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Phytochemicals as potent modulators of autophagy for cancer therapy

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ABSTRACT

The dysregulation of autophagy is involved in the pathogenesis of a broad range of diseases, and accordingly universal research efforts have focused on exploring novel compounds with autophagy-modulating properties. While a number of synthetic autophagy modulators have been identified as promising cancer therapy candidates, autophagy-modulating phytochemicals have also attracted attention as potential treatments with minimal side effects. In this review, we firstly highlight the importance of autophagy and its relevance in the pathogenesis and treatment of cancer. Subsequently, we present the data on common phytochemicals and their mechanism of action as autophagy modulators. Finally, we discuss the challenges associated with harnessing the autophagic potential of phytochemicals for cancer therapy.

Introduction

Phytochemicals (*phyton* means "plant" in Greek) are naturally occurring plant-based compounds. They are mostly composed of non-nutrient chemicals that are found in grains, vegetables, and fruits [1,2]. While over ten thousand phytochemicals have been identified, many others remain unknown and need to be identified [1–3]. Important groups of phytochemicals include phenolic compounds, alkaloids, terpenes, organosulfides, and glucosinolates [1,4,5]. The health benefits of phytochemicals are mostly associated with reducing the risk of developing diverse human diseases [3,5,6]. Such plant-based compounds are easily accessible, often with less toxic effects than synthetic molecules, and possess a wide range of biological and pharmacological effects, including anti-microbial, anti-tumoral, anti-mutagenic, and anti-oxidant or pro-oxidant activities [1,3,5–9]. Positive outcomes in clinical trials have led to the introduction of several phytochemicals into clinical practice in recent decades [6,10]. Particularly in cancer and other chronic diseases that are associated with excessive production of reactive oxygen species (ROS), both the anti-oxidant and pro-oxidant properties of phytochemicals can be utilized to prevent or eradicate cancer, respectively [3,9,11–13]. For example, enriched flavonoids from vegetables and fruits show potent ROS modulating and anti-cancer effects, alone or in combination with standard chemotherapy [14]. Mechanistically, the anti-cancer effects of

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Abbreviations

ATF4	(Activating transcription factor 4)
ATGs	(Autophagy-related genes)
Akt	(Protein kinase B)
Baf A1	(Bafilomycin A1)
BAX	(Bcl-2-associated X protein)
Bcl-2	(B-cell lymphoma 2)
Bcl-xL	(B-cell lymphoma-extra large)
Bif-1	(Bax interacting factor 1)
Ca	(Calcium)
CDK	(Cyclin-dependent kinase)
c-FLIP	(Cellular-FLICE inhibitory protein)
CGL	(Chronic granulocytic leukemia)
CHOP	(C/EBP homologous protein)
CMA	(Chaperone-mediated autophagy)
C_{max}	(Maximum plasma drug concentration)
COX-2	(Cyclooxygenase-2)
CQ	(Chloroquine)
CSCs	(Cancer stem cells)
EGCG	(Epigallocatechin-3-gallate)
EGFR	(Epidermal growth factor receptor)
ER	(Endoplasmic reticulum)
ERK	(Extracellular-signal-regulated kinase)
FoXO3	Forkhead box O3
5-FU	(5-fluorouracil)
GRP78	(Glucose regulated protein 78)
HCQ	(Hydroxychloroquine)
HIF-1α	(Hypoxia-induced factor 1α)
HO-1	(Heme oxygenase 1)
HSP72	(Heat shock protein hsp72)
IGF-I	(Insulin-like growth factor)
IRE1	(Inositol-requiring protein-1)
JNK	(c-Jun N-terminal kinase)
Keap1	(Kelch-like ECH-associated protein 1)
LAMP-1	(Lysosome-associated membrane proteins 1)
LC3	(Light chain 3 complexes)
3-MA	(3-methyladenine)
MAPK	(A mitogen-activated protein kinase)
miR	(microRNAs)
mTOR	(Mammalian target of rapamycin)
NF-κB	(Nuclear factor kappa-light-chain-enhancer of activated B cells)
Nrf2	(Nuclear factor E2-related factor2)
3′-ODI	(3′-hydroxydaidzein)
PARP	(Poly ADP-ribose polymerase)
PAS	(Pre-autophagosomal structure)
PE	(Phosphatidylethanolamine)
PERK	(Protein kinase RNA-like endoplasmic reticulum kinase)
PI3K	(Phosphatidylinositol-3-phosphate kinase)
PKC	(Protein kinase C)
PRKA	(Protein kinase A)
p-STAT3	(Phosphorylation of signal transducer and activator of transcription 3)
PTEN	(Phosphatase and tensin homolog)
ROS	(Reactive oxygen species)
SIRT1	(Silent mating type information regulation 1)
SQSTM1	(Sequestosome 1)
TFEB	(Transcriptional factor EB)
T_{max}	(Time at which Cmax is attained)
TNF-α	(Tumor Necrosis Factor alpha)
TRAIL	(TNF-related apoptosis-inducing ligand)
TSC2	(Tuberous Sclerosis Complex 2)
TUNEL	(Terminal deoxynucleotidyl transferase dUTP nick end labeling)
ULK	(Unc-51-like kinase)
UPR	(Unfolded protein response)
UVRAG	(UV radiation resistance-associated)
VEGF	(Vascular endothelial growth factor)

phytochemicals are mostly mediated through induction of cell-cycle arrest or apoptotic cell death [7–9,15]. In addition, recent studies have uncovered an important role for phytochemicals in governing the autophagy network [7,15–17]. In both normal and malignant cells, autophagy is induced by certain cellular stresses in order to preserve cell survival [18,19]. However, if the stress is not resolved, autophagy leads ultimately to programmed cell death [18–22]. In the context of cancer, autophagy acts as a tumor suppressor at early steps of tumorigenesis. Alternatively, autophagy can promote the growth and survival of established tumors during migration and epithelial-to-mesenchymal transition (EMT) as well as in response to chemotherapy [18,23,24]. In addition, autophagy is involved in cancer stem cell (CSC) survival, escape from immune surveillance and resistance to anoikis [25]. Therefore, autophagy with a double face role inhibits early stages of tumorigenesis while it becomes a driver of tumor invasion and metastasis at later stages [26–28]. Accordingly, manipulation of key factors in the autophagy pathway may be exploited as a novel therapeutic strategy for cancer therapies [20]. However, before proposing phytochemical as anti-cancer and autophagy-modulating agents, a better understanding of their complex mechanism of action needs to be addressed more deeply [5,16,17]. In this review, we represent common phytochemicals as a group of promising autophagy modulators and discuss their therapeutic importance in treating various cancers.

Autophagy in cancer

Autophagy machinery and its regulation

The term “autophagy” was coined by Christian de Duve in 1963. It was derived from Greek meaning “eating of self” [29]. Macro-autophagy (hereafter called autophagy) is responsible for the turnover of cellular components that are sequestered into the double-membrane-bound vesicle, called autophagosome that originates from a precursor structure called phagophore [19,30]. The primarily goal of autophagy is to sustain cell survival under stressful conditions (e.g., starvation and nutrient deprivation) through the recycling of cargo (proteins, organelles, and other cytoplasmic components). Most autophagy stimuli converge at the PI3K/Akt/mTOR pathway. The mammalian target of rapamycin (mTOR) is an important regulator of autophagy that forms two distinct complexes, including mTOR complex1 (mTORC1) and mTORC2. Generally, class I PI3K acts as a negative regulator of autophagy via the mTORC1 pathway. In contrast, class III PI3K is an initiator of autophagy [18,19]. Under normal physiological conditions, mTORC1 phosphorylates Unc-51-like kinase 1/2 (ULK1/2) and autophagy-related gene 13 (Atg13) to inhibit initiation of autophagy process. On the other hand, inactivation of mTORC1 by starvation or other kinds of stress activates the ULK, also known as the ATG1 complex and, in turn, initiates the autophagy pathway

[30,31]. After initiation of autophagy, the class III PI3K complex binds to its core units, including Beclin 1 (the mammalian ortholog of the yeast Atg6) and facilitates the recruitment of other ATGs on the isolation membranes (phagophores) to form autophagosomes (Fig. 1) [30,31]. During autophagosome elongation and maturation, two ubiquitin-like protein systems, including the Atg5–Atg12 and Atg8/microtubule-associated protein light chain 3 (LC3) complex, are involved (Fig. 1). The Atg5–Atg12 complex is conjugated with Atg16L, forming the multimeric Atg5–Atg12–Atg16L complex. LC3 is cleaved by Atg4 to form LC3I and then conjugated to phosphatidylethanolamine (PE) by Atg7 and Atg3 to form LC3II. Following lipidation, LC3II is inserted into the autophagosomal membrane and recruits selective substrates [31] via binding to the autophagic receptor protein p62/SQSTM (p62). Following cargo engraftment, lysosome-associated membrane proteins (LAMP1/2) play a critical role for fusing autophagosomes with the lysosome. Inside the lysosome, cathepsin proteases B and D are required for the maturation of autolysosomes or autophagolysosomes [30,31]. The end-products of autophagy include basic cellular components such as amino acids, which is released into the cytosol by permeases [30,31].

Dual role of autophagy in pathogenesis of cancer

As an adaptive response, autophagy plays an indispensable role in maintaining homeostasis, so that its dysregulation leads to various human diseases, including neurodegenerative disorders and cancer [18,32]. Autophagy has diverse functions in cancer. In the early oncogenic process, autophagy acts as a tumor suppressor. It prevents cellular transformation by maintaining genetic instability and modulating ROS within cells [18,20,27]. Furthermore, emerging evidence has linked defects in autophagy with malignant transformation of CSCs. Under these conditions, autophagy induction seems to be an effective strategy to prevent early tumor formation and development. However, there is another side of the coin where autophagy is required for maintaining the survival of established tumors and CSCs, as well as escape from immune surveillance and resistance to anoikis. Its inhibition could therefore be a beneficial approach in the treatment of cancer [20,24,28]. In addition, autophagy has a dual role in the promotion and inhibition of metastasis. In its early steps, autophagy inhibits metastasis, whereas it becomes a driver of metastasis at later stages [26–28]. The poorly vascularized tumor can survive under low oxygen, low nutrient, TGF-β and other signals by activating autophagy [24,26,27]. Also, autophagy is a direct regulator of the metastatic cascade, particularly during cancer cell migration, invasion and EMT. Autophagy promotes tumor cell migration and focal adhesions turnover via p62-mediated degradation of RhoA GTPase [33]. Fig. 2 illustrates the importance of autophagy at different stages of tumorigenesis. Several autophagic phytochemicals, including anthocyanins, camptothecin, gingerols, and hispolon have shown potent anti-metastatic properties that will be discussed in section 3.

Moreover, the extrinsic resistance of cancer cells is a major problem during chemo- and radiotherapies [23,24,27]. This might be mediated, at least in part, by the protective role of autophagy [23,24,28]. In this regard, inhibition of autophagy sensitizes colon, esophageal and colorectal cells to the therapeutic effect of 5-fluorouracil (5-FU) or cisplatin [34]. Some examples related to the beneficial effects of phytochemicals in combination with autophagy inhibitors in cancer models are provided in Table 1.

Main oncogenes and tumor suppressors involved in autophagy

ATG genes

BECN1 gene encodes the Beclin1 protein that is primarily known as a tumor suppressor in mammalian cells (Fig. 3) [35]. The expression of this autophagic gene is inhibited in different cancers, including breast cancer, prostate, brain, and ovarian cancers [23,36,37]. Deletions or mutations of Atg4, 5, 9, and 12 have also been reported in various cancers. In addition, mutation of Atg4C, as well as deletion of Atg5 and Atg7, have induced tumorigenesis in different models [23,34,36,37]. Loss of Bax interacting factor 1 (Bif-1), a potent regulator of apoptosis and autophagy, is associated with colon adenocarcinoma. Moreover, a mutation in the UV radiation resistance-associated (UVRAG) gene, a protein that interacts with Beclin1, promotes gastric and colorectal tumor formation by inhibiting autophagy [23,34,36,37].

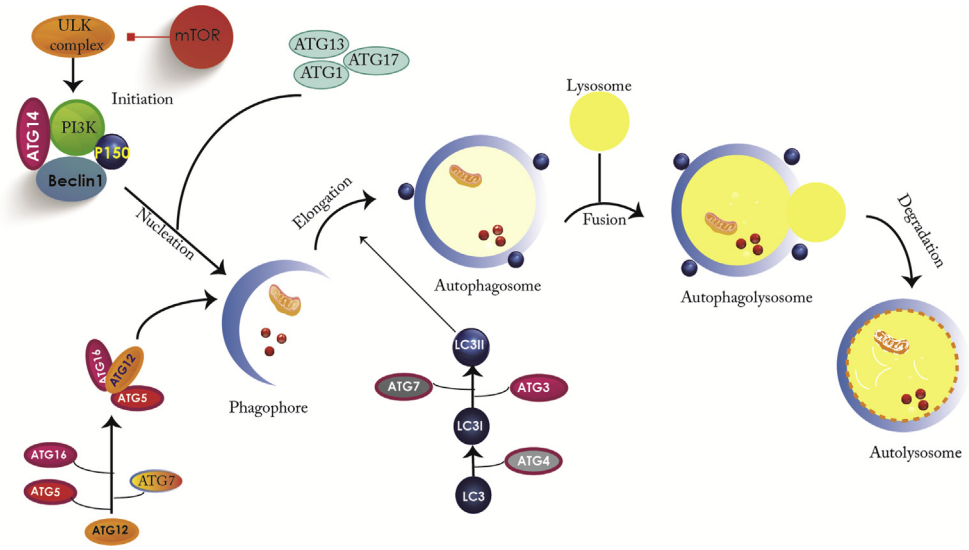


Fig. 1. Macroautophagy process and its mechanism of action. Macroautophagy is initiated by the inhibition of the kinases mammalian target of rapamycin (mTOR) and recruiting class III phosphatidylinositol (PI3K) complex to form phagophores. Two ubiquitin-like (ULK) protein complexes Atg12-Atg5 and Atg8/LC3 mediate nucleation and elongation steps, respectively, leading to formation of autophagosomes. Autophagosomes are then fused with lysosomes to degrade cargo into structures called autolysosomes.

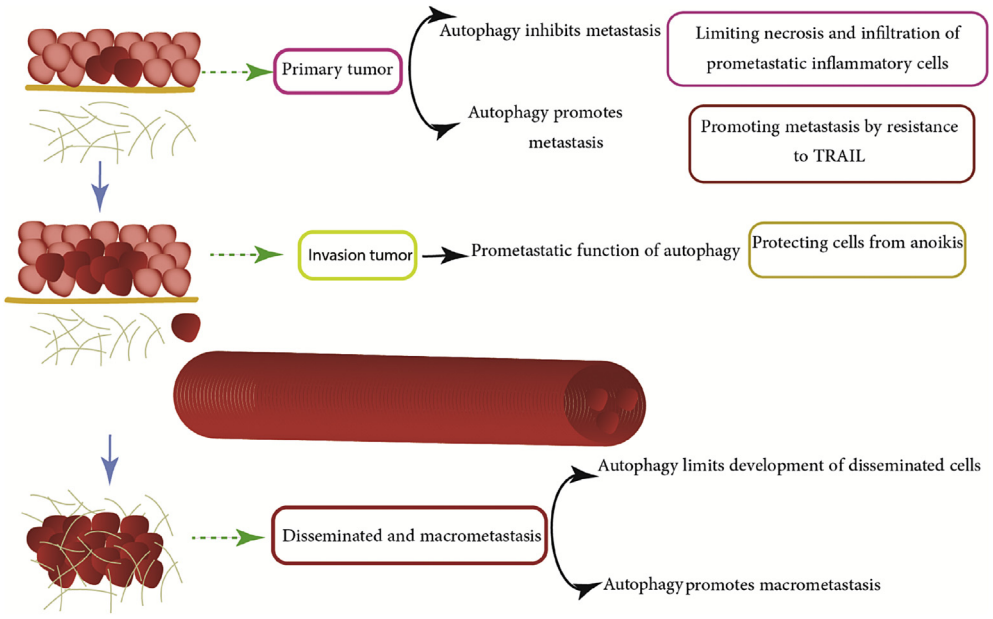


Fig. 2. Dual functions of autophagy during invasion and metastasis of cancer. Autophagy inhibits or promotes cancer based on the type and stage of the tumor. In primary tumors, autophagy initially suppresses metastasis through releasing anti-metastatic factors and then promotes tumor maintenance and progression by allowing the cells to resist against tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis. During invasion stage that cancerous cells spread and enter into the systemic vasculature (lymphatic or blood vessels), autophagy plays a pro-metastatic role via protecting the cells from anoikis activated by cell/extracellular matrix detachment. At macrometastatic stage, autophagy may limit the development of disseminated cancer cells by induction of their dormancy or may inversely sustain cell survival and drug resistance for adapting them to the new microenvironments.

Table 1
Mechanisms of action of some phytochemicals and chemotherapeutic agents, alone or in combination with the autophagy inhibitors bafilomycin A1 (Baf A1), chloroquine (CQ) or 3-methyladenine (3-MA).

Chemicals/ phytochemicals	Mechanisms	Consequence of combination with autophagy inhibitors	Ref
Imantinib mesylate	A tyrosine kinase inhibitor that induces differentiation, apoptosis and autophagy in leukemia cells	Combination with CQ or Baf A1 increases cell death both *in vivo* and *in vitro*	[330]
Saracatinib	Cell-cycle arrest and inhibition of invasion in prostate cancer through autophagy or apoptosis induction	Combination with CQ increases mortality and decrease tumor growth in mice prostate cancer model	[330]
Fluorouracil	An anti-metabolite that induces autophagy and apoptosis	Combination with 3-MA enhances apoptotic cell death	[331,332]
Suberoylanilide hydroxamic acid	A histone deacetylase inhibitor that targets leukemia cells via apoptosis and autophagy	Combination with CQ increases cancer cell death	[333]
Arsenic trioxide	Inducer of apoptosis, necrosis and autophagy in leukemia cells	Combination with 3-MA increases apoptotic cell death in leukemia cells	[333]
Curcumin	Interferes with NFκB, STAT3 and PI3K/Akt pathways and induces autophagy and apoptosis	Combination with CQ increases apoptotic cell death in glioblastomas both *in vitro* and *in vivo*	[334]
Resveratrol	Suppresses ROS/MAPK-mediated autophagy and apoptosis	Combination with Baf A1 increases apoptotic cell death in glioma both *in vitro* and *in vivo*	[335]
Quercetin	Inhibits PI3K/Akt pathway and induces autophagy and apoptosis	Combination with CQ increases apoptotic cell death U373MG cells	[239]
Paclitaxel	Regulates cytokine expression and induces autophagy and apoptosis	Combination with 3-MA increases apoptotic cell death in A549 cells	[226]

PTEN

The activity of the PI3K pathway is negatively regulated by the phosphatase and tensin homolog (PTEN) protein (Fig. 3). This tumor suppressor gene is one of the most frequently mutated, deleted or promoter methylated genes in a large variety of cancers at all stages of tumorogenesis [38]. The overexpression of PTEN induces apoptosis or autophagy through the inhibition of mTOR pathway [39]. In addition, PTEN regulates autophagy by inducing the expression of LC3 and Atg12 through phosphorylation of eIF2α (eukaryotic translation initiation factor 2α) [40]. The crosstalk between the Ras/Raf-1/ERK1/2 and the PI3K/Akt signaling pathways is one of the important regulators that determines the cellular outcomes upon PTEN activation [36].

p53

p53 is a well-known tumor suppressor gene with the highest mutation rate (more than 50%) in human cancers. The protein encoded by this gene is a transcription factor that regulates the expression of mediators of various signaling pathways, such as the apoptotic and autophagic cell death [41]. Among p53 target genes, the damage-regulated autophagy modulator (DRAM) and its signaling pathway are essential for the induction of p53-dependent apoptosis and autophagy. The effects of p53 on autophagy is also cell cycle-dependent and mostly observed in the G_1 phase and rarely in the S phase of cell-cycle [42]. Contrasting with pro-autophagic functions of nuclear p53, cytoplasmic p53 inhibits autophagy by activating mTOR signaling [43] (Fig. 3). In addition,

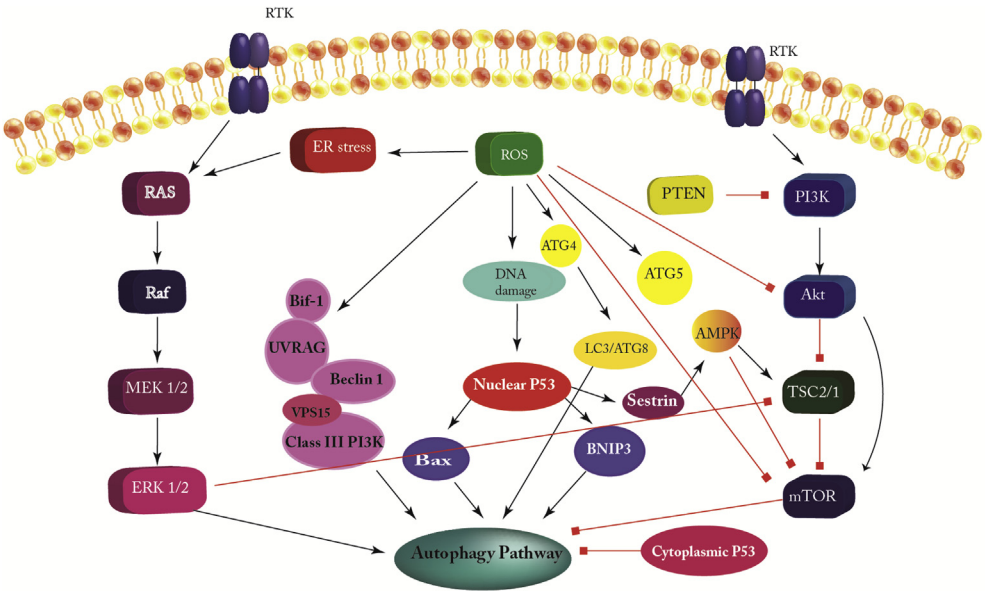


Fig. 3. Key signaling pathways involved in regulating autophagy. Autophagy is regulated positively or negatively by different signaling pathways. PI3K is a master signaling pathway of autophagy that is mostly activated through receptor tyrosine kinases (RTK). PI3K is negatively regulated by PTEN and its activation leads to phosphorylation and activation of AKT. AKT regulates downstream factors such as TSC1/2 in PI3K pathway via phosphorylation. The TSC1/2 blockage leads to an overall inhibition of the mTORC1 complex. Autophagy can also be modulated through the mTOR-independent pathways including RAS/Raf/MEK/ERK. The mitogen-activated protein kinase (MAPK) ERK 1/2 blocks autophagy by inhibiting the TSC1/2 activity or inversely may induce autophagy. Mitochondrial ROS activate autophagy through direct and indirect ways. In a direct way, ROS lead to a release of Beclin1, thereby enhancing autophagy. In an indirect mode, ROS firstly activate the ER stress and DNA damage that results in an autophagy induction. The tumor suppressor p53 exhibits both pro-autophagic and anti-autophagic activities based on its localization. Nuclear p53 exerts the pro-autophagic function, whereas cytoplasmic p53 plays an anti-autophagic role.

p53 post-transcriptionally downregulates LC3 level and controls the autophagic flux [44]. The crosstalk between p53 and autophagy is complex. p53 can modulate autophagy and, in turn, autophagy may suppress p53 function through its degradation by proteasome-mediated pathway. Several phytochemicals induce p53-dependend autophagy. For example, camptothecin stimulates autophagy in MCF-7 through p53 upregulation [45].

There are several other pathways governing autophagy including the ROS, ER stress, and RAS/MAPK pathways (Fig. 3).

Autophagy as a promising target for cancer therapeutics

Given the dual role of autophagy in tumorigenesis, both inhibition and induction of this pathway have a therapeutic potential in treatment of cancer.

Autophagy inhibition

Although chemo- and radiotherapy are two successful strategies for treatment of cancer, the rate of relapse is frequently high due to the occurrence of drug resistance. It has been suggested that autophagy is one of the most important mechanisms to promote cancer cell survival and finally relapse of the disease in patients [23]. Drug resistance observed in colorectal cancer (treated with 5-FU), chronic myeloid leukemia (treated with imatinib) and breast cancer (treated with tamoxifen and trastuzumab) are associated with activation of autophagy [46]. Preclinical research revealed that inhibition of autophagy through pharmacological or genetical tools could improve cancer chemotherapeutic approaches. Most studies are focused on a combination of chemical inhibitors of autophagy with a conventional chemotherapeutic drug. Autophagy inhibitors wortmannin, LY294002, 3-methyladenine (3-MA), chloroquine (CQ), hydroxychloroquine (HCQ), bafilomycin A1 (Baf A), sensitize cancer cells to chemotherapeutic drugs through promoting cell death pathways [23,46]. Among them, wortmannin, LY294002, and 3-MA are early stage inhibitors of autophagy that block autophagosomes formation through inhibiting the PI3K III complex, while other inhibitors block lysosome function at late stages of autophagy [47]. Table 1 summarizes some beneficial effects of chemotherapeutics and phytochemicals in combination with autophagy inhibitors in different cancer models. Downregulation of LC3 via shRNA blocks pro-survival role of autophagy in drug-resistance breast cancer cells and consequently sensitizes them to apoptotic effects of trastuzumab. Similarly, blocking the pro-survival roles of autophagy with RNAi or pharmacological inhibitors stimulates cell death induced by imatinib mesylate in leukemia [23]. In addition, autophagy plays a role in sensitizing HBL-100 cells to radiotherapy. Inhibition of autophagy by 3-MA led to a sensitivity of cancerous cells to pro-death effects of radiotherapy [46].

Autophagy induction

Besides autophagy inhibition, autophagy induction can also represent anti-cancer effects, especially in cancer cells that have a defect in apoptotic cell death pathways. In this condition, autophagy induction can promote apoptosis or act as an alternative form of cell death [48]. Good example in this context is the using of Bcl-2, EGFR, and mTOR inhibitors in the treatment of cancer [49,50]. For example, rapamycin, a well-known inhibitor of mTORC2, induces autophagic cell death in a variety of cancers, such as breast, glioma, and lung cancer. Deforolimus (AP23573, MK-8669) is a mTOR inhibitor that has been recommended for patients with relapsed or refractory hematologic malignancies [51]. Cetuximab, an epidermal growth factor receptor antibody, disrupts the interaction between Bcl-2 and Beclin1 and triggers autophagic cell death in cancerous cells [49].

Phytochemicals as a valuable source of autophagy modulation agents

Epidemiological studies demonstrated that there is a strong association between diet and human cancer mortality so that daily consumption of phytochemicals declines the incidence of different types of cancer [2,52]. Therefore, a lot of research efforts focus on nutrients and non-nutritive phytochemicals to evaluate their chemopreventive and chemotherapeutic potential in *in vitro* and *in vivo* models of cancer [2,6,9,10]. In clinical oncology, natural compounds induce cell death pathways, mostly apoptosis and autophagy, and are considered as a major resource for drug development and improving novel anticancer strategies [2,5,6,8,9]. Although autophagic effects of natural products have been reported in a few recent reviews, their mode of action is highly complex, and thus, the full therapeutic potential of phytochemicals still needs to be discussed [5,7,8]. Given the fundamental importance of autophagy in cancer therapy, we discuss the representative examples of phytochemicals that showed convincing evidence in regulating autophagy-signaling pathways.

Common autophagic phytochemicals and their mechanism of action

The chemical structures of 35 phytochemicals with autophagy-modulating activity are provided in Fig. 4. Also, their mechanism of action and therapeutic applications as new autophagy modulators are summarized in Fig. 5 and Table 2.

Allicin

Allicin (2-propene-1-sulfinothioic acid *S*-2-propenyl ester) is the major ingredient of garlic. This compound is able to inhibit the proliferation and induce cell death of several cancer cells, including colon, gastric, breast, cervix, and lymph tumors. The major mode of action of allicin is to induce oxidative stress and apoptosis [53,54]. For instance, allicin increases ROS and triggers caspase-dependent apoptosis in human liver carcinoma cells [55]. In addition, allicin inhibits proliferation and induces apoptosis through p38 MAPK pathway in gastric cancer MGC-803 cells [56]. Recent studies show that allicin can also stimulate autophagy. For example, autophagy induction by allicin is accompanied by inhibition of cytoplasmic p53, as well as upregulation of Beclin-1 and Bcl-2/Bcl-xL in liver cancer HepG2 cells [54]. Inhibition of autophagic effects of allicin by pharmacological tools led to induction of apoptotic cell death in these cells [54]. A recent report showed that allicin evokes apoptosis in p53-deficient carcinoma cells, whereas an autophagic response occurs in the cells harboring wild-type functional p53 protein [55]. Suppressing expression of cytoplasmic p53 in this condition leads to modulation of AMPK/TSC2 and PI3K/mTOR signaling pathways, as well as disruption of Bcl-2/Beclin1 interaction [15].

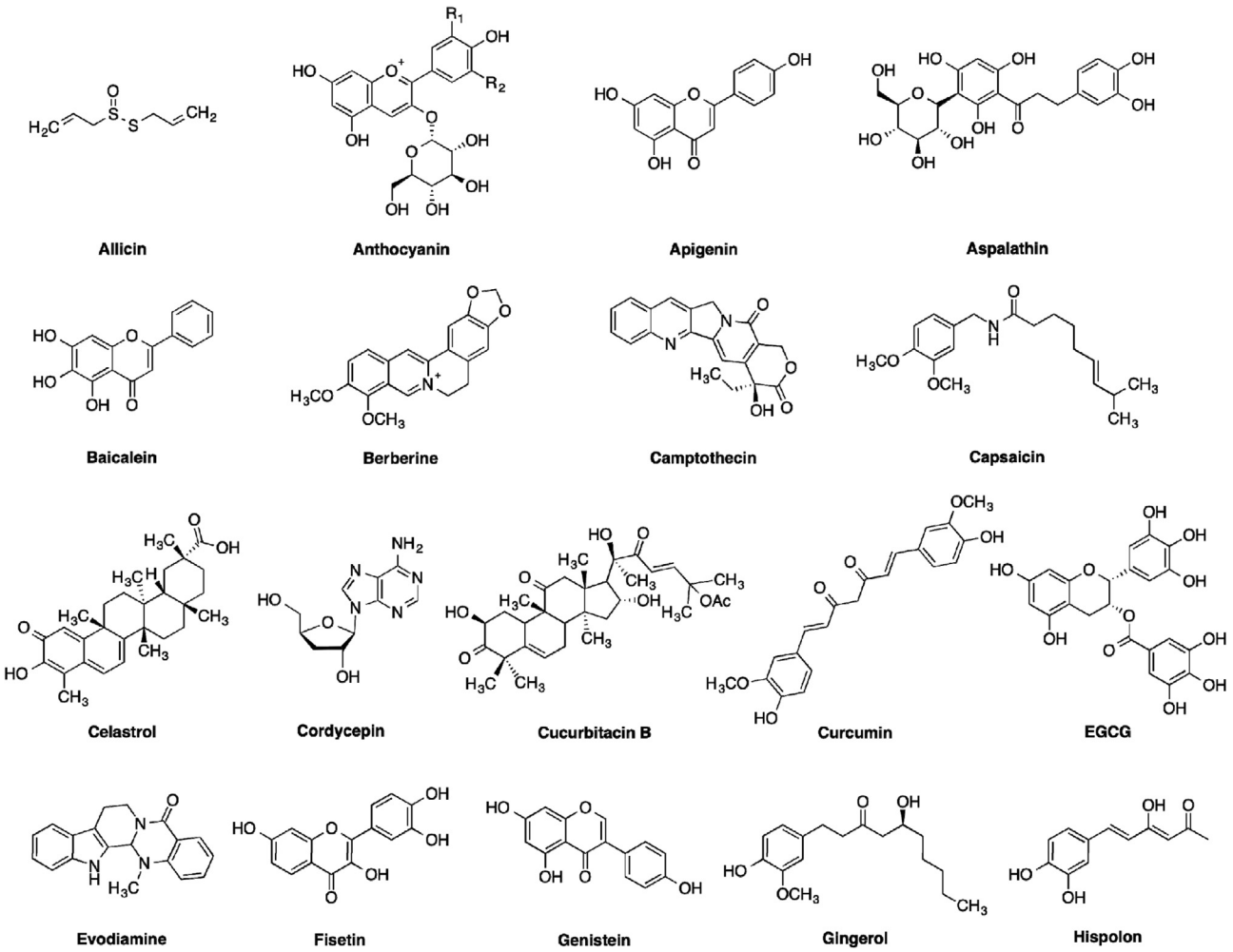


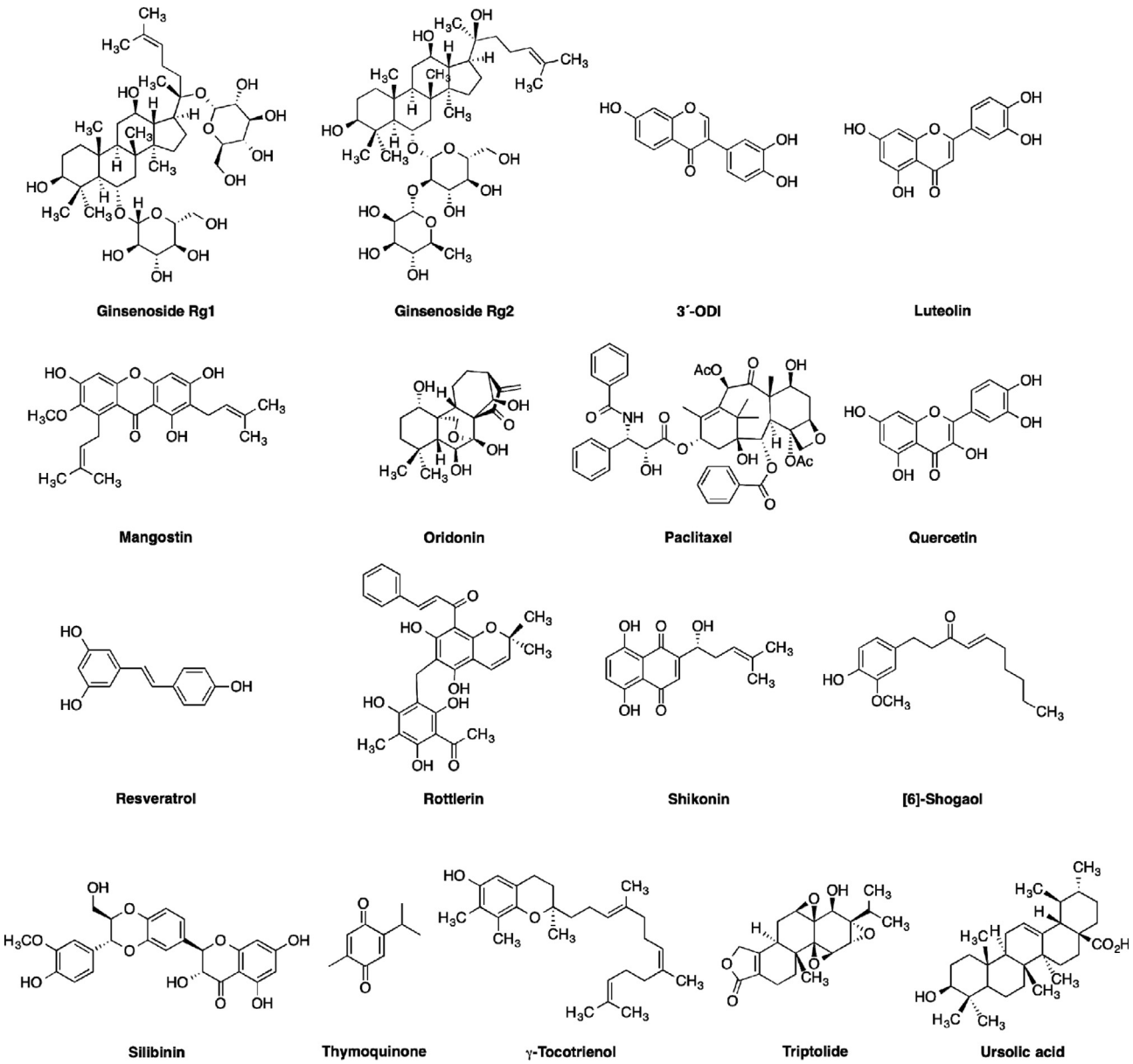
Fig. 4. Chemical structures of phytochemicals affecting authophagy.

Anthocyanins

Anthocyanins are water-soluble pigments extracted from vegetables and fruits, including grapes, blueberries, and red cabbages. These phytochemicals present chemopreventive, anti-oxidant, anti-inflammatory, anti-angiogenetic, and cell death-inducing activities in different cancer models, including esophageal cancer, colon cancer, prostate, breast cancer, skin cancer, and lung cancers [57]. Mechanistically, anthocyanins are able to downregulate the expression of COX-2, VEGF and c-Jun that results in suppressing esophageal tumor development [57]. Anthocyanins extracted from black rice induce apoptosis through activation of caspase-9 and cleavage of poly ADP-ribose polymerase (PARP) in breast cancer MDA-MB-453 cells [58]. One of the first evidence on the autophagic and anti-metastatic effects of anthocyanins was provided when extracts of *Vitis coignetiae* Pulliat ex Planch. were demonstrated to inhibit the EGFR and PI3K/Akt signaling [59]. Another study evidenced that anthocyanins extracted from *P. lentiscus* L. berries have strong anti-oxidant activity, which results in activation of autophagy through downregulation of mTOR and Bcl-2 in hepatocellular carcinoma cells [60]. Inhibition of autophagy in this condition induces an apoptotic cell death response [60]. In contrast, anthocyanins extracted from black soybean (*Glycine max* L.) show a pro-survival autophagic role in protecting human glial cells against oxygen-glucose deprivation [61]. The similar pro-survival role of autophagy has been observed following treatment of human osteosarcoma U2OS cells with anthocyanin, which was through phosphorylated p53, and upregulation of p27 ^{KIP1} and FOXO3a protein [62].

Apigenin

Apigenin (4′,5,7-trihydroxyflavone) is a member of the flavone subclass of flavonoids present in a wide variety of herbs. This compound exhibits potent anti-oxidant, anti-inflammatory, anti-mutagenic, and anti-tumoral activities [63]. Its anti-cancer effects have been documented in different cancer cells such as thyroid, breast, prostate, skin, colon, and cervical [64]. Apigenin induces



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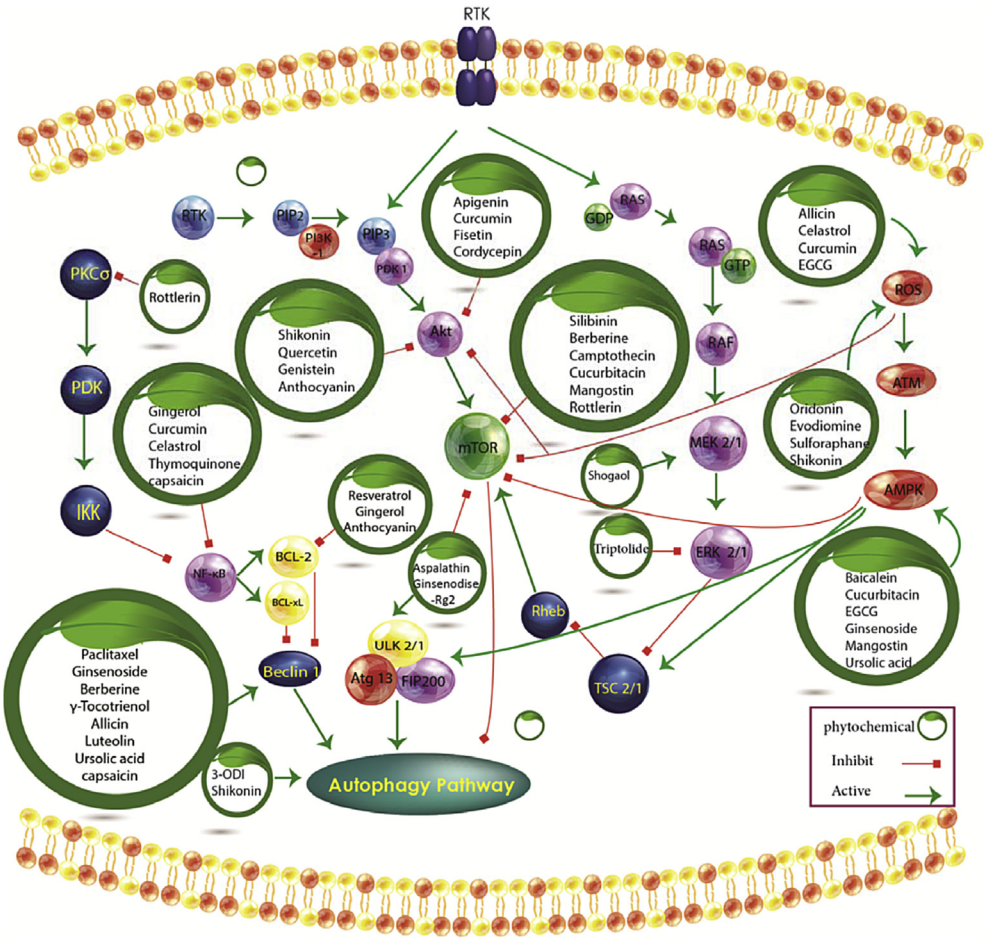

Fig. 5. The autophagic pathway and potential phytochemical targets. Phytochemicals modulate autophagy in tumor cells by inhibition or activation of multiple signaling pathways, including PI3K/Akt/mTOR, NF-κB, Bcl-2, Bcl-xL MEK/ERK, PKC, ROS, and AMPK/TSC2.

cell-cycle arrest and apoptosis through p53-dependent upregulation of $p21^{Cip1}$ in breast cancer [65]. Recent studies revealed that apigenin suppresses the PI3K-Akt pathway and modulates insulin-like growth factor (IGF-I) [66]. The first evidence of the connection of autophagy with apigenin action has been provided by Cao *et al.*, who reported that inhibition of autophagy increases apigenin-induced apoptosis in human breast cancer cells [67]. In this study low doses of apigenin could trigger autophagy by inhibiting the PI3K/Akt/mTOR pathway [67]. In contrast, high concentrations of apigenin decreased Beclin1 and LC3-II and blocked autophagy in colon cancer cells, where autophagy inhibitor 3-MA increased apigenin-induced apoptosis by activation of pro-caspase-9 and -3 [68]. As a chemopreventive bioflavonoid, apigenin also induces AMPK activation, inhibits mTOR signaling and finally induces autophagy in human keratinocytes [69]. Apigenin-induced autophagy-lysosomal degradation of β-catenin in Wnt/β-catenin signaling pathway has been recently reported, pointing out its therapeutic potential for Wnt-related diseases including cancers [70].

Aspalathin

Aspalathin is a dihydrochalcone *C*-glucoside that is present in *Aspalathus linearis* (Burm.f.) R. Dahlgren (commonly known as rooibos). Recent studies have indicated that aspalathin has p53-dependent cytoprotective effects in H9c2 cardiomyocytes and Caov-3 ovarian cancer cells and attenuates doxorubicin-induced cytotoxicity through upregulation of ATGs and AMPK associated with a decrease in P53/mTOR/p62 signaling (Table 2) [71]. In addition, aspalathin modulates glucose and lipid metabolism in 3T3-L1 adipocytes via AMPK phosphorylation and AKT activation, suggesting its therapeutic potential for obesity and type 2 diabetes [72].

Baicalein

Baicalein (5,6,7-trihydroxyflavone) is a natural flavonoid found in the roots of *Scutellaria baicalensis* Georgi and *S. lateriflora* L. Treatment of human cancer cells with baicalein resulted in the induction of autophagy and subsequent cell death, proposing that baicalein induces autophagic cell death through the activation of AMPK/ULK1 pathway while concomitantly inhibiting mTOR [73]. In a recent research performed on male BALB/c mice treated with a mixture of doxorubicin and baicalein, it was observed an increase in the myocardial expression of nuclear factor E2-related factor 2 (Nrf2) and heme oxygenase 1 (HO-1) with an associated decrease in cardiac apoptosis when compared to cardiac tissue from animals exposed to doxorubicin treatment only [74]. In addition, baicalein induced autophagy and protected rat hepatocytes from hypoxia/reoxygenation injury through increased induction of the autophagy marker LC3-II and Atg7 [75]. Baicalein induces a pro-survival autophagic response against ER stress-induced apoptosis in human hepatocellular carcinoma SMMC-7721 and BEL-7402 cells [76]. In contract, autophagy induction by this phytochemical promotes apoptosis in prostate cancer cell lines (Table 2) [76]. A recent study demonstrated that baicalein promotes apoptosis and suppresses

Table 2
Phytochemicals and their role in modulating autophagy.

Phytochemical	Cancer/Model	Autophagic effect	Outcome	Mechanism of action	Dose	Ref
Allicin	**Liver**			Downregulates p53	35 μM	[54]
	HepG2	Activation	Death	Inhibits PI3K/mTOR Upregulates Beclin-1		
Anthocyanin	**Liver**				0.2 mg/mL	
	PLCPRF-5	”	Survival	Disrupts Bcl 2/Beclin-1 interaction		[60]
	Glioblastoma				50- 100 μg/mL	[61]
	U87	”	”	Increases LC3II formation		
Apigenin	**Colon**				25-50 μM	[68]
	HCT116	”	Death	Suppresses PI3K/Akt/mTOR		
	Breast				6 μM	[67]
	T47D	”	Survival	Increases level of LC3- II		
	MDA-MB-231	”	”	”	6 μM	
Aspalathin	**Ovarian**			Induces ATGs and AMPK	0.2 μM	[71]
	Caov-3	”	”	Downregulates p53/mTOR/p62		
Baicalein	**Liver**			Downregulates of Bcl-2 and accumulates LC-3II	100 μM	[336]
	SMMC-7721	Activation (flux)	Survival			
	Bel-7402	”	”	”	100 μM	
	Prostate				0.5–10 μg/mL	[73,77]
	PC-3	”	Death	Activates AMPK/ULK1 Inhibits caveolin-1/AKT/mTOR		
	DU145	”	”	”	”	
	SCID mice (injected with DU-145 cells)	Activation	Inhibiting tumor growth	Inhibits caveolin-1/AKT/mTOR	40 mg/kg per day	
	Breast			Activates AMPK/ULK1	10 μg/mL	
	MDA-MB-231	Activation (flux)	Death			
Berberine	**Liver**			Increases Beclin-1 and suppresses mTOR	50-200 μM	[81]
	Hep-G2	Activation	”			
	MHCC97-L	”	”	”	100-400 μM	
Camptothecin	**Colorectal**					[89]
	HCT116	”	Survival	Regulates AMPK/TSC2/mTOR	20 nM	
	RKO	”	”	”	50 nM	
	Breast					[45]
	MCF-7	”	”	Induces p53	2 μM	
Capsaicin	**Breast**					[96]
	MCF-7	”	”	Increases LC3II formation	250 μM	
	MDA-MB-231	”	”	”	250 μM	
Celastrol	**Gastric**				0.25–1 μM	[106]
	AGS	”	Death	Increases LC3II, ATG5 and Beclin1		
	Mouse model	”	”	Induces HIF-1α and ROS/JNK	1- 2 mg/kg per day	
Cordycepin	**Prostate**					[120]
	LNCaP	Activation (flux)	Survival	Increases LC3II formation	200 μM	
	Brain					[123]
	SH-SY5Y U251	Activation	Death	Upregulates ROS, p53 and LC3II	50-300 μM	
	Breast	”	”	”	”	[114]
	MCF-7	”	”	Increases LC3II formation	200 μM	
	Neuroblastoma					[119]
	SK-N-SH	”	Survival	Increases LC3II formation	200 μM	
	Lung	Activation		Inhibits mTOR and c-FLIP and	50-200	[122]
	H1792	(flux)	Death	increases LC3II and Atg5	μM	
	H1299	”	”	”	”	
	H460	”	”	”	”	
	H157	”	”	”	”	
	A549	”	”		”	
Cucurbitacin	**Glioblastoma**					[126]
	T98G	”	Survival	Decreases HIF-1α, Increases LC3II	245 nM	
	U251	”	”	”	170 nM	
	Mouse model	”	”	”	1 mg/kg per day	
	Cervical	Activation				[131]
	HeLa	flux)	”	Suppresses the mTORC1/p70S6K	1 μM	
	Breast					
	MCF-7	”	”	”	1 μM	
Curcumin	**Colon**					[145,337]
	HCT116	Activation	Death	Increases LC3II formation	10 μM	
	Oral					[338]
	OSCC	”	”	Inhibits Akt/mTOR, phosphorylates p70s6k	10 μM	
	Prostate					[339]
	22rv1	”	”	Upregulates ERK1/2	20 μM	
	Lung			Inhibits Akt/mTOR/p70S6K and activates ERK1/2	20 μM	[340]
	A549	”	”			
	Malignant mesothelioma	Activation		Decreases Akt and JNK, increases	6.25–50 μM	[148]

Table 2 (*continued*)

Phytochemical	Cancer/Model	Autophagic effect	Outcome	Mechanism of action	Dose	Ref
	MM-B1	(flux)	”	ERK1/2 and p38 phosphorylation		
	H-Meso-1	”	”	”	”	
	MM-F1	”	”	”	”	
	C57BL/6		Tumor	–	1.5 mg/kg	
	Moues model	Activation	inhibition			
Epigallocatechin-3-gallate	**Oral**					[341]
	SSC-4	”	”	Increases ROS and LC3II	20 μM	
	Liver					[153]
	HepG2	Activation (flux)	”	Increases LC3II formation	40 μM	
	Mouse model	”	”	”	3.2 g/kg	
Evodiamine	**Gastric**					[162]
	SGC-7901	Activation	Death	Activates beclin, downregulates Bcl-2	10 μM	
	Lung					
	Mouse model	”	Survival	Increases Atg4b, Atg5 and Atg7	1 mg/kg	
Fisetin	**Breast**					[168]
	MCF-7	Inhibition	”	Decreases LC3-II levels	100-200 μM	
	Prostate					[166]
	PC3	Activation	Death	Inhibits mTORC1/2 and activates Akt	40-120 μM	
	DU145	”	”	”	”	
Genistein	**Pancreatic**					[342]
	MIA PaCa-2	”	”	Downregulates bcl-2 and upregulates beclin-1	100 μM	
	Mouse model	”	”	”	1.3 mg/kg	
	Ovarian					[172]
	A2780	”	”	Reduces Akt/mTOR phosphorylation	50-100 μM	
	Breast					[343]
	MCF-7	”	”	Increases ROS levels	100 μM	
Gingerol	**Lung**					[344]
	A549	”	”	Downregulates Bcl-2, NF-kB and Akt	50-100 μM	
	Pancreatic mouse model	”	”	Increases ROS level	100-200 mg/kg	[345]
Ginsenoside	**Breast**					[182]
	MCF-7	”	Survival	Induces beclin-1 and ROS	100 μM	
	Colorectal	Activation (flux)	Death	Converts LC3-I to LC3-II	20 μg/mL	[346]
	HCT-116					
Hispolon	**Liver**					[193]
	HepG2	Activation	”	Increases Hsp70, Hsc70, Hsp90 and LAMP2A and MDM2	20 μg/mL	
	Breast					[196]
	MCF-7	”	”	”	”	
	Cervical					
	HeLa	”	Anti-metastatic	Increases LC3 conversion and acidic vesicular organelle formation	25-00 μM	
	SiHa	”	”	”	”	
3′-ODI	**Melanoma**					[197]
	B16F1	Activation	Anti-melanogenic	Upregulates ATG5	100 μM	
Luteolin	**Liver**			Increases beclin-1 and LC3II	25-100 μM	[347]
	SMMC-7721	”	Death			
	Lung					[204]
	NCI-H460	Activation (flux)	”	Increases LC3II level	100-200 μM	
Mangostin	**Glioblastoma**					[211]
	GBM8401	Activation	”	Inhibits mTOR	5-10 μM	
	Mouse model	”	Reduction in tumors	Increases LC3- II levels	2 mg/kg	
	Leukemia					[212]
	K562	”	Survival	Increases beclin-1 and LC3II	15 μM	
Oridonin	**Prostate**				25 μM	[348]
	PC-3	”	”	Increases LC-3II and inhibits Ras/PI3KCI/Akt		
	Breast					[349]
	MCF-7	”	Death	”	”	
Paclitaxel	**Breast**					[350]
	MCF-7	”	”	Increases LC3II formation	6-50 nM	
	TaxR	”	”	”		
	Colon					[351]
	HCT116	”	Survival	”	50 nM	
Quercetin	**Gastric**	Activation	”	Modulates Akt-mTOR and HiF1α	40 μM	[240]
	MKN28	”	”		160 μM	
	AGS					
	Lymphoma	Activation (flux)		Inhibits Akt/mTOR and Wnt/β-catenin pathways		
	BC3		”		50 μM	

(*continued on next page*)

Table 2 (*continued*)

Phytochemical	Cancer/Model	Autophagic effect	Outcome	Mechanism of action	Dose	Ref	
	BCBL1	”	”	”	”		
	BC1						
	Cervical	Activation	”	Increases beclin-1, LC3II, and S6K1 phosphorylation	”		
	HeLa						
	Neuroglioma					[352]	
	U87	Activation	Death	Inhibition of PI3K/Akt, accumulation of LC3- II and p62	30-50 μg/mL		
	Mouse model	”	Tumor inhibition	”	40-80 mg/kg		
Resveratrol	**Gastric**					[353]	
	HGC-27	Activation	Survival	Increases endogenous levels of dihydroceramides and LC3-II	50 μM		
	Leukemia						
	Molt-4	”	”		Inhibits Akt/mTOR/ p70S6K		200 μM
	Jurkat	”	”				
Rottlerin	**Breast**			Increases LC3-II levels		[354]	
	CSCs	”	Death	Suppresses PI3K/Akt/mTOR	1-2 μM		
	Pancreatic					[265]	
	CSCs	”	Survival	Inhibits Atg7 and beclin-1	2 μM		
Shikonin	**Pancreatic**					[279]	
	BXPC-3	”	Death	Increases LC3-II Suppresses PI3K/Akt/mTOR	2.5−5 μM		
	Lung					[355]	
	A549	Inhibition	Survival	”	0.5-6 μM		
	Mouse model (lung)	”	Tumor inhibition	–	2 mg/kg	[355]	
	Liver					[278]	
	BEL740	Activation	Death	Induces LC3-II accumulation	2.5 μM		
	Huh	”	”	”			
(6)-Shogaol	**Colorectal**					[283]	
	HT-29	”	”	Induces G2/M arrest	60 μM		
Silibinin	**Fibrosarcoma**			Activates ROS- MAPK pathway		[286]	
	HT1080	”	”	Inhibits PI3K/Akt/mTOR	40 μM		
	Renal					[285]	
	786-O	Activation (flux)	Anti-metastatic	Inhibiting PI3K/Akt/mTOR signaling	20-50 μM		
	ACHN	”	”	”	”		
	Breast			Activates ROS, inhibiting PI3K/Akt/mTOR	100 μM	[14]	
	MCF7	Activation	Death				
Sulforaphane	**Prostate**					[292]	
	PC-3	”	Survival	Increases LC3II formation	40 μM		
	LNCaP	”	”	”			
	Breast					[293]	
	MCF-7	”	”	Increases LC3II formation	30 μM		
	MDA-MB-231	”	”	”	”		
	Colon					[294]	
	WiDr	”	”	Increases LC3-II	40 μM		
	Pancreatic					[295]	
	MIA PaCa-2	Inhibition	No effect	Increases ROS, Atg5 and LC3-II	40 μM		
	Panc-1	”	Death	”	”		
Thymoquinone	**Glioblastoma**					[303]	
	U87MG	Inhibition	Death	Increases LC3-II and p62	40 μM		
	Gli36ΔEGFR	”	”	”	”		
	Oral					[300]	
	SASVO3	Activation	Death	Increase expression of LC3-II	40-60 μM		
	SCC-4	”	”	”	”		
	OC2	”	”	”	”		
	SAS	”	”	”	”		
	Mouse Model				10-25 mg/kg		
	Oral cancer	”	”	Increases Bax and LC3II levels			
	Colon			Increases Atg7, Beclin-1, and LC3	2 μM	[305]	
	CPT-11	”	”				
γ-Tocotrienol	**Breast**					[296]	
	MCF-7	”	”	Induces ER stress, beclin-1, LC3-II, cathepsin-D and LAMP-1	40 μmol/L		
	MDA-MB-231	”	”	”	”		
Triptolide	**Neuroblastoma**	”	”	Induces LC3-II formation	100 nM	[307]	
	SH-SY5Y	”	”	Inhibiting NF-κB			
	IMR-32						
	Pancreatic					[309]	
	Hs766T	”	”	Inhibits Akt/mTOR/P70S6K	200 nM		
	S2-VP10	”	”	”	”		
	S2-013	”	”	”	”		
Ursolic acid	**Breast**					[314]	
	MCF-7		Survival	Inhibits PI3k-Akt., increases LC3- II	15-25 μM		

Table 2 (*continued*)

Phytochemical	Cancer/Model	Autophagic effect	Outcome	Mechanism of action	Dose	Ref
		Activation (flux)				
	Glioblastoma					[315]
	U87MG	Activation	Death	”	40 μM	
	Prostate					[356]
	PC3	Activation	Survival	Increases Beclin-1 and Inhibits Akt/mTOR	10-40 μM	
	Colorectal					[311]
	HCT15	Inhibition	Death	Inhibits PI3K/Akt, accumulates LC3-II and p62	4 μM	
	Mouse model	Activation	”	”	75 mg/kg	

metastasis in androgen-independent PCa cells through inhibition of the caveolin-1/AKT/mTOR pathway [77].

Berberine

Berberine is a benzylisoquinoline alkaloid found in stem-bark and roots of *Berberis* species, as well as in several other medicinal plants. Several studies indicated that berberine has anti-microbial and anti-tumoral activities both *in vivo* and *in vitro*. The effect of berberine on blocking the growth of a wide range of cancer cells have been reported that are generally through induction of cell-cycle arrest and/or apoptosis [78]. This natural compound exhibited anti-oxidant effect through inhibition of the lipoxygenase and xanthine oxidase activity [79]. Conversely, berberine triggers cell-cycle arrest and increases ROS in human multiple myeloma cells [80]. Recent reports uncover an autophagic role for berberine. For example, berberine induced autophagy in liver cancer cells [81] and adipocytes [82]. Berberine extracted from *Coptidis Rhizoma* induces autophagic cell death by elevating glucose regulated protein 78 (GRP78) levels in cancer cells [83]. Berberine elicits autophagy in glioblastoma by inhibiting the AMPK/mTOR/ULK1-signaling pathway [84]. With a nearly similar mechanism (*i.e.,* alternating AMPK/mTOR signaling), berberine stimulates autophagy and alleviates low-density lipoprotein-induced inflammation in J774A.1 cells, suggesting a therapeutic potential for the treatment of atherosclerosis [85]. One of the advantages of berberine is enhancing the cytotoxic effect of radiotherapy in tumor cells through apoptosis and autophagy via increased expression of Beclin1 and inhibition of mTOR signaling [86].

Camptothecin

Camptothecin is a quinoline alkaloid that was firstly discovered in Chinese happy tree (*Camptotheca acuminata* Decne.). Camptothecin showed its anti-cancer effects via specifical inhibition of DNA topoisomerase I [87,88]. Low doses of camptothecin induce autophagy through the AMPK/mTOR signaling pathway in human colorectal cancer cells. Mechanistically, camptothecin induces DNA damage and upregulates p53 to evoke pro-survival autophagy. In this condition, autophagy inhibitors shift camptothecin response to apoptosis [89]. Similar autophagic cell death response has been also observed in breast cancer MCF-7 cells exposed to camptothecin [45]. Camptothecin-induced oxidative stress and camptothecin-mediated DNA damage trigger autophagic cell death in metastatic murine osteosarcoma DML8 cells. Interestingly, inhibition of autophagy by lentiviral shRNA resulted in camptothecin-induced cell death in K7M3 cells while apoptosis was prevented in DLM8 cells [90].

Capsaicin

Capsaicin (*trans*-8-methyl-*N*-vanillyl-6-enamide) is a capsaicinoid alkaloid present in chili pepper. The function of capsaicin is controversial in the carcinogenic process; in some conditions, it prevents tumors but in other acts as a tumor promoter [91]. Capsaicin promotes apoptosis through increased expression of Bax in pancreatic cancer [92]. Other studies reported that this compound induced apoptosis associated with activation of JNK or NF-κB inactivation in prostate cancer PC-3 cells [93,94]. In addition to apoptosis, this natural compound could induce autophagy in different cancer cells. Dihydrocapsaicin stimulates autophagy with increasing the conversion of LC3 I to LC3 II protein in HTC116 human colon cancer cells [95]. Also, capsaicin-induced autophagy is mediated by MAPK-dependent activation and the ER stress in breast cancer MDA-MB231 and MCF-7 cells [96]. This pepper's natural ingredient induced ROS-mediated autophagy blockage in prostate cancer cells [97]. Normal prostate PNT2 and RWPE-1 cells were resistant to autophagic effects of capsaicin. In addition, capsaicin inhibited the growth and activated autophagy in human nasopharyngeal carcinoma cells [98]. Moreover, capsaicin increases the phosphorylation of signal transducer and activator of transcription 3 (p-STAT3) and subsequently triggers ROS-dependent autophagy in human hepatoma [99]. Inhibiting autophagy in these cells led to apoptosis [99]. Finally, capsaicin is able to induce a pro-survival autophagic response which drives chemoresistance and epithelial mesenchymal transition in bladder cancer cells via Hedgehog signaling pathway [100].

Celastrol

Celastrol is a quinone methide triterpenoid isolated from the traditional Chinese medicine *Tripterygium wilfordii* Hook. f. (Thunder of God Vine). Celastrol exhibited anti-inflammatory and cytotoxicity activities over various cancer models [101] including breast cancer, prostate cancer, lung cancer, colon cancer, pancreatic cancer, and bladder cancer. Celastrol inhibits cancer progression and downregulates NF-κB via inhibiting IκBα phosphorylation [102]. It significantly induces ROS and inhibits cell-cycle at G2/M phase [103], followed by triggering the ER stress markers Bip, PERK and IRE1 [104]. In addition, celastrol induces AKT-dependent autophagy, ending to a caspase-dependent apoptotic cell death [105]. The simultaneous induction of apoptosis and autophagy has been also observed upon administration of celastrol in different cancer cells, such as gastric [106], neuroblastoma [107], and glioblastoma [103]. Celastrol induces apoptosis and autophagy in both *in vitro* and *in vivo* human osteosarcoma cells via the ROS and JNK signaling pathway [108]. Inhibition of autophagy potentiates celastrol-induced apoptosis in *in vitro* and *in vivo* models of human pancreatic cancer [109]. Celastrol triggers autophagy in prostate cancer cells through targeting AR/miR-101 [110]. Autophagy induction by celastrol in rats is mediated by p62/SQSTM1. Also, this phytochemical engage autophagy for protection against pulmonary fibrosis [111].

Cordycepin

Cordycepin, also termed 3-deoxyadenosine, is a bioactive ingredient of *Cordyceps sinensis* (Berk.) Sacc. (1878), which is able to modulate many biological functions [112], including DNA damage,

cell-cycle arrest, inflammation, apoptosis and autophagy, in different cancers, such as leukemia [113], breast [114], colorectal [115], and glioma [116]. Oral administration of cordycepin (15 mg/kg per day) inhibits melanoma cell growth without adverse effects [117]. This nucleoside analogue induces apoptosis and inhibits cell migration of renal cell carcinoma cells through miR21-mediated regulation of the PTEN/PI3K/Akt pathway [118]. Cordycepin stimulates autophagyic cell death in MDA-MB-231 and MCF-7 human breast cancer cells [114], while autophagy induction by this phytochemical has a pro-survival role in SK-N-SH and BE(2)-M17 neuroblastoma cells [119], as well as in LNCaP prostate cancer cells [120]. In addition, cordycepin reduced growth of tumors in an allograft model of testicular cancer and induced both p38 MAPK-dependent apoptosis and PI3K/AKT-dependent autophagy in MA-10 mouse Leydig tumor cells [121]. A recent report suggests that this phytochemical triggers autophagy and incudes extrinsic apoptosis by down-regulating cellular-FLICE inhibitory protein (c-FLIP) in five human non-small cell lung cancer cells [122]. More recently, cordycepin elicited ROS and apoptosis in both human brain SH-SY5Y and U-251 cancer cell lines through modulation of autophagy [123].

Cucurbitacin

Cucurbitacin is a cucurbitane triterpenoid extracted from the plant family *Cucurbitaceae* [124]. According to their structural features, cucurbitacins are categorized into 12 groups. Among them, cucurbitacin B, D, E, I, and Q have been known for their anti-proliferative [125] and anti-inflammatory activities in a variety of cancers including, pancreatic cancer, hepatocellular carcinoma, melanoma, lung cancer, breast cancer, neuroblastoma, and glioma [126]. The anti-tumoral effects of cucurbitacins are exerted by inhibiting the IKK/NF-κB pathway, leading to inhibition of the inflammatory enzymes COX-2 and iNOS [124]. Cucurbitacin B is able to up-regulate expression of p21 and p27 in breast cancer cells [127]. Moreover, cucurbitacin E promotes apoptosis through induction of caspase-8, -9, and -3 in T24 cells [128]. A ROS-dependent autophagic response is detected following cucurbitacin treatment in MCF-7 cells [129]. Cucurbitacin E-induced autophagy is mediated by regulating the mTORC1 complex via decreasing phosphorylation of p70S6K and ULK1 in HeLa and MCF7 cells [127]. Cucurbitacin induces autophagy through mitochondrial ROS production, which counteracts to limit caspase-dependent apoptosis [130]. Cucurbitacin E induces autophagy in human cancer cells via downregulation of mTORC1 signaling and upregulation of AMPK activity [131]. Cucurbitacin I stimulates an autophagic response that is protective against apoptosis in *in vitro* and *in vivo* models of glioblastoma [126]. In addition, autophagy is associated with cucurbitacin D-induced apoptosis in human T cell leukemia cells [132].

Curcumin

Curcumin (diferuloylmethane) is a yellow colored phenolic pigment extracted from turmeric (*Curcuma longa* L.) and has long been recognized as a promising drug for treatment of various kinds of diseases [133]. The phytochemical is inert in nature so that it is nontoxic even at high doses (12 g/day p.o.) and also is able to target multiple oncogenic pathways [134]. In addition, curcumin can increase the sensitivity of cancer cells to chemotherapy drugs [135]. Owing to these properties, curcumin represented potent anti-cancer activities [136] in various types of malignancies, including bladder [137], gastric [133], pancreatic, prostate, leukemia [138], breast [139], colon [134], and others [15]. NF-kB is a master mediator that links curcumin effects to apoptosis and chemoresistance of human tumors [140,141]. In addition to NF-kB inhibition, curcumin is able to suppress the pro-survival protein kinase Akt, resulting in induction of apoptosis and autophagy [142]. Curcumin-induced autophagy is mostly reported as a death signal, however, cell survival and differentiation features have also been reported as consequence of curcumin treatment [134]. The interplay between autophagy and apoptosis is very complex during curcumin effects [143]. For example, curcumin inhibits proliferation by inducing autophagy in chronic granulocytic leukemia (CGL), glioblastoma, and esophageal cancer [144,145]. Autophagic effects of curcumin are mostly mediated through augmentation of basic ROS levels both *in vitro* and *in vivo*. Autophagy-dependent growth inhibition of cancerous cells is mostly mediated through inhibition of the Akt/mTOR/p70S6 pathway, upregulation of Beclin1 and consequently accumulation of LC3-II [144,145]. More reports suggest that curcumin stimulates autophagy-associated apoptosis in mesothelioma [17] and K562 cells via the PI3K/Akt/mTOR and NF-κB-dependent pathways [17]. However, the cell death-inducing role of curcumin is multiplex and dose-dependent. Indeed, the ROS produced by curcumin induced an ER stress response that causes calcium release and subsequently, mitochondrial-dependent apoptosis. In parallel, autophagy is also activated and plays a role in sustaining the survival of the cells undergoing ER stress, or it can induce cell death [143]. In addition, recent findings suggest that crosstalk between autophagy and apoptosis during curcumin treatment is mediated by iron chelation [146]. Unlike apoptotic effects of curcumin, observed in both androgen-dependent and castration-refractory prostate cancer cells, its autophagic activity is only detected in androgen-dependent prostate cancer cells [147]. A recent report suggested that curcumin has potent anti-cancer effects in both *in vitro* and *in vivo* models of malignant mesothelioma through autophagy blockage and subsequent induction of apoptosis (Table 2) [148]. A major problem in the clinical use of curcumin is related to its low bioavailability. Several strategies based on using nanoparticles such as micelles, liposomes, and dendrimers have been offered to solve this problem, which will be discussed in Section 4 of this paper.

Epigallocatechin gallate (EGCG)

Epigallocatechin gallate, also known as epigallocatechin-3-gallate (EGCG), is the most abundant polyphenol in green tea, which has beneficial anti-oxidant and anti-tumoral effects [149]. Anti-cancer functions of EGCG has been seen in prostate, breast [150], pancreatic, colon [151], and cervical [152] cancer, where EGCG regulates apoptosis, autophagy, and cell-cycle distribution of the cells. It was thought that the beneficial effects of this polyphenol are related to autophagy [153]. For instance, effects of EGCG on hepatic status, cardiovascular complications, and neurodegenerative diseases are regulated by autophagy [153–155]. Cell death-inducing effects of EGCG in cancerous cells are related to caspase-dependent apoptosis [156], however this phytochemical can also modulate autophagy. In this context, EGCG facilitates autophagic cell death through induction of autophagolysosome formation via Atg5 and the Ca^{2+}/CaMKKβ/AMPK and mTOR pathways [154]. EGCG is also able to trigger ROS-dependent autophagy in MDA-MB-361 and MCF-7 breast cancer cell lines [157], and can alternatively reduce autophagy in some conditions, such as in central nervous system disorders. For instance, EGCG reduces autophagy and prevents mitochondrial dysfunction observed in neuronal cell injury after subarachnoid hemorrhage [158].

Evodiamine

Evodiamine is an alkaloid extracted from the fruit of *Evodia rutaecarpa* Benth. A wide range of pharmacological activities of evodiamine has been observed, including anti-cardiovascular disease effects, anti-neurodegenerative action, anti-obesity, and anti-cancer effects [159]. Anti-tumor activities of this alkaloid have

been reported in different cancers such as lung, prostate, gastric, and bladder cancer [160,161]. Both apoptosis and autophagy are activated following treatment with evodiamine in human gastric SGC-7901 cells [162]. In addition, evodiamine is able to induce autophagy in the A549 cell line via enhancing the expression level of Beclin1 [160]. Some reports revealed that oxidative stress induced by evodiamine increases the ROS/NO levels that can either induce or block autophagy via the specific regulation of Atg4 or inhibition of the conversion of LC3I to LC3-II, respectively [163]. Evodiamine is also an up-regulator of Atgs (Atg4b, Atg5 and Atg7) and evokes autophagy in murine Lewis lung carcinoma cells [164]. Recent studies revealed that the intracellular calcium (Ca^{2+}) level plays a major role during apoptosis and autophagy induced by this naturally-occurring compound in U87-MG cells [165]. Some studies showed that this phytochemical mostly affects autophagy as a cell survival mechanism because inhibition of autophagy with 3-MA leads to an increase in apoptosis and cytotoxicity.

Fisetin

Fisetin (3,3′,4′,7,-tetrahydroxyflavone) is a flavonoid extracted from many fruits and vegetables (onion, strawberry, etc.). Fisetin is known for its anti-inflammatory and anti-oxidant activities [166]. *In vitro* and *in vivo* studies demonstrated that this flavone has anti-cancer effects and can induce caspase-dependent apoptosis in cervical cancer cell line (HeLa cells) [167]. It has been shown that anti-tumor function of fisetin in caspase-3-deficient human breast cancer MCF-7 cells is mediated through inhibition of autophagy and induction of mitochondrial apoptosis [168]. This phytochemical induces degradation of phosphorylated tau via autophagy activated by the transcriptional factor EB (TFEB) and nuclear factor E2-related factor 2 (Nrf2), thus can be proposed as a candidate for Alzheimer's disease [169]. While most studies reported that fisetin is able to target both the mTOR and the Akt signaling pathway, some reports point out that it inhibits mTOR complex 1 and 2 leading to induction of autophagy in hormone-independent PC3 cells [166].

Genistein

Genistein (4′,5,7-trihydroxyisoflavone) is an isoflavonoid which is abundant in soy products [170]. Anti-tumoral effects of this isoflavone have been tested in different cancer cells, including leukemia, lung, breast, melanoma, hepatoma, and prostate [170,171]. Genistein is described to have multiple activities involving induction of apoptosis and autophagy, inhibition of protein-tyrosine kinase, suppression of telomerase activity, inhibition of angiogenesis and cell-cycle arrest at G2/M phase [171,172]. Zhang *et al.* reported evidence for genistein inhibition of cell invasion in human prostate IA8-ARCaP and LNCaP cells [170]. Gossner *et al.* reported that genistein exerts cytotoxic effects in several ovarian cancer cell lines through suppression of glucose uptake and inhibition of Akt phosphorylation [144,172]. Resistance to chemotherapeutic drugs is principally due to defect in the apoptotic signaling pathway. In this condition, some phytochemicals such as genistein can stimulate autophagic cell death and may become a good choice in the treatment of ovarian cancer patients [172]. Genistein increases the expression of BAX/Bcl-2 and in parallel, decreases the expression of the anti-apoptotic protein survivin in MCF-7 cell line, which is associated with activation of autophagy [173]. Mohan *et al.* reported that a combination of LC3 shRNA plasmid transfection and genistein treatment leads to a decrease in LC3-II accumulation in rapamycin-treated human malignant neuroblastoma cells [174]. A recent report showed that genistein inhibits N-CoR misfolding in non-small cell lung cancer, which is associated with chaperone mediated autophagy [175].

Gingerol

[6]-gingerol is a naturally occurring plant phenol present in ginger (*Zingiber officinale* Roscoe). It represents anti-metastasis, anti-inflammatory, and anti-cancer properties in various cancer cell lines [176]. Studies demonstrated that [6]-gingerol inhibits phosphorylation of JNK, ERK1-2, and P38 MAPK in pancreatic, hepatocarcinoma and skin cancer cells [176], and downregulates the expression of Cdks (Cdk2, Cdk4, and Cdk6) and cyclin A in pancreatic cancer cells (BxPC-3 cells) [177]. Furthermore, it has also been reported that [6]-gingerol downregulates the expression of Bcl-2, NF-κB and Akt, and upregulates the expression of cytochrome *c*, Bax and TNF-α in HeLa cells. Thus, [6]-gingerol activates cell death through caspase-mediated apoptosis and autophagy in HeLa cells [178]. Moreover, gingerol is capable of sensitizing human lung cancer to TRAIL-induced cell death through inhibiting autophagy flux [179].

Ginsenoside

Ginsenosides or panaxosides are the major active ingredients of ginseng [180]. They are divided into two groups including 4-ring, steroid-like structure dammarane family, and oleanane family [181]. Dammaranes are further subdivided into two classes, including protopanaxadiols (e.g., Rb1, Rb2, Rg3, Rh2, and Rh3) and protopanaxatriols (e.g., Rg1, Rg2, and Rh1) [181]. Among these triterpene saponins, ginsenoside F2 is able to stimulate autophagy via conversion of LC3-I to LC3-II and accumulation of Atg7 and Beclin-1 in breast cancer stem cells [182]. Ginsenoside Rk1 stimulates autophagy with a cytoprotective role in HepG2 cells [183]. Furthermore, ginsenoside Rg3 sensitizes cancer cells to cell death via inhibition of autophagy [184]. Ginsenoside compound K sensitizes colon cancer cells to TRAIL-induced apoptosis via an autophagy-dependent pathway [185]. Ginsenoside Rg1 is a potent inducer of autophagy and inhibitor of apoptosis with beneficial effects on the survival of cardiomyocytes exposed to hypoxia/reoxygenation [186]. Ginsenoside Rb2 restores autophagy and reduces accumulation of hepatic lipids through activation of AMPK [187]. Ginsenoside-Rg3 alleviates mitochondrial dysfunction and prion protein-mediated neurotoxicity by activating an autophagy flux response [188]. The steroidal saponin 20(*S*)-ginsenoside Rg3 (extracted from *Panax ginseng* C. A. Mey.) has been reported as an inhibitor of autophagy and sensitizer of hepatocellular carcinoma to doxorubicin [184]. Ginsenodise Rg2 activates autophagy in a AMPK-ULK1-dependent and an mTOR-independent manner. Induction of autophagy by ginsenoside Rg2 enhances the clearance of protein aggregates in a cell-based model, improves cognitive behaviors in a mouse model of Alzheimer disease, and prevents high-fat diet-induced insulin resistance [189].

Hispolon

Hispolon is a phenol compound isolated from the mushroom *Phellinus linteus (Berk. et Curt.) Aoshima* (Berk. et Curt.) Aoshima that shows anti-oxidant, anti-proliferative, anti-inflammatory, and anti-cancer effects [190,191]. The anti-proliferative effects of hispolon have been observed in breast and bladder cancer cells through exerting murine double minute (MDM2)-recruited ERK1/2 activity [190,191]. Hispolon induces apoptotic cell death in human epidermoid KB cells and human gastric cancer cells via a ROS-mediated mitochondrial pathway [192]. Furthermore, hispolon triggers the TRAIL-induced apoptosis in human colon cancer HCT-116 cells through downregulation of NF-κB and caspase-8-Bid-tBid-Bax pathway [192]. Hispolon-induced down-regulation of MDM2 is mediated through chaperone-mediated autophagy in HepG2 hepatocellular carcinoma and MCF-7 breast cancer cells [193]. Moreover, hispolon is a potent anti-metastatic phytochemical and can suppress cancer cell migration by inhibiting EMT in breast

cancer cells [194]. Anti-metastatic effects of hispolon are mediated through Akt-dependent autophagy in human nasopharyngeal carcinoma cells [195]. A recent report revealed that hispolon inhibits metastasis via autophagic degradation of cathepsin S in cervical cancer cells [196].

3′-hydroxydaidzein (3′-ODI)

3′,4′,7′-trihydroxyisoflavone (3′-hydroxydaidzein, 3′-ODI) is an ortho-dihydroxyisoflavone derivative of fermented soybean paste. Treatment with 3′-ODI significantly reduced α-melanocyte-stimulating hormone (α-MSH)-mediated melanogenesis, but efficiently increased autophagy both in melanoma cells and melanocytes [197]. Furthermore, inhibition of autophagy significantly reduced the anti-melanogenic effects of 3′-ODI in α-MSH-stimulated melanoma cells. Taken together, these results suggest that autophagy mediates the anti-melanogenic activity of 3′-ODI [197].

Luteolin

Luteolin is flavone with strong anti-oxidants and anti-cancer effects due to direct scavenging of ROS [198–200]. Luteolin induces cell-cycle arrest in human melanoma, gastric, and prostate cancer [201], and sensitizes different type of cancer cells to chemotherapeutic drugs. In addition to apoptosis, luteolin is also a potent autophagy inducer. It utilizes autophagy pathways as a cell death mechanism through activating the intracellular acidic lysosomal vacuolization and accumulation of LC3 II protein and finally occurrence of an autophagy flux [202]. Park *et al.* reported that this phytochemical elicits autophagic cell death in U87MG and T98G cells [203], as well as in NCI-H460 human lung carcinoma cells [204]. Conversely, a recent report suggests that luteolin can promote pro-survival autophagy in human cutaneous squamous cell carcinoma cells [205].

Mangostin

Mangostin is a xanthonoid found in mangosteen tree (*Garcinia mangostana* L.) with different biological effects, such as cardioprotective, anti-bacterial [206], and anti-cancer activities [207]. The apoptotic effect of α-mangostin is typically caspase-dependent and mediated via downregulating ERK, Akt and JNK, in human chondrosarcoma cells [208], leukemia cells (HL60 cells) [209], and colon cancer cells [210]. However, α-mangostin can also induce autophagic cell death through activating AMPK and inhibiting mTOR in brain cancer GBM8401 and DBTRG-05MG cells [211]. Autophagic effects of this phytochemical have been also observed in leukemia cells, where blocking autophagy by chloroquine led to an induction of apoptosis [212]. Recently, β-mangostin inhibited α-MSH-mediated melanogenesis in B16F10 melanoma cells by selective autophagy [213].

Oridonin

Oridonin is an active *ent*-kaurane diterpenoid extracted from *Rabdosia rubescens* (Hemsl.) H.Hara [214], regulating cell-cycle, apoptosis, and autophagy [215]. The anti-cancer effects of this compound have been reported in many models including, prostate, non-small lung cancer [216], breast, acute leukemia [217], glioblastoma, human melanoma, and hepatocellular carcinoma cells [218]. Zhang *et al.* showed that oridonin induces both apoptosis and autophagy in HeLa cells through activation of PKC pathway [214]. Moreover, ROS increased by oridonin has a crucial role in different intracellular signaling pathways, resulting in apoptosis and autophagy in human hepatoma HepG2 cells and murine L929 fibrosarcoma cells [214]. A ROS-mediated autophagic pathway is also activated by oridonin in HeLa cells, which is accompanied with an upregulation of Beclin1 and the redox sensitive cysteine protease HsAtg4A (known as an Atg4 family) [214]. Similar autophagy function has been reported in breast cancer cells exposed to oridonin [219]. Li *et al.* demonstrated that this phytochemical is able to induce G2/M cell-cycle arrest along with Beclin1 overexpression and autophagy induction in PC-3 and LNCaP cells [217]. In RPMI8226 cells, oridonin triggers both caspase 3-mediated apoptosis and Beclin1-dependent autophagy. In this study, autophagy inhibition by 3-MA sensitizes the cell to apoptosis, suggesting a pro-survival function of autophagy in this model [220]. Finally, oridonin stimulates an autophagic response that inhibits apoptosis in L929 cells [221].

Paclitaxel (Taxol)

Paclitaxel (Taxol) is a taxane diterpenoid isolated from the Pacific yew tree (*Taxus brevifolia* Nutt.) [222]. It is an active diterpene with strong cytotoxic effects against various cancerous cells [223]. A wide-range of cancers, including breast, lung, and ovarian cancer types are currently cured with this drug [224]. The mechanism underlying taxol action is well-understood and includes impairment of mitosis via microtubules stabilization followed by induction of p53-independent apoptosis [225]. Recently, regulation of autophagy (both induction and blockage) and upregulation of cytokines have been explored as contributors to the mechanism of action of this chemotherapeutic drug in cancerous cells [226]. Basically, the primary response of the cells to paclitaxel and its analogs is a cell-cycle arrest. If the cells cannot cope with the stress, then an apoptosis and autophagic cell death response are activated [227]. Taxol is able to trigger an early autophagy in both hypoxia and normoxia conditions in breast cancer cells that may be followed by apoptosis [228]. Drug-resistance HeLa (HeLa-R) cells represent an upregulated autophagy pathway, as evidenced by the accumulation of Beclin1, LC3-II, Atg7, and Atg12-Atg5, whereby autophagy inhibition can sensitize HeLa-R cells to paclitaxel [229]. The ER stress and the unfolded protein response (UPR) is another known mechanism for drug resistance of breast cancer to paclitaxel. An activation of PERK (after 2 h of incubation) and IRE1α (after 4 h of incubation), two typical branches of the UPR, has been observed in taxol-resistant cells [230]. ATF4, a transcription factor involved in UPR, is upregulated in the hypoxic condition of the tumor, which in turn induces an autophagy response in breast cancer MDA–MB-231 and T47D cells. Also, ATF4-induced autophagy is responsible for resistance against taxol-induced cell death in cancerous cells [230,231]. Recently, a cell-cycle-dependent autophagy response has been observed in MCF-7 and SK-BR-3 breast carcinoma cell lines [227]. Increasing of autophagic markers have been reported in various cancer cells exposed to taxol including U87, A549, PC-3, and HT-29 cells [226]. However, its poor solubility limits taxol effectiveness in clinical protocols [227]. As we discuss later in this paper, this challenge can be solved by nano-based strategies that aim to increase taxol bioavailability [232].

Quercetin

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is a dietary flavonoid with anti-inflammatory, anti-oxidant and anti-cancer activities [233] that inhibits tumor promotion through inducing cell-cycle arrest and also promoting programmed cell death [234,235]. This flavone induces cell death through modulating different signaling pathways, including PI3K, MAPK, ERK, and PKC kinases [236,237]. Moreover, quercetin can down-regulate the expression of oncogenes including Mcl-1, Ras, MEK, and PI3K that is linked to the elimination of cancer cells. Besides these effects, quercetin induces the formation of phagolysosome associated with the accumulation of autophagic biomarkers in epithelial cancer cells [17]. This pentahydroxyflavone also induces autophagy, specifically in the Ha-RAS-transformed cells. Indeed, the expression of oncogenic Ha-RAS has been linked to autophagy to sensitize glioma

and gastric cancer cells to quercetin [238]. There is also some evidence in the literature suggesting that quercetin induces pro-survival autophagy in U373MG cells. Autophagy blockage sensitizes cancerous cells to the chemotherapeutic effects of quercetin [239]. Thus, several reports provided evidence for quercetin-induced apoptosis and autophagy in *in vivo* and *in vitro* models [240]. A caspase-independent autophagy response has been reported in RAS-transformed colon cells treated with quercetin [241]. Mechanistically, quercetin suppresses the phosphorylation of Akt-mTOR in prostate and gastric cells through HIF-1α (hypoxia-induced factor 1α) signaling [240]. Martinez-Outschoorn *et al.* reported that quercetin treatment alleviates mitochondrial dysfunction in cancer-associated fibroblasts by a ROS-mediated autophagy/mitophagy [242]. Quercetin treatment attenuates the activity of proteasomes and results in accumulation of polyubiquitinated protein aggregates that subsequently induces a massive autophagic cell death response in epithelial cancer cells [243]. HSP72-mediated autophagy inhibited apoptosis and attenuated lipopolysaccharide-induced mesothelial cell injury through a JNK signaling pathway. Down-regulation of HSP72 with quercetin induces autophagy that protects the cells against apoptosis. Autophagy inhibition in this condition sensitizes the cells to apoptosis and peritoneal injury increases [244].

Resveratrol

Resveratrol (3,5,4′-trihydroxystilbene) is a polyphenolic compound, which is extracted from grapes, peanuts, berries, and other plant sources [245,246]. This stilbenoid exhibits various pharmacologic properties and represents a good potential candidate for anti-cancer therapy due to apoptosis induction, anti-angiogenesis, anti-inflammation, and anti-metastasis action, as well as controlling cell division activities in various types of cancer [245–249]. The main reason for the anti-cancer ability of resveratrol is because of its apoptotic activity via different signaling pathways, such as down-regulation of surviving and Bcl-2, as well as up-regulation of p53 and Bax [250]. Resveratrol enhances cancer cell death by modulating the levels of Fas and FasL, which was seen in multiple myeloma and T cell leukemia cells [245]. Moreover, resveratrol is able to downregulate CDK2, cyclin E, CDK4, cyclin D1, and retinoblastoma protein [245,251]. Preclinical studies show the beneficial function of this compound in preventing and treating at different stages of cancer [15]. In addition, resveratrol inhibits microRNA 21 *(miR-21)* expression in prostate PC-3M-MM2 cells and regulates the expression of miR-20a and miR-20b in several cancers [252]. The link of resveratrol with autophagy has been also reported in a variety of cancer cells. The first evidence on the autophagic role of resveratrol has been provided by Opipari *et al.,* who reported that this phytochemical induces autophagic cell death in five ovarian cancer cell lines [253]. Resveratrol-induced protective autophagy and delayed apoptosis in human glioma cells were also demonstrated [102]. The silent mating type information regulation 2 homolog 1 (SIRT1) is known as one of the best-characterized targets of resveratrol that is activated during both autophagic and apoptotic effects of this phytochemical [254]. For example, resveratrol stimulates autophagy in lung cells of cigarette smokers through ROS-dependent upregulation of SIRT1 [255]. As a SIRT1-independent mechanism, resveratrol activates autophagy by blocking phosphorylation of Akt or p70S6K [15], whereby modulating the expression of Bcl-XL and Bcl-2. In contrast to the most autophagy-affecting phytochemicals, however, resveratrol did not change the expression of Beclin1 in MCF-7 cells. A recent study showed that resveratrol induces caspase-dependent apoptosis through ROS-dependence in colon cancer HT-29 and COLO201 cells [247]. Importantly, both *in vivo* and *in vitro* evidence revealed that resveratrol significantly inhibits breast cancer stem cells proliferation by inducing autophagy through suppression of the Wnt/β-catenin signaling pathway [256]. There are also several reports suggesting that resveratrol induces autophagy by regulating the mTOR/AKT signaling pathway [257,258]. Autophagy inducing effects of resveratrol can also be mediated through the cAMP/PRKA/AMPK/SIRT1 signaling pathway in endothelial cells [259]. Autophagy is also triggered by resveratrol in leukemia cells via both JNK-mediated p62/SQSTM1 overexpression and AMPK/mTOR activation [260]. As a therapeutic application, a combination of resveratrol and rapamycin, a well-known inducer of autophagy, has been proposed as a strategy for targeting breast cancer cells [261]. Finally, resveratrol, similar to curcumin, induces autophagy blockade that results in premature senescence via downregulation of Rictor [262].

Rottlerin

Rottlerin, also called mallotoxin, is a phloroglucinol which is extracted from *Mallotus philippensis* (Lam.) Müll. Arg. [263] and known as a potent PKCδ inhibitor with apoptotic and/or autophagic activities [264]. Anti-cancer effects of this polyphenol have been tested in various cancer cells, including pancreatic [265], prostate [266], breast [267], and melanoma [268]. Rottlerin suppresses cell proliferation and cell division of colon cancer (SW1116 cells) via regulating DNA methylation and inhibiting the MAPK signaling pathway [269]. The apoptotic and autophagic effects of rottlerin have been reported in a pancreatic stellate cell, in which it acted through ER stress induction via upregulation of CHOP and PERK [270]. In addition, rottlerin significantly inhibits mTORC1 pathway in prostate and breast cancer cells [271]. This phytochemical compound also inhibits NF-κB, induces AMPK, and subsequently stimulates autophagy in tumor cells [17]. An early activation of autophagy has been observed in breast CSCs that is associated with survival and delayed apoptosis through inhibition of the Akt/mTOR signaling pathway and induction of Atg12 and Beclin 1 [272]. Autophagic effects of rottlerin have also been observed in pancreatic cancer stem cells [273] and breast cancer cells [274].

Shikonin

Shikonin is a naphthoquinone isolated from the roots of *Lithospermum erythrorhizon* Siebold & Zucc [275]. Several studies reported that this phytochemical could significantly repress TNF-α-induced proliferation, cause cell-cycle arrest, and induce caspase-mediated apoptosis [276]. Shikonin is able to suppress ERK and AKT phosphorylation, and activate retinoblastoma protein in thyroid cancer cells [277]. In addition, shikonin induces both autophagy and apoptosis through the ROS-dependent mitochondrial pathway in HCC cells [278]. Furthermore, shikonin evokes autophagy to preserve the survival of pancreatic cancer cells (BXPC-3) by repressing the expression of SQSTM1/p62 and PI3K/Akt, and enhancing the expression of LC3–II to promote pancreatic cancer cells autophagy [279]. This natural compound also induced autophagic cell death via regulating Beclin-1 and LC3-II/LC3-I ratio [280]. Shikonin induced autophagy in non-small cell lung cancer cells, where inhibition of autophagy leads to shikonin-induced necroptosis [281]. Shuqing *et al.* reported that shikonin stimulates autophagy in pancreatic cancer cells through the PI3K/Akt signaling pathway [279]. This phytochemical has been reported to present differential effects on induction of immunogenic cell death versus autophagy [282]. Finally, shikonin inhibits the activity of proteasome system and results in accumulating ubiquitinylated proteins that induce autophagy in cancerous cells [282].

Shogaol

[6]-shogaol is a polyphenol of dietary ginger (*Zingiber officinale* Roscoe), that could induce both autophagic and apoptotic death in

human colon adenocarcinoma (HT-29) cells. Recent studies showed that [6]-shogaol induced cell-cycle arrest, autophagy, and apoptosis in HT-29 cells in a time sequence. After 6 h, 6-shogaol induced apparent G2/M arrest, and the HT-29 cells formed numerous autophagosomes in each phase of the cell cycle. After 18 h, increases in acidic vesicles and Lysosome-associated membrane proteins LAMP-1 showed that [6]-shogaol had caused autophagic cell death. After 24 h, cell shrinkage and Caspase-3/7 activities were rising, suggesting that apoptotic cell death had increased. Finally, after 48 h, the result of TUNEL assay indicated the highest occurrence of apoptosis upon [6]-shogaol treatment. It appeared that apoptosis is triggered by autophagy in [6]-shogaol treated HT-29 cells, whereby the damage of autophagic cell death initiated apoptosis program [283].

Silibinin (silybin)

Silibinin (silybin) is a phytochemical belonging to flavonoids, which is extracted mostly from milk thistle seeds (*Silybum marianum* (L.) Gaertn. Anti-cancer activities of silibinin have been reported in different cancers such as lung, skin, colorectal, and prostate cancer both *in vivo* and *in vitro* [284]. Silibinin induces ROS-dependent autophagy through increasing LC3II/LC3I ratio and Atg12-Atg5 formation in breast cancer cell (MCF-7) [14]. It strongly inhibits mTOR pathway, but inversely activates AMPK pathway in renal cell carcinoma [285]. Furthermore, silibinin induces autophagy cell death ROS-dependent MAPK activation along with inhibition of PI3K-Akt in human fibrosarcoma cells (HT1080) [286].

Sulforaphane

Sulforaphane is a phytochemical belonging to isothiocyanates family derived from cruciferous vegetables such as cabbage, brussels sprouts, and broccoli. The anti-cancer activity of sulforaphane is confirmed in various types of cancer, including leukemia [287], prostate [288], breast cancer [289], and hepatoma [290]. Various studies confirmed that this phytochemical promotes cell death and inhibits proliferation through generating ROS [290,291]. Recent studies demonstrated that sulforaphane is a potent inducer of pro-survival autophagy in human prostate [292], colon and breast cancer cells [293,294]. Inhibiting autophagy in these models resulted in apoptosis. However, ROS-dependent cell death and autophagy triggered by sulforaphane are independent of each other in pancreatic carcinoma cells [295].

γ-tocotrienol

Tocotrienols belong to the group of vitamin E and exist in four different isomers, including α-, β-, γ-, and δ-tocotrienol depending on the position and number of the methyl groups in the chromanol ring. The principle dietary sources of tocotrienols include red palm oil and rice bran oil, and among all, γ-tocotrienol possesses many health benefits, including cardioprotection, anti-cancer, and neuroprotective properties [296]. Treatment with γ-tocotrienol caused a time-dependent decrease in cancer cell viability that corresponds to a concurrent induction of both ER stress and autophagy in human breast cancer MCF-7 and MDA-MB-231 cells. Pretreatment with autophagy inhibitors (3-MA or Baf1) blocked γ-tocotrienol-induced cytotoxicity [296]. However, autophagy induction by γ-tocotrienol can be cytoprotective at relatively low concentrations [296]. Similar to resveratrol, autophagy induction by γ-tocotrienol has synergic effects against ischaemia-reperfusion injury, which is mediated in part via the PI3K/Akt/mTOR pathway. It is tempting to speculate that autophagy along with an enhanced survival signal helps to maintain the basic cell functions [297].

Thymoquinone

Thymoquinone is the main bioactive compound extracted from *Nigella sativa* L. or black cumin. This phytochemical exhibits anti-fungal, anti-viral, immunomodulatory, anti-inflammatory, anti-oxidant, and anti-cancer effects in both *in vitro* and *in vivo* models [298,299]. [300] Anti-cancer activity of thymoquinone is mediated through targeting various signaling pathways, including DNA synthesis, ROS, cell-cycle and apoptosis [299]. In addition, thymoquinone modulates autophagy activity in different cancer models. Experiments on mouse xenograft model of prostate cancer showed that the administration of thymoquinone, alone, has no toxic effect, but its combination with cisplatin synergistically inhibits tumor growth and angiogenesis by suppressing the AKT and ERK pathways [301,302]. This natural compound blocks autophagic flux in glioblastoma cells, which consequently leads to perturbation of the lysosomal membrane and cathepsin-mediated cell death [303]. Also, it synergistically enhances the cytotoxic effects of temozolomide via a transcriptional inhibition of autophagy in glioblastoma U87MG cells [304]. A recent study revealed that thymoquinone evokes an autophagic cell death accompanied with caspase-9-dependent apoptosis in both *in vitro* and *in vivo* models of oral cancer [300]. In addition, this phytochemical activates caspase-independent autophagic cell death via induction of JNK and p38 MAPKs, as well as mitochondrial outer membrane permeability in CPT-11-R colon cancer cells [305].

Triptolide

Triptolide is a diterpenoid isolated from *Tripterygium wilfordii* Hook. f. (Thunder God Vine). The anti-cancer activity of this compound has been tested in different tumor models both *in vitro* and *in vivo* [306]. Triptolide can counteract the NF-κB pathway [307] and induces autophagy as a pro-death mechanism in pancreatic cancer cells [308]. It is also able to induce autophagy through inhibiting the Akt/mTO/P70S6K pathway and activating the ERK pathway in HS766T, s2-013, and s2-vp10 cells [309]. The autophagic role of triptolide along with the accumulation of LC3-II protein have been also reported in neuroblastoma cells (SH-SY5Y) [307].

Ursolic acid

Ursolic acid is a triterpenoid phytochemical enriched in a variety of plants. Ursolic acid has anti-tumor activity through inhibiting proliferation, suppressing the DNA replication, inducing the Ca^{2+} release and activating caspase in several cancer cells, including breast carcinoma, melanoma, leukemia, hepatoma, and prostate cancer [310]. Ursolic acid is a potent repressor of NF-κB, thus inhibiting effects of inflammatory agents and tumor promoters [310]. This compound enhances cell death and modulates autophagy via activating the JNK pathway [311] or inhibiting the PI3k/Akt pathway in colorectal cancer cells [312]. However, ursolic acid can also induce cell death through autophagy blockage in apoptosis-resistant colorectal cancer cells [311]. The autophagic effect of this triterpenoid in cervical cancer TC-1 cells is accompanied by an increase in LC3-II conversion and upregulation of Atg5 [313]. In addition, ursolic acid activates autophagy in breast cancer MCF-7 cells through ER stress [314]. In another report, ursolic acid induced autophagy via three different pathways, including PERK-eIF2α-CHOP, CaMMK (calmodulin-dependent kinase protein kinase)/AMPK/mTOR, and IRE1α-JNK signaling in glioblastoma U87MG cells [315].

Challenges in using phytochemicals as drugs

Despite the therapeutic benefits of phytochemicals, two main obstacles including, poor bioavailability [316] and lack of correlation between *in vitro* and *in vivo* concentrations, hinder their clinical use [317]. The term “bioavailability” means the concentration of the absorbed compound, or its metabolite, in a specific organ that is

related to the primary target for the therapeutic action and is determined by the chemical structure of the compounds [318]. Pharmacokinetic studies showed that low solubility and rapid metabolism are the most critical reasons for the low bioavailability of phytochemicals in *in vivo* studies [319]. Nanotechnology offers a novel promising solution for enhancing bioavailability of phytochemicals [320]. Nanoparticles (NPs) and nano-size drug carriers, such as micelles, dendrimers, and liposomes, are extremely useful to increase bioavailability and to enhance anti-cancer agent delivery [316,319,321]. Many phytochemicals, such as polyphenols and carotenoids, are poorly soluble and the delivery of such phytochemicals can be significantly improved by the use of nano-carriers that modulate their solubility, crystallinity, lipophilicity, and other physicochemical properties [322]. For example, complexation of curcumin with phospholipids significantly increased the half-life and maximum plasma concentration (C_{max}) of the drug when administrated to male rats orally at a dose of 100 mg/kg. The C_{max} of curcumin free form was 267 ng/mL, while it increased up to 600 ng/mL for the curcumin-phospholipid complex [319,323]. Microemulsion of curcumin with a particle size less than 100 nm showed approximately 3.9-fold increase in absorption in comparison with curcumin suspension in mice models [324]. *In vivo* pharmacokinetic study indicated that polymeric micellar curcumin exhibited 60-fold higher biological half-life compared to plain curcumin in rats [325]. Moreover, a formulation of curcumin solid lipid NPs with P-glycoprotein enhanced solubility and bioavailability of curcumin. The curcumin suspension showed C_{max} value of 0.24 ± 0.05 μg/mL with T_{max} of 30 min (poor oral absorption), while curcumin solid lipid NPs indicated significantly higher C_{max} values (0.58 ± 0.03 μg/mL) [326]. Similar nano-based strategies could also enhance bioavailability of many other phytochemicals, such as taxol, resveratrol and quercetin [232,327,328]. For example, novel nanomaterials based on liposomes, nanocapsules and microspheres have been known to optimize bioavailability and therapeutic efficacy of quercetin [329].

Conclusion and prospective

Despite the growing knowledge of cancer pathogenesis and its treatment, developing targeted chemotherapeutics remains a major challenge in modern medicine. Current cancer therapies are unable to target cancer stem cells, and in most cases, a relapse of the disease might be observed. Additionally, multi-drug resistance is another substantial problem in the clinical application of current chemotherapeutic drugs. In this line, autophagy modulators may serve as promising anti-cancer agents to combat the unresolved problem of drug resistance and improve current cancer therapeutic strategies. Currently, over 30 clinical trials are studying the effects of autophagy modulators, alone or in combination with chemotherapeutic drugs, in various human cancers [17]. The results of these clinical trials are critical for better understanding the role of autophagy in cancer biology and therapy. In this context, natural products can be considered as an important resource for drug development due to their inducing effects on both apoptosis and autophagy. The autophagic potential of phytochemicals can aid overcoming drug resistance or might be used as an alternative approach for inducing cell death in apoptotic-resistant cells. In this review, we discussed the most common phytochemicals that showed autophagy-modulating properties. The autophagic effects of phytochemicals depend on dose and treatment times, as well as on type and content of the cells. For example, baicalein induces both autophagy and apoptosis in different cancer models. The autophagic response induced by baicalein is cytoprotective in human hepatocellular carcinoma cells, while an apoptotic cell death response is occurring following autophagy induction by this phytochemical in prostate cancer cells. The anticancer effects of fisetin are higher in human breast cancer MCF-7 than in MDA-MB-231 cells. The induction of cell death in caspase-3-deficient MCF-7 cells by fisetin is mediated through autophagy inhibition as additional route to prompt its anticancer activity. Also, anticancer effects of ursolic acid are mediated through autophagy blockage in apoptosis-resistant colorectal cancer cells. Therefore, phytochemicals may induce or inhibit autophagy and such autophagy-modulating effects of phytochemicals may suppress or promote apoptosis. Moreover, autophagic potential of phytochemicals might be considered as an alternative way for cell death in cells resistant to apoptosis. Since these natural compounds have been proved to possess low cytotoxicity and reduced side effects, they can be considered as a good choice for a single therapy or in combination with FDA-approved drugs for the treatment of cancer. However, phytochemicals have limitations such as poor bioavailability and multi-target properties, which hinder their clinical applications. Novel nanotechnology strategies, including liposomes, polymer micelles, phospholipid complexes, microemulsions, and NPs, are promising to address these limitations. NPs can interact with phenolic compounds through hydrogen bonds and hydrophobic interactions to encapsulate phenolic compounds and promote their aqueous solubility. Moreover, nano-capsules can protect drug degradation in biological fluids and improve their cell penetration. Finally, because NPs represent potent autophagic activity *per se*, they can synergize the autophagic potential of phytochemicals as therapeutic or even theragnostic (both for therapy and diagnosis) agents.

Conflicts of interest

None.

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References

[1] M.J. Tuorkey, Cancer therapy with phytochemicals: present and future perspectives, Biomed. Environ. Sci. 28 (2015) 808–819.
[2] M. Russo, C. Spagnuolo, I. Tedesco, G.L. Russo, Phytochemicals in cancer prevention and therapy: truth or dare? Toxins 2 (2010) 517–551.
[3] R.H. Liu, Potential synergy of phytochemicals in cancer prevention: mechanism of action, J. Nutr. 134 (2004) 3479S–3485S.
[4] G.-L. Russo, M. Russo, C. Spagnuolo, The pleiotropic flavonoid quercetin: from its metabolism to the inhibition of protein kinases in chronic lymphocytic leukemia, Food Funct. 19 (2014) 16340–16365.
[5] B.Y.K. Law, et al., New potential pharmacological functions of Chinese herbal medicines via regulation of autophagy, Molecules 21 (2016) 359.
[6] H. Si, D. Liu, Dietary antiaging phytochemicals and mechanisms associated with prolonged survival, J. Nutr. Biochem. 25 (2014) 581–591.
[7] M.-K. Kim, et al., Autophagy as a target for anticancer therapy and its modulation by phytochemicals, J. Food Drug Anal. 20 (2012) 241–245.
[8] H. Gali-Muhtasib, R. Hmadi, M. Kareh, R. Tohme, N. Darwiche, Cell death mechanisms of plant-derived anticancer drugs: beyond apoptosis, Apoptosis 20 (2015) 1531–1562.

[9] M.M. Grabacka, M. Gawin, M. Pierzchalska, Phytochemical modulators of mitochondria: the search for chemopreventive agents and supportive therapeutics, Pharmaceuticals 7 (2014) 913–942.
[10] F. Aqil, R. Munagala, J. Jeyabalan, M.V. Vadhanam, Bioavailability of phytochemicals and its enhancement by drug delivery systems, Canc. Lett. 334 (2013) 133–141.
[11] J. Wang, J. Yi, Cancer cell killing via ROS: to increase or decrease, that is the question, Canc. Biol. Ther. 7 (2008) 1875–1884.
[12] D. Trachootham, J. Alexandre, P. Huang, Targeting cancer cells by ROS-mediated mechanisms: a radical therapeutic approach? Nat. Rev. Drug Discov. 8 (2009) 579.
[13] M.A. Moosavi, et al., Photodynamic N-TiO2 nanoparticle treatment induces controlled Ros-mediated autophagy and terminal differentiation of leukemia cells, Sci. Rep. 6 (2016) 34413.
[14] K. Jiang, et al., Silibinin, a natural flavonoid, induces autophagy via ROS-dependent mitochondrial dysfunction and loss of ATP involving BNIP3 in human MCF7 breast cancer cells, Oncol. Rep. 33 (2015) 2711–2718.
[15] S.-F. Zhang, X.-L. Wang, X.-Q. Yang, N. Chen, Autophagy-associated targeting pathways of natural products during cancer treatment, Asian Pac. J. Cancer Prev. APJCP: Asian Pac. J. Cancer Prev. APJCP 15 (2014) 10557.
[16] V. Naponelli, A. Modernelli, S. Bettuzzi, F. Rizzi, Roles of autophagy induced by natural compounds in prostate cancer, BioMed Res. Int. 2015 (2015).
[17] N. Hasima, B. Ozpolat, Regulation of autophagy by polyphenolic compounds as a potential therapeutic strategy for cancer, Cell Death Dis. 5 (2014) e1509.
[18] B. Levine, G. Kroemer, Autophagy in the pathogenesis of disease, Cell 132 (2008) 27–42.
[19] D.J. Klionsky, Autophagy: from phenomenology to molecular understanding in less than a decade, Nat. Rev. Mol. Cell Biol. 8 (2007) 931–937.
[20] D.C. Rubinsztein, J.E. Gestwicki, L.O. Murphy, D.J. Klionsky, Potential therapeutic applications of autophagy, Nat. Rev. Drug Discov. 6 (2007) 304–312.
[21] A. Bergmann, Autophagy and cell death: no longer at odds, Cell 131 (2007) 1032–1034.
[22] B.Y.K. Law, et al., Natural small-molecule enhancers of autophagy induce autophagic cell death in apoptosis-defective cells, Sci. Rep. 4 (2014).
[23] S. Chen, et al., Autophagy is a therapeutic target in anticancer drug resistance, Biochim. Biophys. Acta Rev. Canc 1806 (2010) 220–229.
[24] K. Sun, et al., Paradoxical roles of autophagy in different stages of tumorigenesis: protector for normal or cancer cells, Cell Biosci. 3 (2013) 35.
[25] E.E. Mowers, M.N. Sharifi, K.F. Macleod, Autophagy in cancer metastasis, Oncogene 36 (2017) 1619.
[26] C.M. Kenific, A. Thorburn, J. Debnath, Autophagy and metastasis: another double-edged sword, Curr. Opin. Cell Biol. 22 (2010) 241–245.
[27] B. Janji, E. Viry, J. Baginska, K. Van Moer, G. Berchem, Role of Autophagy in Cancer and Tumor Progression. autophagy: A Double-Edged Sword-Cell Survival or Death, 189–215, 2013.
[28] R. Mathew, V. Karantza-Wadsworth, E. White, Role of autophagy in cancer, Nat. Rev. Canc. 7 (2007) 961–967.
[29] R.L. Deter, C. De Duve, Influence of glucagon, an inducer of cellular autophagy, on some physical properties of rat liver lysosomes, J. Cell Biol. 33 (1967) 437–449.
[30] Z. Yang, D.J. Klionsky, Mammalian autophagy: core molecular machinery and signaling regulation, Curr. Opin. Cell Biol. 22 (2010) 124–131.
[31] D.J. Klionsky, The molecular machinery of autophagy: unanswered questions, J. Cell Sci. 118 (2005) 7–18.
[32] P. Mokarram, et al., New frontiers in the treatment of colorectal cancer: autophagy and the unfolded protein response as promising targets, Autophagy 13 (2017) 781–819.
[33] P.-M. Coly, P. Gandolfo, H. Castel, F. Morin, The autophagy machinery: a new player in chemotactic cell migration, Front. Neurosci. 11 (2017).
[34] X. Yang, et al., The role of autophagy induced by tumor microenvironment in different cells and stages of cancer, Cell Biosci. 5 (2015) 14.
[35] H. Heath-Engel, N. Chang, G. Shore, The endoplasmic reticulum in apoptosis and autophagy: role of the BCL-2 protein family, Oncogene 27 (2008) 6419–6433.
[36] D. Gozuacik, A. Kimchi, Autophagy as a cell death and tumor suppressor mechanism, Oncogene 23 (2004) 2891–2906.
[37] Y. Ávalos, et al., Tumor suppression and promotion by autophagy, BioMed Res. Int. 2014 (2014).
[38] R. Errafiy, et al., PTEN Increases Autophagy and Inhibits the Ubiquitin-Proteasome Pathway in Glioma Cells Independently of its Lipid Phosphatase Activity, 2013.
[39] S. Arico, et al., The tumor suppressor PTEN positively regulates macroautophagy by inhibiting the phosphatidylinositol 3-kinase/protein kinase B pathway, J. Biol. Chem. 276 (2001) 35243–35246.
[40] E.J. White, et al., Autophagy regulation in cancer development and therapy, Am. J. Canc. Res. 1 (2011) 362.
[41] F. Kruiswijk, C.F. Labuschagne, K.H. Vousden, p53 in survival, death and metabolic health: a lifeguard with a licence to kill, Nat. Rev. Mol. Cell Biol. 16 (2015) 393–405.
[42] E. Morselli, et al., Mutant p53 protein localized in the cytoplasm inhibits autophagy, Cell Cycle 7 (2008) 3056–3061.
[43] B. Levine, J. Abrams, p53: the Janus of autophagy? Nat. Cell Biol. 10 (2008) 637–639.
[44] M. Li, P. Gao, J. Zhang, Crosstalk between autophagy and apoptosis: potential and emerging therapeutic targets for cardiac diseases, Int. J. Mol. Sci. 17 (2016) 332.
[45] M. Abedin, D. Wang, M. McDonnell, U. Lehmann, A. Kelekar, Autophagy delays apoptotic death in breast cancer cells following DNA damage, Cell Death Differ. 14 (2007) 500–510.
[46] R.T. Marquez, B.W. Tsao, N.F. Faust, L. Xu, Drug Resistance and Molecular Cancer Therapy: Apoptosis versus Autophagy, 2013.
[47] Z.J. Yang, C.E. Chee, S. Huang, F. Sinicrope, Autophagy modulation for cancer therapy, Canc. Biol. Ther. 11 (2011) 169–176.
[48] E. Tasdemir, et al., p53 represses autophagy in a cell cycle-dependent fashion, Cell Cycle 7 (2008) 3006–3011.
[49] X. Li, Z. Fan, The epidermal growth factor receptor antibody cetuximab induces autophagy in cancer cells by downregulating HIF-1α and Bcl-2 and activating the beclin 1/hVps34 complex, Canc. Res. 70 (2010) 5942–5952.
[50] U. Akar, et al., Silencing of Bcl-2 expression by small interfering RNA induces autophagic cell death in MCF-7 breast cancer cells, Autophagy 4 (2008) 669–679.
[51] D.A. Rizzieri, et al., A phase 2 clinical trial of deforolimus (AP23573, MK-8669), a novel mammalian target of rapamycin inhibitor, in patients with relapsed or refractory hematologic malignancies, Clin. Canc. Res. 14 (2008) 2756–2762.
[52] Y.-J. Surh, Cancer chemoprevention with dietary phytochemicals, Nat. Rev. Canc. 3 (2003) 768–780.
[53] J.Y. Yang, M.A. Della-Fera, C. Nelson-Dooley, C.A. Baile, Molecular mechanisms of apoptosis induced by ajoene in 3T3-L1 adipocytes, Obesity 14 (2006) 388–397.
[54] Y.-L. Chu, C.-T. Ho, J.-G. Chung, R. Rajasekaran, L.-Y. Sheen, Allicin induces p53-mediated autophagy in Hep G2 human liver cancer cells, J. Agric. Food Chem. 60 (2012) 8363–8371.
[55] Y.-L. Chu, et al., Allicin induces anti-human liver cancer cells through the p53 gene modulating apoptosis and autophagy, J. Agric. Food Chem. 61 (2013) 9839–9848.
[56] X. Zhang, Y. Zhu, W. Duan, C. Feng, X. He, Allicin induces apoptosis of the MGC-803 human gastric carcinoma cell line through the p38 mitogen-activated protein kinase/caspase-3 signaling pathway, Mol. Med. Rep. 11 (2015) 2755–2760.
[57] L.-S. Wang, G.D. Stoner, Anthocyanins and their role in cancer prevention, Canc. Lett. 269 (2008) 281–290.
[58] C. Hui, et al., Anticancer activities of an anthocyanin-rich extract from black rice against breast cancer cells in vitro and in vivo, Nutr. Canc. 62 (2010) 1128–1136.
[59] J.N. Lu, et al., The inhibitory effect of anthocyanins on Akt on invasion and epithelial-mesenchymal transition is not associated with the anti-EGFR effect of the anthocyanins, Int. J. Oncol. 44 (2014) 1756–1766.
[60] L. Longo, et al., Autophagy inhibition enhances anthocyanin-induced apoptosis in hepatocellular carcinoma, Mol. Canc. Therapeut. 7 (2008) 2476–2485.
[61] Y.K. Kim, et al., Anthocyanin extracts from black soybean (Glycine max L.) protect human glial cells against oxygen-glucose deprivation by promoting autophagy, Biomolecules Therapeut. 20 (2012) 68.
[62] Y.-J. Choe, et al., Anthocyanins in the black soybean (Glycine max L.) protect U2OS cells from apoptosis by inducing autophagy via the activation of adenosyl monophosphate-dependent protein kinase, Oncol. Rep. 28 (2012) 2049–2056.
[63] D. Patel, S. Shukla, S. Gupta, Apigenin and cancer chemoprevention: progress, potential and promise (review), Int. J. Oncol. 30 (2007) 233–245.
[64] S. Shukla, S. Gupta, Apigenin: a promising molecule for cancer prevention, Pharmaceut. Res. 27 (2010) 962–978.
[65] E.J. Choi, G.-H. Kim, Apigenin causes G 2/M arrest associated with the modulation of p21 Cip1 and Cdc2 and activates p53-dependent apoptosis pathway in human breast cancer SK-BR-3 cells, J. Nutr. Biochem. 20 (2009) 285–290.
[66] M.A. Babcook, S. Gupta, Apigenin: a promising anticancer agent for the modulation of the Insulin-like Growth Factor (IGF) Axis in prostate cancer, Biomed. Res. 23 (2012) 55–68.
[67] X. Cao, et al., Autophagy inhibition enhances apigenin-induced apoptosis in human breast cancer cells, Chin. J. Canc. Res. 25 (2013) 212.
[68] Y. Lee, et al., Apigenin-induced apoptosis is enhanced by inhibition of autophagy formation in HCT116 human colon cancer cells, Int. J. Oncol. 44 (2014) 1599–1606.
[69] X. Tong, K.A. Smith, J.C. Pelling, Apigenin, a chemopreventive bioflavonoid, induces AMP-activated protein kinase activation in human keratinocytes, Mol. Carcinog. 51 (2012) 268–279.
[70] C.-M. Lin, et al., Apigenin-induced lysosomal degradation of β-catenin in Wnt/β-catenin signaling, Sci. Rep. 7 (2017) 372.
[71] R. Johnson, S. Shabalala, J. Louw, A.P. Kappo, C.J.F. Muller, Aspalathin reverts doxorubicin-induced cardiotoxicity through increased autophagy and decreased expression of p53/mTOR/p62 signaling, Molecules 22 (2017) 1589.
[72] S.E. Mazibuko, et al., Aspalathin improves glucose and lipid metabolism in 3T3-L1 adipocytes exposed to palmitate, Mol. Nutr. Food Res. 59 (2015) 2199–2208.
[73] P. Aryal, et al., Baicalein induces autophagic cell death through AMPK/ULK1 activation and downregulation of mTORC1 complex components in human cancer cells, FEBS J. 281 (2014) 4644–4658.
[74] B.D. Sahu, et al., Baicalein alleviates doxorubicin-induced cardiotoxicity via suppression of myocardial oxidative stress and apoptosis in mice, Life Sci.

144 (2016) 8–18.
[75] A. Liu, et al., Baicalein pretreatment reduces liver ischemia/reperfusion injury via induction of autophagy in rats, Sci. Rep. 6 (2016) 25042.
[76] H. Liu, et al., The fascinating effects of baicalein on cancer: a review, Int. J. Mol. Sci. 17 (2016) 1681.
[77] Z. Guo, et al., Baicalein inhibits prostate cancer cell growth and metastasis via the caveolin-1/AKT/mTOR pathway, Mol. Cell. Biochem. 406 (2015) 111–119.
[78] L. Wang, et al., Berberine induces caspase-independent cell death in colon tumor cells through activation of apoptosis-inducing factor, PLoS One 7 (2012) e36418.
[79] Y. Sun, K. Xun, Y. Wang, X. Chen, A systematic review of the anticancer properties of berberine, a natural product from Chinese herbs, Anti Canc. Drugs 20 (2009) 757–769.
[80] H.-y. Hu, et al., Set9, NF-κB, and microRNA-21 mediate berberine-induced apoptosis of human multiple myeloma cells, Acta Pharmacol. Sin. 34 (2013) 157–166.
[81] N. Wang, et al., Berberine induces autophagic cell death and mitochondrial apoptosis in liver cancer cells: the cellular mechanism, J. Cell. Biochem. 111 (2010) 1426–1436.
[82] Y. Deng, et al., Berberine attenuates autophagy in adipocytes by targeting BECN1, Autophagy 10 (2014) 1776–1786.
[83] X. La, L. Zhang, Z. Li, P. Yang, Y. Wang, Berberine-induced autophagic cell death by elevating GRP78 levels in cancer cells, Oncotarget 8 (2017) 20909.
[84] J. Wang, et al., Berberine induces autophagy in glioblastoma by targeting the AMPK/mTOR/ULK1-pathway, Oncotarget 7 (2016) 66944.
[85] X. Fan, et al., Berberine alleviates ox-LDL induced inflammatory factors by up-regulation of autophagy via AMPK/mTOR signaling pathway, J. Transl. Med. 13 (2015) 92.
[86] M. Tillhon, L.M.G. Ortiz, P. Lombardi, A.I. Scovassi, Berberine: new perspectives for old remedies, Biochem. Pharmacol. 84 (2012) 1260–1267.
[87] G. Kai, et al., Biosynthesis and biotechnological production of anti-cancer drug Camptothecin, Phytochemistry Rev. 14 (2015) 525–539.
[88] Y. Pommier, Topoisomerase I inhibitors: camptothecins and beyond, Nat. Rev. Canc. 6 (2006) 789–802.
[89] J.-w. Zhang, et al., Autophagy inhibition switches low-dose camptothecin-induced premature senescence to apoptosis in human colorectal cancer cells, Biochem. Pharmacol. 90 (2014) 265–275.
[90] M.G. Hollomon, N. Gordon, J.M. Santiago-O'Farrill, E.S. Kleinerman, Knockdown of autophagy-related protein 5, ATG5, decreases oxidative stress and has an opposing effect on camptothecin-induced cytotoxicity in osteosarcoma cells, BMC Canc. 13 (2013) 500.
[91] Y.-J. Surh, More than spice: capsaicin in hot chili peppers makes tumor cells commit suicide, J. Natl. Cancer Inst. 94 (2002) 1263–1265.
[92] R. Zhang, I. Humphreys, R.P. Sahu, Y. Shi, S.K. Srivastava, In vitro and in vivo induction of apoptosis by capsaicin in pancreatic cancer cells is mediated through ROS generation and mitochondrial death pathway, Apoptosis 13 (2008) 1465–1478.
[93] A.M. Sánchez, et al., Apoptosis induced by capsaicin in prostate PC-3 cells involves ceramide accumulation, neutral sphingomyelinase, and JNK activation, Apoptosis 12 (2007) 2013–2024.
[94] A. Mori, et al., Capsaicin, a component of red peppers, inhibits the growth of androgen-independent, p53 mutant prostate cancer cells, Canc. Res. 66 (2006) 3222–3229.
[95] S.H. Oh, et al., Dihydrocapsaicin (DHC), a saturated structural analog of capsaicin, induces autophagy in human cancer cells in a catalase-regulated manner, Autophagy 4 (2008) 1009–1019.
[96] C.-H. Choi, Y.-K. Jung, S.-H. Oh, Autophagy induction by capsaicin in malignant human breast cells is modulated by p38 and extracellular signal-regulated mitogen-activated protein kinases and retards cell death by suppressing endoplasmic reticulum stress-mediated apoptosis, Mol. Pharmacol. 78 (2010) 114–125.
[97] Á. Ramos-Torres, A. Bort, C. Morell, N. Rodríguez-Henche, I. Díaz-Laviada, The pepper's natural ingredient capsaicin induces autophagy blockage in prostate cancer cells, Oncotarget 7 (2016) 1569.
[98] Y.-T. Lin, et al., Capsaicin induces autophagy and apoptosis in human nasopharyngeal carcinoma cells by downregulating the PI3K/AKT/mTOR pathway, Int. J. Mol. Sci. 18 (2017) 1343.
[99] X. Chen, et al., Inhibiting ROS-STAT3-dependent autophagy enhanced capsaicin–induced apoptosis in human hepatocellular carcinoma cells, Free Radic. Res. 50 (2016) 744–755.
[100] C. Amantini, et al., Capsaicin triggers autophagic cell survival which drives epithelial mesenchymal transition and chemoresistance in bladder cancer cells in an Hedgehog-dependent manner, Oncotarget 7 (2016) 50180.
[101] J.-H. Lee, et al., Inhibition of NF-κB activation through targeting IκB kinase by celastrol, a quinone methide triterpenoid, Biochem. Pharmacol. 72 (2006) 1311–1321.
[102] J. Li, Z. Qin, Z. Liang, The prosurvival role of autophagy in Resveratrol-induced cytotoxicity in human U251 glioma cells, BMC Canc. 9 (2009) 215.
[103] S. Boridy, P. Le, K. Petrecca, D. Maysinger, Celastrol targets proteostasis and acts synergistically with a heat-shock protein 90 inhibitor to kill human glioblastoma cells, Cell Death Dis. 5 (2014) e1216.
[104] W.B. Wang, et al., Paraptosis accompanied by autophagy and apoptosis was induced by celastrol, a natural compound with influence on proteasome, ER stress and Hsp90, J. Cell. Physiol. 227 (2012) 2196–2206.
[105] R. Kannaiyan, et al., Celastrol inhibits tumor cell proliferation and promotes apoptosis through the activation of c-Jun N-terminal kinase and suppression of PI3 K/Akt signaling pathways, Apoptosis 16 (2011) 1028–1041.
[106] H.-W. Lee, et al., Celastrol inhibits gastric cancer growth by induction of apoptosis and autophagy, BMB Rep 47 (2014) 697–702.
[107] Y.-N. Deng, J. Shi, J. Liu, Q.-M. Qu, Celastrol protects human neuroblastoma SH-SY5Y cells from rotenone-induced injury through induction of autophagy, Neurochem. Int. 63 (2013) 1–9.
[108] H. Li, et al., Celastrol induces apoptosis and autophagy via the ROS/JNK signaling pathway in human osteosarcoma cells: an in vitro and in vivo study, Cell Death Dis. 6 (2015) e1604.
[109] X. Zhao, et al., Inhibition of autophagy strengthens celastrol-induced apoptosis in human pancreatic cancer in vitro and in vivo models, Curr. Mol. Med. 14 (2014) 555–563.
[110] J. Guo, X. Huang, H. Wang, H. Yang, Celastrol induces autophagy by targeting AR/miR-101 in prostate cancer cells, PLoS One 10 (2015), e0140745.
[111] T. Divya, A. Sureshkumar, G. Sudhandiran, Autophagy induction by celastrol augments protection against bleomycin-induced experimental pulmonary fibrosis in rats: role of adaptor protein p62/SQSTM1, Pulm. Pharmacol. Therapeut. 45 (2017) 47–61.
[112] H.S. Tuli, D. Kashyap, A.K. Sharma, Cordycepin: a cordyceps metabolite with promising therapeutic potential, Fungal Metabolites 761–782 (2017).
[113] Y. Liao, et al., Cordycepin induces cell cycle arrest and apoptosis by inducing DNA damage and up-regulation of p53 in Leukemia cells, Cell Cycle 14 (2015) 761–771.
[114] S. Choi, et al., Cordycepin-induced apoptosis and autophagy in breast cancer cells are independent of the estrogen receptor, Toxicol. Appl. Pharmacol. 257 (2011) 165–173.
[115] H.S. Tuli, A.K. Sharma, S.S. Sandhu, D. Kashyap, Cordycepin: a bioactive metabolite with therapeutic potential, Life Sci. 93 (2013) 863–869.
[116] Y. Chen, et al., Cordycepin induces apoptosis of C6 glioma cells through the adenosine 2A receptor-p53-caspase-7-PARP pathway, Chem. Biol. Interact. 216 (2014) 17–25.
[117] N. Yoshikawa, et al., Antitumour activity of cordycepin in mice, Clin. Exp. Pharmacol. Physiol. 31 (2004).
[118] C. Yang, L. Zhao, W. Yuan, J. Wen, Cordycepin induces apoptotic cell death and inhibits cell migration in renal cell carcinoma via regulation of microRNA-21 and PTEN phosphatase, Biomed. Res. 38 (2017) 313–320.
[119] Y. Li, et al., Cordycepin induces apoptosis and autophagy in human neuroblastoma SK-N-SH and BE (2)-M17 cells, Oncol. Lett. 9 (2015) 2541–2547.
[120] H.H. Lee, et al., Involvement of autophagy in cordycepin-induced apoptosis in human prostate carcinoma LNCaP cells, Environ. Toxicol. Pharmacol. 38 (2014) 239–250.
[121] B.S. Pan, Y.K. Wang, M.S. Lai, Y.F. Mu, B.M. Huang, Cordycepin induced MA-10 mouse Leydig tumor cell apoptosis by regulating p38 MAPKs and PI3K/AKT signaling pathways, Sci. Rep. 5 (2015) 13372.
[122] X. Yu, et al., Cordycepin induces autophagy-mediated c-FLIPL degradation and leads to apoptosis in human non-small cell lung cancer cells, Oncotarget 8 (2017) 6691.
[123] N. Chaicharoenaudomrung, T. Jaroonwitchawan, P. Noisa, Cordycepin induces apoptotic cell death of human brain cancer through the modulation of autophagy, Toxicol. Vitro 46 (2018) 113–121.
[124] D.H. Lee, G.B. Iwanski, N.H. Thoennissen, Cucurbitacin: ancient compound shedding new light on cancer treatment, Sci. World J. 10 (2010) 413–418.
[125] N. Wakimoto, et al., Cucurbitacin B has a potent antiproliferative effect on breast cancer cells in vitro and in vivo, Canc. Sci. 99 (2008) 1793–1797.
[126] G. Yuan, et al., Cucurbitacin I induces protective autophagy in glioblastoma in vitro and in vivo, J. Biol. Chem. 289 (2014) 10607–10619.
[127] Q.-B. Zha, et al., Cucurbitacin E Induces Autophagy via Downregulating mTORC1 Signaling and Upregulating AMPK Activity, 2015.
[128] W.-W. Huang, et al., Cucurbitacin E induces G 2/M phase arrest through STAT3/p53/p21 signaling and provokes apoptosis via Fas/CD95 and mitochondria-dependent pathways in human bladder cancer T24 cells, Evid. base Compl. Alternative Med. 2012 (2012).
[129] G. Ren, et al., Cucurbitacin B induces DNA damage and autophagy mediated by reactive oxygen species (ROS) in MCF-7 breast cancer cells, J. Nat. Med. 1–9 (2015).
[130] T. Zhang, et al., Cucurbitacin induces autophagy through mitochondrial ROS production which counteracts to limit caspase-dependent apoptosis, Autophagy 8 (2012) 559–576.
[131] Q.-B. Zha, et al., Cucurbitacin E induces autophagy via downregulating mTORC1 signaling and upregulating AMPK activity, PLoS One 10 (2015), e0124355.
[132] T. Nakanishi, et al., Autophagy is associated with cucurbitacin D-induced apoptosis in human T cell leukemia cells, Med. Oncol. 33 (2016) 30.
[133] A. Haghi, H. Azimi, R. Rahimi, A comprehensive review on pharmacotherapeutics of three phytochemicals, curcumin, quercetin, and allicin, in the treatment of gastric cancer, J. Gastrointest. Canc. 48 (2017) 314–320.
[134] C. Kantara, et al., Curcumin promotes autophagic survival of a subset of colon cancer stem cells, which are ablated by DCLK1-siRNA, Canc. Res. 74 (2014) 2487–2498.
[135] S. Toden, et al., Curcumin mediates chemosensitization to 5-fluorouracil through miRNA-induced suppression of epithelial-to-mesenchymal transition in chemoresistant colorectal cancer, Carcinogenesis 36 (2015) 355–367.
[136] F.H. Sarkar, Y. Li, Z. Wang, S. Padhye, Lesson learned from nature for the

development of novel anti-cancer agents: implication of isoflavone, curcumin, and their synthetic analogs, Curr. Pharmaceut. Des. 16 (2010) 1801.
[137] G. Chadalapaka, et al., Curcumin decreases specificity protein expression in bladder cancer cells, Canc. Res. 68 (2008) 5345–5354.
[138] M. Salemi, A. Ghavamzadeh, M. Nikbakht, Anti-Vascular endothelial growth factor targeting by curcumin and thalidomide in acute myeloid leukemia cells, Asian Pac. J. Cancer Prev. APJCP 18 (2017) 3055–3061.
[139] R. Singh, J.W. Lillard, Targeted delivery of curcumin to improve therapeutic outcome in breast cancer, Canc. Res. 74 (2014), 4476–4476.
[140] L.-L. Yu, J.-G. Wu, N. Dai, H.-G. Yu, J.-M. Si, Curcumin reverses chemoresistance of human gastric cancer cells by downregulating the NF-κB transcription factor, Oncol. Rep. 26 (2011) 1197–1203.
[141] G.G. Mackenzie, et al., Curcumin induces cell-arrest and apoptosis in association with the inhibition of constitutively active NF-kB and STAT3 pathways in Hodgkin's lymphoma cells, Int. J. Cancer 123 (2008) 56–65.
[142] H. Hatcher, R. Planalp, J. Cho, F. Torti, S. Torti, Curcumin: from ancient medicine to current clinical trials, Cell. Mol. Life Sci. 65 (2008) 1631–1652.
[143] A. Moustapha, et al., Curcumin induces crosstalk between autophagy and apoptosis mediated by calcium release from the endoplasmic reticulum, lysosomal destabilization and mitochondrial events, Cell Death Discov. 1 (2015) 15017.
[144] K. Singletary, J. Milner, Diet, autophagy, and cancer: a review, Cancer Epidemiol. Biomark. Prev. 17 (2008) 1596–1610.
[145] Y.J. Lee, N.-Y. Kim, Y.-A. Suh, C. Lee, Involvement of ROS in curcumin-induced autophagic cell death, KOREAN J. PHYSIOL. PHARMACOL. 15 (2011) 1–7.
[146] C. Yang, et al., Curcumin induces apoptosis and protective autophagy in castration-resistant prostate cancer cells through iron chelation, Drug Des. Dev. Ther. 11 (2017) 431.
[147] B.C. Jordan, C.D. Mock, R. Thilagavathi, C. Selvam, Molecular mechanisms of curcumin and its semisynthetic analogues in prostate cancer prevention and treatment, Life Sci. 152 (2016) 135–144.
[148] L. Masuelli, et al., Curcumin blocks autophagy and activates apoptosis of malignant mesothelioma cell lines and increases the survival of mice intraperitoneally transplanted with a malignant mesothelioma cell line, Oncotarget 8 (2017) 34405–34422.
[149] L. Chen, et al., Autophagy inhibition contributes to the synergistic interaction between EGCG and doxorubicin to kill the hepatoma Hep3B cells, 2014.
[150] E.C. Stuart, M.J. Scandlyn, R.J. Rosengren, Role of epigallocatechin gallate (EGCG) in the treatment of breast and prostate cancer, Life Sci. 79 (2006) 2329–2336.
[151] J.-T. Hwang, et al., Apoptotic effect of EGCG in HT-29 colon cancer cells via AMPK signal pathway, Canc. Lett. 247 (2007) 115–121.
[152] W.S. Ahn, et al., A major constituent of green tea, EGCG, inhibits the growth of a human cervical cancer cell line, CaSki cells, through apoptosis, G1 arrest, and regulation of gene expression, DNA Cell Biol. 22 (2003) 217–224.
[153] J. Zhou, et al., Epigallocatechin-3-gallate (EGCG), a green tea polyphenol, stimulates hepatic autophagy and lipid clearance, PLoS One 9 (2014) e87161.
[154] H.-S. Kim, V. Montana, H.-J. Jang, V. Parpura, J.-a. Kim, Epigallocatechin gallate (EGCG) stimulates autophagy in vascular endothelial cells a potential role for reducing lipid accumulation, J. Biol. Chem. 288 (2013) 22693–22705.
[155] J.-H. Lee, et al., EGCG-mediated autophagy flux has a neuroprotection effect via a class III histone deacetylase in primary neuron cells, Oncotarget 6 (2015) 9701.
[156] C. Chen, et al., Epigallocatechin-3-gallate-induced stress signals in HT-29 human colon adenocarcinoma cells, Carcinogenesis 24 (2003) 1369–1378.
[157] W. Li, et al., EGCG stimulates autophagy and reduces cytoplasmic HMGB1 levels in endotoxin-stimulated macrophages, Biochem. Pharmacol. 81 (2011) 1152–1163.
[158] Y. Chen, et al., Reduction in autophagy by (-)-Epigallocatechin-3-Gallate (EGCG): a potential mechanism of prevention of mitochondrial dysfunction after subarachnoid hemorrhage, Mol. Neurobiol. 54 (2017) 392–405.
[159] J. Jiang, C. Hu, Evodiamine: a novel anti-cancer alkaloid from Evodia rutaecarpa, Molecules 14 (2009) 1852–1859.
[160] J.-Y. Hong, S.H. Park, H.-Y. Min, H.J. Park, S.K. Lee, Anti-proliferative effects of evodiamine in human lung cancer cells, J. Cancer Prev. 19 (2014) 7.
[161] T.-J. Lee, et al., Caspase-dependent and caspase-independent apoptosis induced by evodiamine in human leukemic U937 cells, Mol. Canc. Therapeut. 5 (2006) 2398–2407.
[162] A. Rasul, et al., Cytotoxic effect of evodiamine in SGC-7901 human gastric adenocarcinoma cells via simultaneous induction of apoptosis and autophagy, Oncol. Rep. 27 (2012) 1481–1487.
[163] J. Yang, L.-J. Wu, S.-I. Tashino, S. Onodera, T. Ikejima, Reactive oxygen species and nitric oxide regulate mitochondria-dependent apoptosis and autophagy in evodiamine-treated human cervix carcinoma HeLa cells, Free Radic. Res. 42 (2008) 492–504.
[164] Y.-J. Tu, X. Fan, X. Yang, C. Zhang, H.-P. Liang, Evodiamine activates autophagy as a cytoprotective response in murine Lewis lung carcinoma cells, Oncol. Rep. 29 (2013) 481–490.
[165] A.-J. Liu, et al., Evodiamine, a plant alkaloid, induces calcium/JNK-mediated autophagy and calcium/mitochondria-mediated apoptosis in human glioblastoma cells, Chem. Biol. Interact. 205 (2013) 20–28.
[166] Y. Suh, et al., Fisetin induces autophagic cell death through suppression of mTOR signaling pathway in prostate cancer cells, Carcinogenesis 31 (2010) 1424–1433.
[167] T.-H. Ying, et al., Fisetin induces apoptosis in human cervical cancer HeLa cells through ERK1/2-mediated activation of caspase-8-/caspase-3-dependent pathway, Arch. Toxicol. 86 (2012) 263–273.
[168] P.-M. Yang, H.-H. Tseng, C.-W. Peng, W.-S. Chen, S.-J. Chiu, Dietary flavonoid fisetin targets caspase-3-deficient human breast cancer MCF-7 cells by induction of caspase-7-associated apoptosis and inhibition of autophagy, Int. J. Oncol. 40 (2012) 469–478.
[169] S. Kim, et al., Fisetin stimulates autophagic degradation of phosphorylated tau via the activation of TFEB and Nrf2 transcription factors, Sci. Rep. 6 (2016).
[170] L.-l. Zhang, et al., A novel anti-cancer effect of genistein: reversal of epithelial mesenchymal transition in prostate cancer cells, Acta Pharmacol. Sin. 29 (2008) 1060–1068.
[171] M.H. Ravindranath, S. Muthugounder, N. Presser, S. Viswanathan, in Complementary and Alternative Approaches to Biomedicine, Springer, 2004, pp. 121–165.
[172] G. Gossner, et al., Genistein-induced apoptosis and autophagocytosis in ovarian cancer cells, Gynecol. Oncol. 105 (2007) 23–30.
[173] R. Prietsch, et al., Genistein induces apoptosis and autophagy in human breast MCF-7 cells by modulating the expression of proapoptotic factors and oxidative stress enzymes, Mol. Cell. Biochem. 390 (2014) 235–242.
[174] N. Mohan, M. Chakrabarti, N.L. Banik, S.K. Ray, Combination of LC3 shRNA plasmid transfection and genistein treatment inhibited autophagy and increased apoptosis in malignant neuroblastoma in cell culture and animal models, PLoS One 8 (2013).
[175] A.B. Ali, D.S. Nin, J. Tam, M. Khan, Role of chaperone mediated autophagy (CMA) in the degradation of misfolded N-CoR protein in non-small cell lung cancer (NSCLC) cells, PLoS One 6 (2011) e25268.
[176] E. Radhakrishnan, et al., [6]-Gingerol induces caspase-dependent apoptosis and prevents PMA-induced proliferation in colon cancer cells by inhibiting MAPK/AP-1 signaling, 2014.
[177] Y.J. Park, J. Wen, S. Bang, S.W. Park, S.Y. Song, [6]-Gingerol induces cell cycle arrest and cell death of mutant p53-expressing pancreatic cancer cells, Yonsei Med. J. 47 (2006) 688–697.
[178] D. Chakraborty, et al., [6]-Gingerol induces caspase 3 dependent apoptosis and autophagy in cancer cells: drug–DNA interaction and expression of certain signal genes in HeLa cells, Eur. J. Pharmacol. 694 (2012) 20–29.
[179] U.M. Nazim, et al., Inhibition of the autophagy flux by gingerol enhances TRAIL-induced tumor cell death, Oncol. Rep. 33 (2015) 2331–2336.
[180] A.S. Attele, J.A. Wu, C.-S. Yuan, Ginseng pharmacology: multiple constituents and multiple actions, Biochem. Pharmacol. 58 (1999) 1685–1693.
[181] Y. Liang, S. Zhao, Progress in understanding of ginsenoside biosynthesis, Plant Biol. 10 (2008) 415–421.
[182] T.T. Mai, et al., Ginsenoside F2 induces apoptosis accompanied by protective autophagy in breast cancer stem cells, Canc. Lett. 321 (2012) 144–153.
[183] H. Ko, Y.-J. Kim, J.-S. Park, J.H. Park, H.O. Yang, Autophagy inhibition enhances apoptosis induced by ginsenoside Rk1 in hepatocellular carcinoma cells, Biosci. Biotechnol. Biochem. 73 (2009) 2183–2189.
[184] D.-G. Kim, et al., 20 (S)-Ginsenoside Rg3 is a novel inhibitor of autophagy and sensitizes hepatocellular carcinoma to doxorubicin, Oncotarget 5 (2014) 4438.
[185] L. Chen, et al., Ginsenoside compound K sensitizes human colon cancer cells to TRAIL-induced apoptosis via autophagy-dependent and-independent DR5 upregulation, Cell Death Dis. 7 (2016) e2334.
[186] Z.-L. Zhang, Y. Fan, M.-L. Liu, Ginsenoside Rg1 inhibits autophagy in H9c2 cardiomyocytes exposed to hypoxia/reoxygenation, Mol. Cell. Biochem. 365 (2012) 243–250.
[187] Q. Huang, T. Wang, L. Yang, H.-Y. Wang, Ginsenoside Rb2 alleviates hepatic lipid accumulation by restoring autophagy via induction of Sirt1 and activation of AMPK, Int. J. Mol. Sci. 18 (2017) 1063.
[188] J.-H. Moon, J.-H. Lee, Y.-J. Lee, S.-Y. Park, Autophagy flux induced by ginsenoside-Rg3 attenuates human prion protein-mediated neurotoxicity and mitochondrial dysfunction, Oncotarget 7 (2016) 85697.
[189] Y. Fan, et al., Identification of natural products with neuronal and metabolic benefits through autophagy induction, Autophagy 13 (2017) 41–56.
[190] T.-L. Lu, et al., Hispolon from Phellinus linteus has antiproliferative effects via MDM2-recruited ERK1/2 activity in breast and bladder cancer cells, Food Chem. Toxicol. 47 (2009) 2013–2021.
[191] Q. Wu, et al., The anticancer effects of hispolon on lung cancer cells, Biochem. Biophys. Res. Commun. 453 (2014) 385–391.
[192] J.H. Kim, Y.C. Kim, B. Park, Hispolon from Phellinus linteus induces apoptosis and sensitizes human cancer cells to the tumor necrosis factor-related apoptosis-inducing ligand through upregulation of death receptors, Oncol. Rep. 35 (2016) 1020–1026.
[193] T.-L. Lu, et al., Hispolon promotes MDM2 downregulation through chaperone-mediated autophagy, Biochem. Biophys. Res. Commun. 398 (2010) 26–31.
[194] Z. Zhao, Y.-S. Sun, W. Chen, L.-X. Lv, Y.-Q. Li, Hispolon inhibits breast cancer cell migration by reversal of epithelial-to-mesenchymal transition via suppressing the ROS/ERK/Slug/E-cadherin pathway, Oncol. Rep. 35 (2016) 896–904.
[195] H.Y. Ho, et al., Hispolon suppresses migration and invasion of human nasopharyngeal carcinoma cells by inhibiting the urokinase-plasminogen activator through modulation of the Akt signaling pathway, Environ. Toxicol. 32 (2017) 645–655.
[196] M.-C. Hsin, et al., Hispolon suppresses metastasis via autophagic degradation

of cathepsin S in cervical cancer cells, Cell Death Dis. 8 (2017) e3089.
[197] E.S. Kim, et al., Autophagy mediates anti-melanogenic activity of 3′-ODI in B16F1 melanoma cells, Biochem. Biophys. Res. Commun. 442 (2013) 165–170.
[198] E.-J. Lee, S.-Y. Oh, M.-K. Sung, Luteolin exerts anti-tumor activity through the suppression of epidermal growth factor receptor-mediated pathway in MDA-MB-231 ER-negative breast cancer cells, Food Chem. Toxicol. 50 (2012) 4136–4143.
[199] J. Sung, J. Lee, Anti-inflammatory activity of butein and luteolin through suppression of NF κ B activation and induction of heme oxygenase-1, J. Med. Food 18 (2015) 557–564.
[200] R.K. Ambasta, et al., Comparative study of anti-angiogenic activities of luteolin, lectin and lupeol biomolecules, J. Transl. Med. 13 (2015) 1.
[201] Y. Lin, R. Shi, X. Wang, H.-M. Shen, Luteolin, a flavonoid with potential for cancer prevention and therapy, Curr. Cancer Drug Targets 8 (2008) 634–646.
[202] M.J. Tuorkey, Molecular targets of luteolin in cancer, Eur. J. Canc. Prev. 25 (2016) 65–76.
[203] M. Chakrabarti, S.K. Ray, Anti-tumor activities of luteolin and silibinin in glioblastoma cells: overexpression of miR-7-1-3p augmented luteolin and silibinin to inhibit autophagy and induce apoptosis in glioblastoma in vivo, Apoptosis 21 (2016) 312–328.
[204] S.-H. Park, et al., Induction of endoplasmic reticulum stress-mediated apoptosis and non-canonical autophagy by luteolin in NCI-H460 lung carcinoma cells, Food Chem. Toxicol. 56 (2013) 100–109.
[205] L. Verschooten, et al., Autophagy inhibitor chloroquine enhanced the cell death inducing effect of the flavonoid luteolin in metastatic squamous cell carcinoma cells, PLoS One 7 (2012) e48264.
[206] M. Sarawut Jindarat, Xanthones from mangosteen (Garcinia mangostana): multi-targeting pharmacological properties, J. Med. Assoc. Thai. 97 (2014) S196–S201.
[207] M.Y. Ibrahim, et al., α-Mangostin from Garcinia mangostana Linn: an updated review of its pharmacological properties, Arabian J. Chem. 9 (2016) 317–329.
[208] A. Krajarng, Y. Nakamura, S. Suksamrarn, R. Watanapokasin, α-Mangostin induces apoptosis in human chondrosarcoma cells through downregulation of ERK/JNK and Akt signaling pathway, J. Agric. Food Chem. 59 (2011) 5746–5754.
[209] K. Matsumoto, et al., Preferential target is mitochondria in α-mangostin-induced apoptosis in human leukemia HL60 cells, Bioorg. Med. Chem. 12 (2004) 5799–5806.
[210] R. Watanapokasin, et al., Effects of α-mangostin on apoptosis induction of human colon cancer, World J. Gastroenterol.: WJG 17 (2011) 2086.
[211] A.-C. Chao, Y.-L. Hsu, C.-K. Liu, P.-L. Kuo, α-Mangostin, a dietary xanthone, induces autophagic cell death by activating the AMP-activated protein kinase pathway in glioblastoma cells, J. Agric. Food Chem. 59 (2011) 2086–2096.
[212] J.-J. Chen, et al., Inhibition of autophagy augments the anticancer activity of α-mangostin in chronic myeloid leukemia cells, Leuk. Lymphoma 55 (2014) 628–638.
[213] H.W. Ryu, et al., Depigmentation of α-melanocyte-stimulating hormone-treated melanoma cells by β-mangostin is mediated by selective autophagy, Exp. Dermatol. 26 (2017) 585–591.
[214] Y.-h. Zhang, Y.-l. Wu, S.-i. Tashiro, S. Onodera, T. Ikejima, Reactive oxygen species contribute to oridonin-induced apoptosis and autophagy in human cervical carcinoma HeLa cells, Acta Pharmacol. Sin. 32 (2011) 1266–1275.
[215] C.-y. Li, E.-q. Wang, Y. Cheng, J.-k. Bao, Oridonin: an active diterpenoid targeting cell cycle arrest, apoptotic and autophagic pathways for cancer therapeutics, Int. J. Biochem. Cell Biol. 43 (2011) 701–704.
[216] G.-B. Zhou, et al., Oridonin, a diterpenoid extracted from medicinal herbs, targets AML1-ETO fusion protein and shows potent antitumor activity with low adverse effects on t (8; 21) leukemia in vitro and in vivo, Blood 109 (2007) 3441–3450.
[217] X. Li, X. Li, J. Wang, Z. Ye, J.-C. Li, Oridonin up-regulates expression of P21 and induces autophagy and apoptosis in human prostate cancer cells, Int. J. Biol. Sci. 8 (2012) 901.
[218] J.-F. Zhang, et al., Oridonin inhibits cell growth by induction of apoptosis on human hepatocelluar carcinoma BEL-7402 cells, Hepatol. Res. 35 (2006) 104–110.
[219] Y. Li, et al., Oridonin phosphate-induced autophagy effectively enhances cell apoptosis of human breast cancer cells, Med. Oncol. 32 (2015) 1–8.
[220] R. Zeng, Y. Chen, S. Zhao, G.-h Cui, Autophagy counteracts apoptosis in human multiple myeloma cells exposed to oridonin in vitro via regulating intracellular ROS and SIRT1, Acta Pharmacol. Sin. 33 (2012) 91–100.
[221] Y. Cheng, F. Qiu, T. Ikejima, Molecular mechanisms of oridonin-induced apoptosis and autophagy in murine fibrosarcoma L929 cells, Autophagy 5 (2009) 430–431.
[222] S. Tyagi, G. Singh, A. Sharma, G. Aggarwal, Phytochemicals as candidate therapeutics: an overview, Int. J. Pharmaceut. Sci. Rev. Res. 3 (2010) 53–55.
[223] A.J. Wood, E.K. Rowinsky, R.C. Donehower, Paclitaxel (taxol), N. Engl. J. Med. 332 (1995) 1004–1014.
[224] P.C. Liao, S.K. Tan, C.H. Lieu, H.K. Jung, Involvement of endoplasmic reticulum in paclitaxel-induced apoptosis, J. Cell. Biochem. 104 (2008) 1509–1523.
[225] S.S. Bacus, et al., Taxol-induced apoptosis depends on MAP kinase pathways (ERK and p38) and is independent of p53, Oncogene 20 (2001) 147–155.
[226] G. Xi, et al., Autophagy inhibition promotes paclitaxel-induced apoptosis in cancer cells, Canc. Lett. 307 (2011) 141–148.
[227] R. Veldhoen, et al., The chemotherapeutic agent paclitaxel inhibits autophagy through two distinct mechanisms that regulate apoptosis, Oncogene 32 (2013) 736–746.
[228] A. Notte, N. Ninane, T. Arnould, C. Michiels, Hypoxia counteracts taxol-induced apoptosis in MDA-MB-231 breast cancer cells: role of autophagy and JNK activation, Cell Death Dis. 4 (2013) e638.
[229] X. Peng, et al., Autophagy promotes paclitaxel resistance of cervical cancer cells: involvement of Warburg effect activated hypoxia-induced factor 1-α-mediated signaling, Cell Death Dis. 5 (2014) e1367.
[230] A. Notte, et al., Taxol-induced unfolded protein response activation in breast cancer cells exposed to hypoxia: ATF4 activation regulates autophagy and inhibits apoptosis, Int. J. Biochem. Cell Biol. 62 (2015) 1–14.
[231] T. Rzymski, M. Milani, D.C. Singleton, A.L. Harris, Role of ATF4 in regulation of autophagy and resistance to drugs and hypoxia, Cell Cycle 8 (2009) 3838–3847.
[232] D. Pandita, et al., Development of lipid-based nanoparticles for enhancing the oral bioavailability of paclitaxel, AAPS PharmSciTech 12 (2011) 712–722.
[233] C. Chen, J. Zhou, C. Ji, Quercetin: a potential drug to reverse multidrug resistance, Life Sci. 87 (2010) 333–338.
[234] J. Ravindran, S. Prasad, B.B. Aggarwal, Curcumin and cancer cells: how many ways can curry kill tumor cells selectively? AAPS J. 11 (2009) 495–510.
[235] S.J. Park, et al., Autophagy inhibition promotes quercetin induced apoptosis in MG-63 human osteosarcoma cells, Int. J. Oral Biol. 40 (2015) 85–91.
[236] Y.-D. Min, et al., Quercetin inhibits expression of inflammatory cytokines through attenuation of NF-κB and p38 MAPK in HMC-1 human mast cell line, Inflamm. Res. 56 (2007) 210–215.
[237] F. Dajas, Life or death: neuroprotective and anticancer effects of quercetin, J. Ethnopharmacol. 143 (2012) 383–396.
[238] F.H. Psahoulia, et al., Quercetin mediates preferential degradation of oncogenic Ras and causes autophagy in Ha-RAS-transformed human colon cells, Carcinogenesis 28 (2007) 1021–1031.
[239] H. Kim, J.Y. Moon, K.S. Ahn, S.K. Cho, Quercetin induces mitochondrial mediated apoptosis and protective autophagy in human glioblastoma U373MG cells, Oxidative Med. Cell. Longevity 2013 (2013).
[240] K. Wang, et al., Quercetin induces protective autophagy in gastric cancer cells: involvement of Akt-mTOR-and hypoxia-induced factor 1α-mediated signaling, Autophagy 7 (2011) 966–978.
[241] F.O. Ranelletti, et al., Quercetin inhibits p21-RAS expression in human colon cancer cell lines and in primary colorectal tumors, Int. J. Canc. 85 (2000) 438–445.
[242] U.E. Martinez-Outschoorn, et al., Oxidative stress in cancer associated fibroblasts drives tumor-stroma co-evolution: a new paradigm for understanding tumor metabolism, the field effect and genomic instability in cancer cells, Cell Cycle 9 (2010) 3276–3296.
[243] A.K. Klappan, S. Hones, I. Mylonas, A. Brüning, Proteasome inhibition by quercetin triggers macroautophagy and blocks mTOR activity, Histochem. Cell Biol. 137 (2012) 25–36.
[244] S. Li, et al., Heat shock protein 72 enhances autophagy as a protective mechanism in lipopolysaccharide-induced peritonitis in rats, Am. J. Pathol. 179 (2011) 2822–2834.
[245] Y. Shukla, R. Singh, Resveratrol and cellular mechanisms of cancer prevention, Ann. N. Y. Acad. Sci. 1215 (2011) 1–8.
[246] L.G. Carter, J.A. D'Orazio, K.J. Pearson, Resveratrol and cancer: focus on in vivo evidence, Endocr. Relat. Canc. 21 (2014) R209–R225.
[247] H. Miki, et al., Resveratrol induces apoptosis via ROS-triggered autophagy in human colon cancer cells, Int. J. Oncol. 40 (2012) 1020–1028.
[248] K.P. Bhat, J.M. Pezzuto, Cancer chemopreventive activity of resveratrol, Ann. N. Y. Acad. Sci. 957 (2002) 210–229.
[249] M. Athar, et al., Resveratrol: a review of preclinical studies for human cancer prevention, Toxicol. Appl. Pharmacol. 224 (2007) 274–283.
[250] A. Ghorbani, A. Hosseini, Cancer therapy with phytochemicals: evidence from clinical studies, Avicenna J. Phytomed. 5 (2015) 84–97.
[251] B.B. Aggarwal, et al., Role of resveratrol in prevention and therapy of cancer: preclinical and clinical studies, Anticancer Res. 24 (2004) 2783–2840.
[252] S. Sheth, et al., Resveratrol reduces prostate cancer growth and metastasis by inhibiting the Akt/MicroRNA-21 pathway, 2012.
[253] A.W. Opipari, et al., Resveratrol-induced autophagocytosis in ovarian cancer cells, Canc. Res. 64 (2004) 696–703.
[254] S. Chung, et al., Regulation of SIRT1 in cellular functions: role of polyphenols, Arch. Biochem. Biophys. 501 (2010) 79–90.
[255] J.-w. Hwang, et al., Cigarette smoke-induced autophagy is regulated by SIRT1–PARP-1-dependent mechanism: implication in pathogenesis of COPD, Arch. Biochem. Biophys. 500 (2010) 203–209.
[256] Y. Fu, et al., Resveratrol inhibits breast cancer stem-like cells and induces autophagy via suppressing Wnt/β-catenin signaling pathway, 2014.
[257] S. Selvaraj, Y. Sun, P. Sukumaran, B.B. Singh, Resveratrol activates autophagic cell death in prostate cancer cells via downregulation of STIM1 and the mTOR pathway, Mol. Carcinog. 55 (2016) 818–831.
[258] F. Scarlatti, R. Maffei, I. Beau, P. Codogno, R. Ghidoni, Role of non-canonical Beclin 1-independent autophagy in cell death induced by resveratrol in human breast cancer cells, Cell Death Differ. 15 (2008) 1318–1329.
[259] M.-l. Chen, et al., Resveratrol attenuates vascular endothelial inflammation by inducing autophagy through the cAMP signaling pathway, Autophagy 9 (2013) 2033–2045.

[260] A. Puissant, et al., Resveratrol promotes autophagic cell death in chronic myelogenous leukemia cells via JNK-mediated p62/SQSTM1 expression and AMPK activation, Canc. Res. 70 (2010) 1042–1052.
[261] A. Alayev, S.M. Berger, M.Y. Kramer, N.S. Schwartz, M.K. Holz, The combination of rapamycin and resveratrol blocks autophagy and induces apoptosis in breast cancer cells, J. Cell. Biochem. 116 (2015) 450–457.
[262] J.H. Back, et al., Resveratrol-mediated downregulation of rictor attenuates autophagic process and suppresses UV-induced skin carcinogenesis, Photochem. Photobiol. 88 (2012) 1165–1172.
[263] E. Maioli, C. Torricelli, G. Valacchi, Rottlerin and cancer: novel evidence and mechanisms, Sci. World J. 2012 (2012).
[264] J.H. Lim, J.-W. Park, K.S. Choi, Y.B. Park, T.K. Kwon, Rottlerin induces apoptosis via death receptor 5 (DR5) upregulation through CHOP-dependent and PKC δ-independent mechanism in human malignant tumor cells, Carcinogenesis 30 (2009) 729–736.
[265] B.N. Singh, D. Kumar, S. Shankar, R.K. Srivastava, Rottlerin induces autophagy which leads to apoptotic cell death through inhibition of PI3K/Akt/mTOR pathway in human pancreatic cancer stem cells, Biochem. Pharmacol. 84 (2012) 1154–1163.
[266] D. Kumar, S. Shankar, R.K. Srivastava, Rottlerin induces autophagy and apoptosis in prostate cancer stem cells via PI3K/Akt/mTOR signaling pathway, Canc. Lett. 343 (2014) 179–189.
[267] C. Torricelli, et al., Rottlerin inhibits the nuclear factor κB/Cyclin-D1 cascade in MCF-7 breast cancer cells, Life Sci. 82 (2008) 638–643.
[268] E. Daveri, G. Valacchi, R. Romagnoli, E. Maellaro, E. Maioli, Antiproliferative effect of rottlerin on Sk-Mel-28 melanoma cells, Evid. base Compl. Alternative Med. 2015 (2015).
[269] A.S. Ali, S. Ali, B.F. El-Rayes, P.A. Philip, F.H. Sarkar, Exploitation of protein kinase C: a useful target for cancer therapy, Canc. Treat Rev. 35 (2009) 1–8.
[270] H.-Y. Su, R. Waldron, R. Gong, S. Pandol, A. Lugea, Rottlerin induces ER stress-mediated cell death in pancreatic stellate cells, Canc. Res. 75 (2015), 1769–1769.
[271] W. Lu, C. Lin, Y. Li, Rottlerin induces Wnt co-receptor LRP6 degradation and suppresses both Wnt/β-catenin and mTORC1 signaling in prostate and breast cancer cells, Cell. Signal. 26 (2014) 1303–1309.
[272] D. Kumar, S. Shankar, R.K. Srivastava, Rottlerin-induced autophagy leads to the apoptosis in breast cancer stem cells: molecular mechanisms, Mol. Canc. 12 (2013) 171.
[273] C. Torricelli, et al., Alternative pathways of cancer cell death by rottlerin: apoptosis versus autophagy, Evid. base Compl. Alternative Med. 2012 (2012).
[274] E.J. Park, T.K. Kwon, Rottlerin enhances IL-1β-induced COX-2 expression through sustained p38 MAPK activation in MDA-MB-231 human breast cancer cells, Exp. Mol. Med. 43 (2011) 669–675.
[275] M.-J. Lee, et al., Shikonin time-dependently induced necrosis or apoptosis in gastric cancer cells via generation of reactive oxygen species, Chem. Biol. Interact. 211 (2014) 44–53.
[276] X. Zhang, W. Hu, F. Wu, X. Yuan, J. Hu, Shikonin inhibits TNF-α-induced growth and invasion of rat aortic vascular smooth muscle cells, Can. J. Physiol. Pharmacol. 93 (2015) 615–624.
[277] Q. Yang, M. Ji, H. Guan, B. Shi, P. Hou, Shikonin inhibits thyroid cancer cell growth and invasiveness through targeting major signaling pathways, J. Clin. Endocrinol. Metabol. 98 (2013) E1909–E1917.
[278] K. Gong, Z. Zhang, Y. Chen, H.-B. Shu, W. Li, Extracellular signal-regulated kinase, receptor interacting protein, and reactive oxygen species regulate shikonin-induced autophagy in human hepatocellular carcinoma, Eur. J. Pharmacol. 738 (2014) 142–152.
[279] S. Shi, H. Cao, Shikonin promotes autophagy in BXPC-3 human pancreatic cancer cells through the PI3K/Akt signaling pathway, Oncol. Lett. 8 (2014) 1087–1089.
[280] Z. Zhang, G. Zhang, Q. Liu, Shikonin-induced autophagy and suppression of pancreatic cancer cell proliferation, Zhejiang J. Integrated Tradit. Chin. West. Med. 3 (2013) 007.
[281] K.E. Hwang, E.T. Jeong, H.R. Kim, Eur Respiratory Soc, 2016.
[282] N.-S. Yang, S.-Y. Lin, T.-S. Wu, Differential effects of phytochemical shikonin on induction of immunogenic cell death versus autophagy: potential application to DC-based cancer vaccine, Faseb. J. 29 (2015) LB117.
[283] T.-Y. Li, B.-H. Chiang, 6-shogaol induces autophagic cell death then triggered apoptosis in colorectal adenocarcinoma HT-29 cells, Biomed. Pharmacother. 93 (2017) 208–217.
[284] H. Kauntz, S. Bousserouel, F. Gosse, J. Marescaux, F. Raul, Silibinin, a natural flavonoid, modulates the early expression of chemoprevention biomarkers in a preclinical model of colon carcinogenesis, Int. J. Oncol. 41 (2012) 849–854.
[285] F. Li, et al., Autophagy induction by silibinin positively contributes to its anti-metastatic capacity via AMPK/mTOR pathway in renal cell carcinoma, Int. J. Mol. Sci. 16 (2015) 8415–8429.
[286] W.-J. Duan, et al., Silibinin activated p53 and induced autophagic death in human fibrosarcoma HT1080 cells via reactive oxygen species-p38 and c-Jun N-terminal kinase pathways, Biol. Pharm. Bull. 34 (2011) 47–53.
[287] H.S. Shang, et al., Sulforaphane-induced apoptosis in human leukemia HL-60 cells through extrinsic and intrinsic signal pathways and altering associated genes expression assayed by cDNA microarray, Environ. Toxicol. 32 (2017) 311–328.
[288] G. Watson, et al., SUV39H1/H3K9me3 attenuates sulforaphane-induced apoptotic signaling in PC3 prostate cancer cells, Oncogenesis 3 (2014) e131.
[289] L.L. Atwell, et al., Epigenetic regulation by sulforaphane: opportunities for breast and prostate cancer chemoprevention, Curr. Pharmacol. Rep. 1 (2015) 102–111.
[290] H. Kim, et al., Sulforaphane sensitizes tumor necrosis factor–related apoptosis-inducing ligand (TRAIL)–resistant hepatoma cells to TRAIL-induced apoptosis through reactive oxygen species–mediated up-regulation of DR5, Canc. Res. 66 (2006) 1740–1750.
[291] S.V. Singh, et al., Sulforaphane-induced cell death in human prostate cancer cells is initiated by reactive oxygen species, J. Biol. Chem. 280 (2005) 19911–19924.
[292] A. Herman-Antosiewicz, D.E. Johnson, S.V. Singh, Sulforaphane causes autophagy to inhibit release of cytochrome C and apoptosis in human prostate cancer cells, Canc. Res. 66 (2006) 5828–5835.
[293] S. Kanematsu, et al., Autophagy inhibition enhances sulforaphane-induced apoptosis in human breast cancer cells, Anticancer Res 30 (2010) 3381–3390.
[294] T. Nishikawa, et al., Inhibition of autophagy potentiates sulforaphane-induced apoptosis in human colon cancer cells, Ann. Surg Oncol. 17 (2010) 592–602.
[295] P. Naumann, et al., Autophagy and cell death signaling following dietary sulforaphane act independently of each other and require oxidative stress in pancreatic cancer, Int. J. Oncol. 39 (2011) 101–109.
[296] R.V. Tiwari, P. Parajuli, P.W. Sylvester, γ-Tocotrienol-induced endoplasmic reticulum stress and autophagy act concurrently to promote breast cancer cell death, Biochem. Cell. Biol. 93 (2015) 306–320.
[297] I. Lekli, et al., Co-ordinated autophagy with resveratrol and γ-tocotrienol confers synergetic cardioprotection, J. Cell Mol. Med. 14 (2010) 2506–2518.
[298] M. Khader, P.M. Eckl, Thymoquinone: an emerging natural drug with a wide range of medical applications, Iran. J. Basic Med. Sci. 17 (2014) 950.
[299] M.A. Khan, M. Tania, S. Fu, J. Fu, Thymoquinone, as an anticancer molecule: from basic research to clinical investigation, Oncotarget 8 (2017) 51907.
[300] S.-C. Chu, Y.-S. Hsieh, C.-C. Yu, Y.-Y. Lai, P.-N. Chen, Thymoquinone induces cell death in human squamous carcinoma cells via caspase activation-dependent apoptosis and LC3-II activation-dependent autophagy, PLoS One 9 (2014), e101579.
[301] T. Yi, et al., Thymoquinone inhibits tumor angiogenesis and tumor growth through suppressing AKT and extracellular signal-regulated kinase signaling pathways, Mol. Canc. Therapeut. 7 (2008) 1789–1796.
[302] S.H. Jafri, et al., Thymoquinone and cisplatin as a therapeutic combination in lung cancer: in vitro and in vivo, J. Exp. Clin. Canc. Res. 29 (2010) 87.
[303] I.O. Racoma, W.H. Meisen, Q.-E. Wang, B. Kaur, A.A. Wani, Thymoquinone inhibits autophagy and induces cathepsin-mediated, caspase-independent cell death in glioblastoma cells, PLoS One 8 (2013) e72882.
[304] M. Pazhouhi, R. Sariri, A. Rabzia, M. Khazaei, Thymoquinone synergistically potentiates temozolomide cytotoxicity through the inhibition of autophagy in U87MG cell line, Iran. J. Basic Med. Sci. 19 (2016) 890.
[305] M.-C. Chen, et al., Thymoquinone induces caspase-independent, autophagic cell death in CPT-11-resistant lovo colon cancer via mitochondrial dysfunction and activation of JNK and p38, J. Agric. Food Chem. 63 (2015) 1540–1546.
[306] Q. Liu, Triptolide and its expanding multiple pharmacological functions, Int. Immunopharm. 11 (2011) 377–383.
[307] T.C. Krosch, et al., Triptolide-mediated cell death in neuroblastoma occurs by both apoptosis and autophagy pathways and results in inhibition of nuclear factor–kappa B activity, Am. J. Surg. 205 (2013) 387–396.
[308] N. Mujumdar, A.K. Saluja, Autophagy in pancreatic cancer, Autophagy 6 (2010).
[309] N. Mujumdar, et al., Triptolide induces cell death in pancreatic cancer cells by apoptotic and autophagic pathways, Gastroenterology 139 (2010) 598–608.
[310] S. Shishodia, S. Majumdar, S. Banerjee, B.B. Aggarwal, Ursolic acid inhibits nuclear factor-κB activation induced by carcinogenic agents through suppression of IκBα kinase and p65 phosphorylation correlation with down-regulation of cyclooxygenase 2, matrix metalloproteinase 9, and cyclin D1, Canc. Res. 63 (2003) 4375–4383.
[311] C.P. Xavier, et al., Ursolic acid induces cell death and modulates autophagy through JNK pathway in apoptosis-resistant colorectal cancer cells, J. Nutr. Biochem. 24 (2013) 706–712.
[312] C.P. Xavier, et al., Luteolin, quercetin and ursolic acid are potent inhibitors of proliferation and inducers of apoptosis in both KRAS and BRAF mutated human colorectal cancer cells, Canc. Lett. 281 (2009) 162–170.
[313] S. Leng, et al., Ursolic acid promotes cancer cell death by inducing Atg5-dependent autophagy, Int. J. Canc. 133 (2013) 2781–2790.
[314] C. Zhao, et al., Autophagy-dependent EIF2AK3 activation compromises ursolic acid-induced apoptosis through upregulation of MCL1 in MCF-7 human breast cancer cells, Autophagy 9 (2013) 196–207.
[315] S. Shen, Y. Zhang, R. Zhang, X. Tu, X. Gong, Ursolic acid induces autophagy in U87MG cells via ROS-dependent endoplasmic reticulum stress, Chem. Biol. Interact. 218 (2014) 28–41.
[316] J. Xie, et al., Nanotechnology for the delivery of phytochemicals in cancer therapy, Biotechnol. Adv. 34 (2016) 343–353.
[317] Z. Li, H. Jiang, C. Xu, L. Gu, A review: using nanoparticles to enhance absorption and bioavailability of phenolic phytochemicals, Food Hydrocolloids 43 (2015) 153–164.
[318] B. Holst, G. Williamson, Nutrients and phytochemicals: from bioavailability

to bioefficacy beyond antioxidants, Curr. Opin. Biotechnol. 19 (2008) 73–82.
[319] W. Liu, et al., Oral bioavailability of curcumin: problems and advancements, J. Drug Target. 24 (2016) 694–702.
[320] A. Shehzad, S. Khan, O. Shehzad, Y. Lee, Curcumin therapeutic promises and bioavailability in colorectal cancer, Drugs Today 46 (2010) 523.
[321] B.N. Singh, V.K. Gupta, J. Chen, A.G. Atanasov, Organic nanoparticle-based combinatory approaches for gene therapy, Trends Biotechnol. 35 (2017) 1121–1124.
[322] Q. Huang, H. Yu, Q. Ru, Bioavailability and delivery of nutraceuticals using nanotechnology, J. Food Sci. 75 (2010) R50–R57.
[323] A. Liu, H. Lou, L. Zhao, P. Fan, Validated LC/MS/MS assay for curcumin and tetrahydrocurcumin in rat plasma and application to pharmacokinetic study of phospholipid complex of curcumin, J. Pharmaceut. Biomed. Anal. 40 (2006) 720–727.
[324] J. Cui, et al., Enhancement of oral absorption of curcumin by self-microemulsifying drug delivery systems, Int. J. Pharm. 371 (2009) 148–155.
[325] Z. Ma, A. Shayeganpour, D.R. Brocks, A. Lavasanifar, J. Samuel, High-performance liquid chromatography analysis of curcumin in rat plasma: application to pharmacokinetics of polymeric micellar formulation of curcumin, Biomed. Chromatogr. 21 (2007) 546–552.
[326] H. Ji, et al., Curcumin-loaded solid lipid nanoparticles with Brij78 and TPGS improved in vivo oral bioavailability and in situ intestinal absorption of curcumin, Drug Deliv. 23 (2016) 459–470.
[327] M.A. Augustin, L. Sanguansri, T. Lockett, Nano-and micro-encapsulated systems for enhancing the delivery of resveratrol, Ann. N. Y. Acad. Sci. 1290 (2013) 107–112.
[328] F. Figueiró, et al., Resveratrol-loaded lipid-core nanocapsules treatment reduces in vitro and in vivo glioma growth, J. Biomed. Nanotechnol. 9 (2013) 516–526.
[329] W. Wiczkowski, et al., Quercetin from shallots (Allium cepa L. var. aggregatum) is more bioavailable than its glucosides, J. Nutr. 138 (2008) 885–888.
[330] S. Zhou, et al., Autophagy in tumorigenesis and cancer therapy: Dr. Jekyll or Mr. Hyde? Canc. Lett. 323 (2012) 115–127.
[331] J. Li, et al., Inhibition of autophagy by 3-MA enhances the effect of 5-FU-induced apoptosis in colon cancer cells, Ann. Surg Oncol. 16 (2009) 761–771.
[332] J. Li, N. Hou, A. Faried, S. Tsutsumi, H. Kuwano, Inhibition of autophagy augments 5-fluorouracil chemotherapy in human colon cancer in vitro and in vivo model, Eur. J. Canc. 46 (2010) 1900–1909.
[333] J. Li, et al., Proteomic analysis revealed association of aberrant ROS signaling with suberoylanilide hydroxamic acid-induced autophagy in Jurkat T-leukemia cells, Autophagy 6 (2010) 711–724.
[334] A. Zanotto-Filho, et al., Autophagy inhibition improves the efficacy of curcumin/temozolomide combination therapy in glioblastomas, Canc. Lett. 358 (2015) 220–231.
[335] C.-J. Lin, et al., Resveratrol enhances the therapeutic effect of temozolomide against malignant glioma in vitro and in vivo by inhibiting autophagy, Free Radic. Biol. Med. 52 (2012) 377–391.
[336] Z. Wang, et al., Baicalein induces apoptosis and autophagy via endoplasmic reticulum stress in hepatocellular carcinoma cells, BioMed Res. Int. 2014 (2014).
[337] G. Mosieniak, et al., Curcumin induces permanent growth arrest of human colon cancer cells: link between senescence and autophagy, Mech. Ageing Dev. 133 (2012) 444–455.
[338] J.Y. Kim, et al., Curcumin-induced autophagy contributes to the decreased survival of oral cancer cells, Arch. Oral Biol. 57 (2012) 1018–1025.
[339] M.-H. Teiten, et al., Anti-proliferative potential of curcumin in androgen-dependent prostate cancer cells occurs through modulation of the Wingless signaling pathway, Int. J. Oncol. 38 (2011) 603.
[340] F. Liu, et al., Curcumin induced autophagy anticancer effects on human lung adenocarcinoma cell line A549, Oncol. Lett. 14 (2017) 2775–2782.
[341] A.I. Irimie, et al., Epigallocatechin-3-gallate suppresses cell proliferation and promotes apoptosis and autophagy in oral cancer SSC-4 cells, OncoTargets Ther. 8 (2015) 461.
[342] R. Suzuki, et al., Genistein potentiates the antitumor effect of 5-Fluorouracil by inducing apoptosis and autophagy in human pancreatic cancer cells, Anticancer Res 34 (2014) 4685–4692.
[343] R. Prietsch, et al., Genistein induces apoptosis and autophagy in human breast MCF-7 cells by modulating the expression of proapoptotic factors and oxidative stress enzymes, Mol. Cell. Biochem. 390 (2014) 235–242.
[344] J.-Y. Hung, et al., 6-Shogaol, an active constituent of dietary ginger, induces autophagy by inhibiting the AKT/mTOR pathway in human non-small cell lung cancer A549 cells, J. Agric. Food Chem. 57 (2009) 9809–9816.
[345] M. Akimoto, M. Iizuka, R. Kanematsu, M. Yoshida, K. Takenaga, Anticancer effect of ginger extract against pancreatic cancer cells mainly through reactive oxygen species-mediated autotic cell death, PLoS One 10 (2015), e0126605.
[346] A. Kim, et al., A ginseng metabolite, compound K, induces autophagy and apoptosis via generation of reactive oxygen species and activation of JNK in human colon cancer cells, Cell Death Dis. 4 (2013) e750.
[347] Z. Cao, et al., Luteolin promotes cell apoptosis by inducing autophagy in hepatocellular carcinoma, Cell. Physiol. Biochem. 43 (2017) 1803–1812.
[348] X. Li, X. Li, J. Wang, Z. Ye, J.-C. Li, Oridonin up-regulates expression of P21 and induces autophagy and apoptosis in human prostate cancer cells, Int. J. Biol. Sci. 8 (2012) 901–912.
[349] Q. Cui, S.-i. Tashiro, S. Onodera, M. Minami, T. Ikejima, Autophagy preceded apoptosis in oridonin-treated human breast cancer MCF-7 cells, Biol. Pharm. Bull. 30 (2007) 859–864.
[350] G. Ajabnoor, T. Crook, H.M. Coley, Paclitaxel resistance is associated with switch from apoptotic to autophagic cell death in MCF-7 breast cancer cells, Cell Death Dis. 3 (2012) e260.
[351] S. Wu, X. Wang, J. Chen, Y. Chen, Autophagy of cancer stem cells is involved with chemoresistance of colon cancer cells, Biochem. Biophys. Res. Commun. 434 (2013) 898–903.
[352] M. Granato, et al., Quercetin induces apoptosis and autophagy in primary effusion lymphoma cells by inhibiting PI3K/AKT/mTOR and STAT3 signaling pathways, J. Nutr. Biochem. 41 (2017) 124–136.
[353] G. Jiao, et al., Resveratrol induces apoptosis and autophagy in T-cell acute lymphoblastic leukemia cells by inhibiting Akt/mTOR and activating p38-MAPK, Biomed. Environ. Sci. 26 (2013) 902–911.
[354] D. Kumar, S. Shankar, R.K. Srivastava, Rottlerin-induced autophagy leads to the apoptosis in breast cancer stem cells: molecular mechanisms, Mol. Canc. 12 (2013) 1.
[355] H.J. Kim, et al., Shikonin-induced necroptosis is enhanced by the inhibition of autophagy in non-small cell lung cancer cells, J. Transl. Med. 15 (2017) 123.
[356] S.W. Shin, S.Y. Kim, J.-W. Park, Autophagy inhibition enhances ursolic acid-induced apoptosis in PC3 cells, Biochim. Biophys. Acta Mol. Cell Res. 1823 (2012) 451–457.