly after caspase activation denoted by plasma membrane destruction [104]. Similarly, this sesquiterpene lactone also led to atypical necrosis that was indicated by prompt membrane rupture [104]. Parthenolide and several sesquiterpene lactones alter membrane integrity by affecting lipid oxidation and disruption [105]. Thyroid carcinoma cells treated with parthenolide resulted in induction

Table 2 Triterpenoids anticancer compounds as autophagic regulators

Terpenoid	Cancer models	Autophagy mechanism and effects	Reference
Triterpenoids			
Alisol	Hep3B, HepG2, HeLa, SK-BR-3, MDA-MB231, MCF-7, PC3, C666-1 cells	↑autophagosomes, ↑intracellular calcium→ ER stress, ↑CaMKK/AMPK/mTOR, ↑LC3-II, ↓p62/SQSTM1 →Autophagic cell death	[168]
	HCT116 colorectal cancer cells	↑LC3-II, ↓SQSTM1/p62, ↑ROS, ↑JNK →Autophagic cell death	[169]
	MDA-MB-231 breast cancer cells	↑autophagosomes, ↑LC3-II, ↓NF-kB pathway, ↓PI3K/AKT/mTOR, → Autophagic cell death	[172]
	MDA-MB-231 breast cancer cells	↑ROS, ↑LC3-II → Autophagic cell death	[307]
Betulinic acid	HeLa, A549, MCF-7, SW480 and U937 cells	↑autophagosomes, ↑LC3-II, ↓p62 ↓cytochrome c, mitochondrial damage → Autophagic cell death	[182]
	KM3 multiple myeloma	↑LC3-II, ↑p62, ↓Beclin 1 →Inhibits autophagy	[193]
	PLC/PRF/5 and MHCC79L hepatocellular carcinoma cells in vitro *and* in vivo	↑LC3-II, ↑p62, →Inhibits autophagy	[194]
	U87MG glioblastoma cells	↑LC3-II, ↓PI3K/AKT/mTOR, ↑autophagosomes, v Autophagic cell death	[195]
	HCT116, HT29, SW480 colorectal cancer cells	↓PI3K/AKT/mTOR pathway, → Autophagic cell survival	[196]
	HepG2 and SMMC-7721 hepatocellular carcinoma cells	↓PI3K/AKT/mTOR pathway, →Autophagic cell death	[186]
	BV-2 microglial	↑LC3-II,↑autophagosomes, ↑p62 →Inhibits autophagy	[189]
Oleanolic acid	A549 lung cancer and PANC-1 pancreatic cancer cells	↑LC3-II, ↑JNK pathway and ↓mTOR pathway, → Autophagic cell survival	[236]
	A549 lung cancer	↑ROS, PINK1 activation, ↑mitophagy → Autophagic cell survival	[237]
	SGC-7901, MGC-803, BGC-823 human gastric cancer cells in vitro *and* in vivo	↑LC3-II,↑autophagosomes, ↓PI3K/AKT/mTOR → Autophagic cell death	[238]
	HepG2 and SMC-7721 hepatocellular carcinoma cells	↑MSD uptake, ↑LC3-II, ↓PI3K/AKT/mTOR pathway, ↑ROS, → Autophagic cell death	[239]
	SMMC-7721 hepatocellular carcinoma cells	↓intracellular mitochondrial membrane potential, ↓ATP concentration, ↓p-AKT, ↓p-mTOR, ↓p62, ↑LC3-II, ↑Beclin 1 → Autophagic cell survival	[240]
	HepG2 in vitro *and* in vivo	↓Bcl2 → Autophagic cell death	[242]
	T24 and EJ bladder cancer cells	↑AMPK, ↓mTOR, ↑ULK1, v Autophagic cell survival	[246]
Platycodin D	PC-12 pheochromocytoma of rat adrenal medulla	↑ROS, ↓mitochondrial membrane potential, ↓Bcl-2, ↑Bid, ↑autophagic vesicles v Autophagic cell death	[269]
	HepG2 hepatocellular carcinoma cells	↑autophagic vesicles, ↑LC3-II, ↑autophagosomes, ↑ERK1/2 pathway, → Autophagic cell survival	[270]
	NCI-H460 and A549 non small cell lung cancer cells	↑ATG3, ↑ATG7, ↑Beclin 1, ↑LC3-II, ↓PI3K/AKT/mTOR, ↑JNK/p38MAPK, ↓p-ERK1/2, → Autophagic cell death	[271]
	RKO human colorectal cancer cells, A549 human lung adenocarcinoma epithelial cells, and MCF7 human breast adenocarcinoma cells	↑cytoplasmic pinocytic and autophagic vacuolation, ↑AMPK → Autophagic cell death	[272]

Table 2 (continued)

Terpenoid	Cancer models	Autophagy mechanism and effects	Reference
	BEL-7402 hepatoma cells in vitro *and* in vivo	↑cytoplasmic vacuoles, ↑LC3-II, ↑MSD uptake, ↓Bcl-2, ↑apoptosis, ↑ERK/JNK pathways, → Autophagic cell survival	[274]
	glioblastoma multiforme cells	↓autophagosomes degradation →Inhibits autophagy	[279]
Ursolic acid	T47D, MCF-7, and MDA-MB-231 breast cancer cells	↓PI3K/AKT, ↑GSK activity, ↓NFkB, ↑LC3-II, → Autophagic cell death	[296]
	MCF-7, MDA-MB-231, and SK-BR-3 breast cancer cells	↓p-ERK1/2, ↑ROS, ↓p-AKT and ↑-pATM, ↑AMPK, → Autophagic cell death	[287]
	TC-1 mouse hybridoma lymphoblast derived cervical cancer cells	↑cytoplasmic vacuoles, ↑LC3-II, ↑ATG5 → Autophagic cell death	[297]
	MCF-7 breast cancer cells	↑ER stress, ↑MAPK1/3 pathway → Autophagic cell death	[298]
	PC-3 prostate cancer cells	↑LC3-II, ↑MSD uptake, ↑autophagosomes, ↑Beclin 1, ↑ATG5, ↓AKT/mTOR → Autophagic cell survival	[300]

AKT protein kinase B; *AMPK* AMP-activated protein kinase; *ATG* autophagy-related gene; *ATM* ataxia-telangiectasia mutated Serine/Threonine Kinase; *Bcl2* B-cell lymphoma 2; *Bid* BH3-interacting domain death agonist; *CaMKK* calcium/calmodulin-dependent protein kinase; ER, sarcoplasmic/endoplasmic reticulum; *ERK* extracellular signal-regulated kinase; *GSK* glycogen synthase kinase; *JNK* c-jun N-terminal kinase; *LC3* microtubule-associated protein light chain 3; *MAPK* mitogen-activated protein kinase; *MSD* monodansylcadaverine; *mTOR* mechanistic target of rapamycin; *NF-kB* nuclear factor-kB; *p-* phosphorylated; *PI3K* phosphoinositide 3-kinase; *PINK* PTEN (Phosphatase and tensin homolog)-induced kinase; *ROS* reactive oxygen species; *SQSTM1* sequestosome 1; *ULK1* Unc-51 like autophagy activating kinase 1

of autophagy through an increase in LC3-II and Beclin1 [93] inhibiting autophagy by blocking ATG5 abrogated apoptosis [106].

Oridonin and anticancer activities

Oridonin is a natural tetracyclic diterpenoid extracted mainly from *Rabdosia rubescens* that exhibits potent antitumor properties in various types of human cancer cells [8, 107–111]. Oridonin was shown to act as an anti-inflammatory, anti-bacterial and anti-proliferative compound [112]. In vitro and in vivo studies revealed its antitumor effect on a variety of solid tumors including liver, pancreas, cervix, prostate, breast, lung, and colorectal cancers, fibrosarcoma, melanoma, and osteoma [107, 113–120]. Oridonin exhibited antitumor effects in different forms of leukemia, lymphoma, and multiple myeloma as well [110, 121]. This diterpenoid was shown to influence several cellular events such as cell cycle arrest, apoptosis, ferroptosis, autophagy, differentiation, angiogenesis, and metastasis [15, 122–124]. The major oridonin-induced cancer cell death mechanism is apoptosis [110]. Several studies reported that this diterpenoid was able to block the NF-kB pathway by disrupting NF-kB protein/DNA interaction [15, 110]. Moreover, the blockade of NF-kB and p38 pathways was preceded by AP-1 downregulation in response to oridonin treatment contributing to apoptosis in a colorectal cancer model [15]. Oridonin induced apoptosis in tumor cells through the suppression of PI3K/AKT signaling, forkhead box class O (FOXO) transcription factor expression, and glycogen synthase kinase 3 (GSK3) [15]. This diterpenoid inhibited epithelial mesenchymal transition (EMT) and halted metastasis by abrogating the AKT/STAT3 pathway in nasopharyngeal carcinoma cells [125]. Oridonin effect was p53-depended as a reversal in oridonin anti-proliferative activity was observed upon p53 inhibition by pifithrin-α in gastric cancer cells [109]. These findings were further supported by a study showing that apoptosis was the adopted cell death mechanism in wild-type p53 colorectal cancer (CRC) cells while other mechanisms were prompted in mutant p53 cancer cells such as autophagy [108]. Other studies revealed the contribution of caspase 3, caspase 8, Bcl-2/Bax, ROS, and cytochrome c in oridonin-induced apoptosis [107, 120, 126]. However, the detailed mechanism of the antitumor effect of this diterpenoid is yet to be elucidated, especially after the emerging indication regarding its influence on autophagy and its association with apoptosis.

Oridonin and autophagy

Reports in the literature described that autophagy is another cell death mechanism adopted by oridonin-treated cancer cells besides apoptosis [15, 108, 112, 127, 128]. However, the relationship between these two mechanisms remains controversial. [15, 112]. A study by Yao et al. stated an interesting finding that no significant apoptotic

activity was observed in oridonin-treated CRC SW480 cells, despite of its clear anti-proliferative effect [108]. The same report indicated that oridonin deactivated AMPK which downregulated the glucose transporter 1 (GLUT1) and the monocarboxylate transporter 1 (MCT1) both in vitro and in vivo, thus inhibiting glucose uptake and lactate export. However, ATP levels were not affected which suggests that oridonin is triggering autophagy: the major source of ATP in cancer cells. Others reported these two models of cell death frequently occur in parallel in tumor progression [74, 129]. Oridonin was shown to induce autophagy and apoptosis acting in synergy in fibrosarcoma [15] and breast cancer cells [112]. On the contrary, it was suggested that oridonin induced autophagy by activating PI3K/AKT, a signaling pathway that suppresses apoptosis. These observations were further supported by a study on CRC cells detecting LC3-II concomitant with rapid deactivation of p-AMPK upon oridonin treatment which confirmed the presence of autophagy and the inhibition of apoptosis [108].

Various studies demonstrated that oridonin induced pro-apoptotic autophagy in A549 lung cancer and PC3 prostate cancer cells [130, 131]. This was indicated by a decrease in the LC3B-1/LC3B-2 ratio and by an increase in Beclin 1 levels. Furthermore, the inhibition of autophagy by 3-MA led to a decrease in apoptotic bodies. This elucidates that autophagy acts in synergy with apoptosis in oridonin-treated cells. Additionally, the induction of autophagy was mainly through the inhibition of c-met (hepatocyte growth factor receptor) which is a potent inhibitor of the ERK signaling pathway. By this means, ERK pathway is induced which in turn activates the autophagic signaling pathways [130]. In normal liver cells THLE-2, oridonin activated autophagy and protected against steatosis [132].

In addition, co-treatment of oridonin with other therapeutics such as NVP-BEZ235 (inhibitor of AKT/mTOR pathway) and c-tocotrienol led to higher levels of LC3B-2 and Bcl-1 which highlights the importance of using combined treatments for cancer therapy [133, 134]. In fact, combining oridonin to chemotherapy and immunotherapy sensitized cancer cells to oridonin-induced apoptosis and activated autophagy [135–137].

In contrast with previous findings, oridonin induced anti-apoptotic autophagy in human multiple myeloma through the regulation of ROS and sirtuin 1 suggesting that autophagy acted as a protective mechanism against apoptosis [138]. This concurs with another study where autophagy, induced by this compound, inhibited apoptosis of human histiocytic lymphoma U937 cells through the regulation of inflammation [139]. Finally, further studies need to investigate the dichotomous effects of oridonin on autophagy and the signaling pathways involved.

Triptolide and anticancer activities

Triptolide, a compound found in the Chinese herb *Tripterygium wilfordii* Hook F [140], is a diterpene triepoxide that is mainly used in Chinese cultures for treating inflammation [141–143], fibrosis [144–146], kidney, neurological, and autoimmune diseases [8, 147–150]. This diterpene has anti-inflammatory and antioxidant characteristics which makes it an attractive drug for cancer therapy [151].

Triptolide inhibits growth of various cancer cell lines in vitro and in vivo, namely in prostate LNCaP and PC-3 [152, 153], pancreatic cancer PANC1, ASPC1, and SW1990 [154, 155], breast cancer MCF7 cells [156], and osteosarcoma MG63 cells [157], leukemia WEHI-3 [158], lung cancer A549 [143] and NSCLC NCI-H1299 and NCI-H460 [159], and CRC HCT116, CT26, HT29, CT16, and Raw264.7 cells [154, 160, 161]. Triptolide was shown to result in apoptosis by intrinsic and extrinsic mechanisms, triggering cellular stress and DNA damage, in evading immune surveillance [162], remodeling the immune microenvironment [161], and prompting tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) [163]. In addition, triptolide was shown to inhibit angiogenesis through HIF-1α and VEGF suppression [157] and metastasis through B-catenin reduction, therefore targeting EMT [159].

Triptolide and autophagy

The antitumor effects of triptolide were initially demonstrated to be only apoptotic. However, recent studies have shown that triptolide also induces autophagy in several cancer types [150]. Compelling evidence showed that this compound induced autophagy in in vitro and in vivo tumor models, in murine leukemia, breast cancer, pancreatic cancer [156, 158, 163, 164], osteosarcoma [157], and cervical cancer [165]. When treated with triptolide, tumor cells exhibited high levels of LC3B-II, Beclin 1, and autophagolysosomes. In addition, an increase in autophagic markers such as ATG5, ATG7, and ATG12 was detected. Importantly, it was reported that triptolide-induced autophagy activates ERK1/2 and inhibits AKT/mTOR pathway [156, 165]. Furthermore, triptolide activated p38, p53, and MAPK while inhibiting forkhead box O3 (Foxo3a). In osteosarcoma cells, triptolide triggered autophagy by reducing the Wnt/βcatenin signaling [157]. Interestingly, in the presence of the autophagy inhibitor 3-MA, apoptosis was triggered which indicates one more time the presence of a cross-talk between autophagy and apoptosis [164]. In ovarian cancer cells SKOV3/DDP that are resistant to

cisplatin, triptolide inhibited JAK2/STAT3 pathway, and induced ROS which resulted in lethal autophagy [166]. Another study demonstrated that triptolide increased intracellular calcium (Ca^{2+}) in SY5Y neuroblastoma cells by inhibiting NF-κB pathway and by decreasing heat shock factor 1 (HSF1) and HSP70. The high levels of intracellular Ca^{2+} [167] and the inhibition of mTOR triggered cell death by autophagy [160]. On the other hand, the inhibition of autophagy in triptolide-treated PC-3 cells increased the cytotoxicity of this compound suggesting that autophagy was triggered as a protective survival mechanism against the cytotoxic effect of triptolide [164]. Therefore, new studies have shown the possibility considering the combination of triptolide with autophagy inhibitors to surpass its induced chemoresistance.

Alisol and anticancer activities

Alisol and derivatives are natural triterpenoids of protostane-type extracted from the Chinese medical herb, rhizomes of *Alisma orientale* [15, 168, 169]. Wide range of physiological activities were reported by alisol including treatment of hypertension, hyperlipidemia, osteoporotic, and urological disorders [15]. Importantly, these compounds have anti-metabolic, anti-viral, anti-bacterial, anti-inflammatory, immunomodulatory, and anticancer activities [152, 154]. Alisol has shown antitumor activities in breast, prostate, gastric, CRC, liver, and ovarian cancers [168–174]. Alisol mediated cell cycle arrest at either G1 phase, via CDK4, 6 and cyclin D1 downregulation [168, 169], or G2/M phase [15] followed by cell death. Inhibiting PI3K/AKT pathway was also shown to be involved in the apoptosis induction of cancer cells [15, 170, 171].This triterpenoid caused PARP, caspase-3, and caspase-9 cleavage, increased Bax/Bcl2 [175], increased ROS [174], and induced Apaf-1 in cancer cells [171]. It also decreased MMP2 and MMP9, resulting in reduced migration and invasion. Finally, alisol chemosensitized tumor cells by blocking P-glycoprotein-mediated drug resistance [176, 177].

Alisol and autophagy

Studies have shown that alisol induced Ca^{2+} mobilization from internal stores [168] causing endoplasmic reticulum stress [15]. This also triggered autophagy through the activation of CaMKK-AMPK-mTOR pathway [168]. Concomitantly, the disruption of calcium homeostasis activated apoptosis in alisol-treated cells [15, 168]. Notably, this compound targets and blocks the sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase (SERCA) leading to the above-mentioned consequences [15, 168]. A study in CRC revealed that upon treatment with alisol, an increase in the LC3-II was observed simultaneously with a degradation of p62/QSTM1 [168] and thus leading to the activation of autophagy [129, 178–180]. These results were further supported as 3-MA inhibition of autophagy led to apoptosis abrogation as well [169]. The same study demonstrated that inhibiting ROS or phosphorylation of JNK, that are induced by alisol treatment, attenuated autophagy. Alisol-treated breast cancer cells increased LC3-II and ROS production, induced DNA damage, and promoted autophagy-dependent apoptosis [172, 173]. All these findings indicate that in cancer cells, alisol leads to apoptotic cell death induced by autophagy.

Betulinic acid and anticancer activities

Betulinic acid is a pentacyclic triterpene with lupane skeleton extracted generally from the bark of the white birch tree [35, 181–185]. This compound has been reported to have a plethora of bioactivities against the human immunodeficiency virus (HIV), herpes simplex viruses-1 (HSV-1), bacteria, malaria, helminths, pain, inflammation, immunomodulation, angiogenesis, metastasis [184, 185], and anticancer activities [35, 181–185]. This antitumor activity is believed to be mediated mainly through the mitochondrial pathway of apoptosis leading to the death of cancer cells [35, 181, 182, 185]. Betulinic acid showed high selectivity to tumor versus normal cells [186]. Hela cells treated with betulinic acid triggered ER pathway and ROS-mediated mitochondrial pathways leading to apoptosis [187]. Using caspase inhibitors failed to block apoptosis in the same treated cells [182]. Additional features of apoptosis were prominent upon betulinic acid treatment in different cancer types, such as DNA fragmentation [188, 189], upregulation of Bak and Bax protein levels [182], augmentation of cytochrome c release, caspases 3, 8, and 9 activation, ROS generation [190], and inhibition of migration and invasion [191]. Furthermore, the apoptotic activity of betulinic acid was enhanced by hypoxic conditions in NSCLC cells [192]. Several animal models of human cancers confirmed the antitumor potential of betulinic acid [185].

Betulinic acid and autophagy

Autophagy was shown to have a great impact in several betulinic acid-treated tumor cells; however, it was inhibited by cyclosporine A (CsA), an inhibitor of the mitochondrial membrane permeability transition pore. Blocking cytochrome c release from mitochondria, inhibited autophagy, thus implying that the latter occurred via mitochondrial damage [182]. However, caspase 3 induction resulted in a decrease in Beclin 1 levels showing that

betulinic acid treatment in multiple myeloma KM3 cells blocked autophagy while enhancing apoptosis [193]. Betulinic acid induced cell death by autophagy-independent apoptosis in hepatocellular carcinoma cells [194]. A semisynthetic derivative of betulinic acid inhibited the phosphorylation of AKT and induced autophagy in glioblastoma cells [195]. Inhibiting autophagy by RNAi of ATG7, ATG5, or Beclin 1 led to inhibition of lysosomal cell death and caspase-3 mediated apoptosis. Similar results were obtained in different tumor cells where betulinic acid inhibited cellular growth, triggered apoptosis, and induced autophagy via blocking PI3K/AKT/mTOR signaling pathway [186, 196]. Betulinic acid treatment of microglial BV-2 cells led to the increase of LC3-II levels and the formation of autophagosomes [189]. However, the observed accumulation of p62 indicates a blockade of autophagy, meanwhile apoptosis was still taking place.

Oleanolic acid and anticancer activities

Oleanolic acid, a multifunctional pentacyclic triterpenoid, has been isolated from several fruits and medicinal herbs [197–201]. It has numerous biological activities which include anti-inflammatory [202], antioxidant [203], anti-diabetic [204], anti-HIV [205], hepato-protective [206, 207], and prevents cardiovascular disease progression [208, 209]. In addition, it has a marked anticancer activity in several types of tumors [210–216]. Its antitumor activity affects initiation, proliferation, cell cycle arrest, apoptotic induction, ferroptosis, angiogenesis, invasion, migration, and metastasis [178, 179, 215, 217–229]. Many studies have shown that oleanolic acid and its derivatives have anticancer effects through the activation of the intrinsic and extrinsic cell death pathways in breast cancer cells [178], induction of cell cycle arrest in human leukemia K562 cells [179], and attenuation of the NF-κB pathway and thus cytokine production and cell survival in human liver cancer Huh7 cells [230]. Oleanolic acid mainly causes cell death through apoptosis by increasing the ratio of Bax to Bcl-2, releasing cytochrome c, and leading to mitochondrial cell death [230, 231]. Furthermore, oleanolic acid reduced PDL1 and DNA demethylase TET3 expression, and NF-κB activity in gastric cancer cells suggesting that this triterpenoid can be further considered as an epigenetic and immunotherapy modulator [232]. Oleanolic acid enhanced apoptosis and reduced multi-drug resistance in lung cancer cells by nanoparticle formulation with cisplatin [233]. However, the non-specificity, side effects, and poor water solubility has driven research into creating oleanolic acid synthetic derivatives that would enhance its efficacy and pharmacological properties [234, 235].

Oleanolic acid and autophagy

Recently, several studies reported yet another oleanolic acid antitumor mechanism which involves a dose and time-dependent autophagy induction in a wide panel of human cancer cell lines: lung A549, breast MCF-7, osteosarcoma U2OS, pancreatic BXPC3, prostate PANC-1 and PC-3 [236, 237], gastric SGC-7901, MGC-803, and BGC-823 cells [238], hepatocellular carcinoma HepG2 and SMC7721 [239, 240], Lv-KRAS12V-infected MCF10A and gastric mucosal cells [241]. Interestingly, oleanolic acid can induce autophagy in normal cells as well but without cytotoxicity, as such cell survival is not affected [241]. Moreover, inhibition of certain cancer cells proliferation and invasiveness was primarily via an autophagy-dependent mechanism, for this inhibition was abolished in the presence of an autophagy inhibitor which was demonstrated in vitro and in vivo [238, 239, 241, 242]. Meanwhile, in other cancer cell lines, autophagy inhibition potentiated the apoptotic death of cancer cells treated with this triterpenoid [236, 238]. Concerning the signaling pathways involved, it was shown that oleanolic acid-induced autophagy is mediated via JNK activation and mTOR suppression, whereby an increase in phosphorylated c-Jun with a dose-dependent decrease in the expression of phosphorylated RPS6KB1, RPS6 (ribosomal protein S6), 4EBP1 (eukaryotic translation initiation factor 4E binding protein 1), PI3K, and AKT were observed [236, 239, 241]. Furthermore, ROS plays a pivotal role in autophagy induction by oleanolic acid [243–245]. A dose-dependent early increase in ROS was reported in Oleanolic acid HepG2 cells. ROS, such as superoxide (O^{2-}), hydroxyl radical (HO^{-}), and hydrogen peroxide (H_2O_2) causes buildup of the ATG8-phosphoethanolamine precursor for autophagosome formation by inactivating the cysteine protease ATG4, hence directly activating autophagy [244]. NAC pretreated cells resulted in a significant decrease in LC3-II production and cell death. Therefore, oleanolic acid-induced autophagy in HepG2 cells is ROS dependent [239]. On the other hand, this compound can initiate autophagy as a protective mechanism and inhibit the pro-apoptotic effect of this drug in cancer cells either through the activation of JNK pathway in a number of cancer cells or alteration of the AMPK-mTOR-ULK-1 signaling pathway [236, 240, 242, 246]. Therefore, combining oleanolic acid with autophagy inhibitors may enhance the antitumor properties of this compound. Mitophagy is a mechanism by which autophagy targets and degrades mitochondria, resulting in cell survival or death [247]. In lung cancer A541 oleanolic acid-treated cells, mitophagy was observed dependent on PINK1 activation [237].

Platycodin D and anticancer activities

Platycodin D, isolated from the Chinese medicinal herb *Platycodonis Radix*, is a triterpenoid saponin with an eclectic variety of activities, namely anti-inflammatory [248, 249], anti-nociceptive [250], anti-obesity [251, 252], anti-atherogenic [253], immune-stimulatory [254], and neuroprotective [255]. In addition, it exhibits antitumor activity on diverse cancer types both in vitro and in vivo. The broad spectrum of cytotoxicity it has on tumor cells occurs via multiple mechanisms of action that involve proliferation suppression [256–259], cell cycle arrest, and apoptosis induction through inhibition of NF-κB, PI3K/AKT, and JAK2/STAT3 pathways [256, 257, 260–264], angiogenesis, invasion, and metastasis inhibition [263, 265, 266]. Platycodin D reversed chemotherapy resistance via histone deacetylase inhibitor (HDACi) and ERK1/2 inhibition in hepatocellular carcinoma cells [267].

Platycodin D and autophagy

Morphological features such as cytoplasmic vacuole accumulation is often observed in cells undergoing autophagy [268]. Several studies demonstrated how various human cancer dosages of platycodin D in prostate PC-12 [269], hepatocellular HepG2 and Hep3B, breast MCF-7, MDA-MB-231, lung A549 and 95D [270], and NCI-H460 [271], CRC RKO cells [272], and CML K562 cells [273]. Results showed that LC3-II levels increased in a concentration- and time-dependent manner in hepatoma BEL-7402 cells in addition to all the previously mentioned cancer cell lines [269–271, 274]. However, platycodin D-triggered autophagy seems to be a universal phenomenon, for non-cancer cell lines as LO-2 and H9c2 formed cytoplasmic vacuoles in association with up-regulation of LC3-II as well, however without being cytotoxic [270].

AKT/mTOR pathway is a one of the crucial regulatory pathways of autophagy [275]. However, platycodin D-induced autophagy in HepG2, NCI-H460, and A549 cells was shown to be independent of this pathway. Instead, autophagy was mediated through MAPK signaling pathway in the hepatocellular and lung carcinoma cancer cells [270, 271]. Moreover, in BEL-7402 cells, ERK and JNK pathways cooperate to regulate platycodin D- triggered autophagy. This triterpenoid increased c-Jun phosphorylation at Ser73 which is the site of JNK regulation [276]. Pretreatment with SP600125, an inhibitor of JNK [277], blocked c-Jun phosphorylation which resulted in a decrease of LC3-II. Co- and pre-treatment of cells with SP600126 and U0126 (inhibitor of MEK) [278] blocked both ERK and JNK pathways, resulting in suppression of platycodin D-induced LC3-II expression [274]. In therapy regimen that combines platycodin D and chloroquine or bafilomycin A1, both autophagy inhibitors, is a promising regimen for hepatocellular carcinoma treatment since it enhanced platycodin D-induced cytotoxicity and apoptosis in HepG2 and BEL-7402 cells [270, 274]. Recently, Platycodin D treatment was shown to inhibit autophagy while promoting cell death in glioblastoma cells [279].

Ursolic acid and anticancer activities

Ursolic acid is a pentacyclic triterpenoid which is extracted from medicinal herbs such as *Rosmarinns officinalis*, *Ocimum sanctum*, and *Eriobotrya japonica* [235, 280]. It is known that ursolic acid has low toxicity, anti-proliferative [281–283], anti-inflammatory [284, 285], and immuno-modulatory properties [286]. In addition, ursolic acid selectively inhibits the growth of numerous cancer cell types via cell cycle arrest, increase in p21, and promotion of oxidative stress and DNA damage [287], increase in JNK-dependent lysosomal associated cell death [288], activation of p53 [289], and induction of apoptosis [290], mainly through intrinsic mechanism [291]. The key immune checkpoints programmed cell death protein 1 (PD-1) and its ligand PDL-1 were downregulated by ursolic acid in treated tumor cells [292, 293]. Recently, ursolic acid was shown to suppress Wnt signaling in breast cancer stem cells [294].

Ursolic acid and autophagy

Recently, it was shown that ursolic acid induced cell death of cancer cells via autophagy through the PI3K-AKT-GSK signaling pathway [295]. In T47D breast cancer cells, ursolic acid downregulated PI3K/AKT which in turn increased GSK levels. Activation of GSK downregulated cyclin D1 which is an essential inhibitor of autophagy [296]. A similar study demonstrated that ursolic acid induced oxidative stress which decreased phosphorylated AKT and increased phosphorylated ATM. This led to a high elevation of AMPK which triggered cytotoxic autophagy [287]. Similarly, this triterpenoid induced autophagy in TC-1 cervical cancer cells by the regulation of ATG5 and through the PI3K signaling pathway [297]. However, ursolic acid induced autophagy in MCF-7 human breast cancer cells through the activation of MAPK1/3 pathway and not through the inhibition of mTOR which highlights the ubiquitous effects of this compound [298]. In addition, ursolic acid can be a potent stimulator of autophagy when combined with other molecules. A study indicated that the synergistic effects of ursolic acid and ZOL (inhibitor of osteoclast-mediated bone resorption)

induced autophagy in osteosarcoma cells, whereas this triterpenoid alone did not show any effects [299]. In contrast with previous results, ursolic acid can also induce protective autophagy against apoptosis. A study conducted on prostate cancer PC3 cells showed that treatment with a low dose of ursolic acid increased the levels of LC3B-II and the number of autophagolysosomes [300]. It was reported also that Beclin 1 and ATG5 played a major role in the induction of autophagy which was mediated through the AKT/mTOR pathway. However, when inhibiting autophagy, there was a reduction in cell viability and enhanced apoptosis postulating that autophagy acted as a protective mechanism against cell death [300–303]. Combining ursolic acid to chemotherapy promoted ER stress induced apoptosis and sensitized tumor cells [304].

Conclusion

Evading cell death is one of the crucial hallmarks of cancer whereby a wide range of therapeutics are now targeting these latter signaling pathways [305]. Accumulating evidence suggests that autophagy plays an important role in carcinogenesis; therefore, targeting autophagic signaling pathways could be a novel therapeutic potential against cancer. Interestingly, terpenoids have been demonstrated to trigger molecular mechanisms by which cell death by autophagy is induced in cancer cells. These natural compounds have been studied for their role in treating inflammation, autoimmune diseases, and cancer. Studies report apoptosis as the major mechanism through which terpenoids induce cell death. However, the role of autophagy remained elusive. In this review, we highlighted the importance of representative terpenoids in inducing autophagic cell death in cancer cells, alongside their use as cancer therapeutics. It was demonstrated that the discussed terpenoids induced autophagy via many signaling pathways such as MAPK/ERK/JNK, PI3K/AKT/mTOR, AMPK, NF-kB, and ROS (Fig. 2). This highlights the numerous mechanisms by which terpenoids induce autophagy. In fact, combining terpenoids with chemotherapeutics sensitized tumor cells to cell death. In addition, this review sheds light on the intricate relationship between apoptosis and autophagy. Even though these two processes have their own molecular and physiological pathways, they seem to crosstalk under certain circumstances. It was shown that autophagy can counteract apoptosis as a tumor survival mechanism, while in other cases it promoted apoptotic cell death in a synergistic way. Therefore, due to the complex dichotomy of autophagy, deciphering its role in tumorigenesis would open new possibilities in cancer therapeutics. Activating autophagy in some cancer cells may increase their sensitivity to apoptosis while inhibiting autophagy in others may enhance apoptotic cell death. This review highlighted the major contribution of triterpenoids in plant-derived autophagic modulators. It remains to be determined whether any chemical structure in this terpenoid subclass enhanced autophagy induction in treated tumor cells. In conclusion, the effects of terpenoids on autophagy need more investigation to fully understand the complexity of the signaling pathways involved and to build a more effective therapeutic strategy against cancer.

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Conflict of interest Disclosure of conflict of interest none.

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