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REVIEW

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Phytochemical-mediated modulation of autophagy and endoplasmic reticulum stress as a cancer therapeutic approach

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Abstract

Autophagy and endoplasmic reticulum (ER) stress are conserved processes that generally promote survival, but can induce cell death when physiological thresholds are crossed. The pro-survival aspects of these processes are exploited by cancer cells for tumor development and progression. Therefore, anticancer drugs targeting autophagy or ER stress to induce cell death and/or block the pro-survival aspects are being investigated extensively. Consistently, several phytochemicals have been reported to exert their anticancer effects by modulating autophagy and/or ER stress. Various phytochemicals (e.g., celastrol, curcumin, emodin, resveratrol, among others) activate the unfolded protein response to induce ER stress-mediated apoptosis through different pathways. Similarly, various phytochemicals induce autophagy through different mechanisms (namely mechanistic target of Rapamycin [mTOR] inhibition). However, phytochemical-induced autophagy can function either as a cytoprotective mechanism or as programmed cell death type II. Interestingly, at times, the same phytochemical (e.g., 6-gingerol, emodin, shikonin, among others) can induce cytoprotective autophagy or programmed cell death type II depending on cellular contexts, such as cancer type. Although there is well-documented mechanistic interplay between autophagy and ER stress, only a one-way modulation was noted with some phytochemicals (carnosol, capsaicin, cryptotanshinone, guangsangon E, kaempferol, and δ-tocotrienol): ER stress-dependent autophagy. Plant extracts are sources of potent phytochemicals and while numerous phytochemicals have been investigated in preclinical and clinical studies, the search for novel phytochemicals with anticancer effects is ongoing from plant extracts used in traditional medicine (e.g., *Origanum majorana*). Nonetheless, the clinical translation of phytochemicals, a promising

List of Abbreviations: AMPK, AMP kinase; ATF6, activating transcription factor 6; ATG, autophagy-related genes; BiP, binding immunoglobulin protein; bZIP, basic zipper; CHOP, CAAT/enhancer-binding protein homologous protein; CMA, Chaperone-mediated autophagy; CRC, colorectal cancer; EGCG, epigallocatechin gallate; EGFR, epidermal growth factor receptor; eIF2α, eukaryotic translation initiator factor-2; EMT, epithelial-mesenchymal transition; ER, endoplasmic reticulum; ERAD, ER-associated degradation; HSC70, heat shock chaperon 70; IL, interleukin; IRE1α, inositol-requiring enzyme 1α; mTORC1, mammalian target of rapamycin complex 1; NSCLC, non-small cell lung cancer; PE, phosphatidylethanolamine; PERK, protein kinase R-like endoplasmic reticulum kinase; PI3K, phosphatidylinositol-3 kinase; RER, rough ER; RIDD, regulated IRE1α-dependent decay; ROS, reactive oxygen species; SER, smooth ER; TCM, traditional Chinese medicine; TKI, tyrosine kinase inhibitor; TNBC, triple-negative breast cancer; UPR, unfolded protein response; VEGF, vascular endothelial growth factor; Vps, vesicular protein sorting; XBP1, X-box binding protein 1.

Mazoun Al Azzani and Zohra Nausheen Nizami contributed equally to this work.

avenue for cancer therapeutics, is hindered by several limitations that need to be addressed in future studies.

KEYWORDS
anticancer drugs, autophagy, ER stress, phytochemicals, plant extracts, unfolded protein response

1 | INTRODUCTION

Autophagy and endoplasmic reticulum (ER) stress are two distinct physiological processes that normal cells use to (1) promote survival under stress conditions or (2) mediate cell death under sustained and chronic conditions that have greatly damaged the cell (Almanza et al., 2019; Debnath et al., 2023). Given this dual, context-dependent role of both autophagy and ER stress, it is unsurprising that these two processes have broader and far-reaching implications in cancer development, progression, and cancer therapeutics. The present review explores the role of autophagy and ER stress as mechanisms underlying the anticancer effects of phytochemical compounds and plant extracts.

2 | AUTOPHAGY

Autophagy is a highly conserved degradative recycling process that maintains homeostasis and promotes survival. Through this process, organelles, proteins, and other macromolecules are degraded in lysosomes in response to various stresses, including nutrient depletion and hypoxia (Glick et al., 2010; Parzych & Klionsky, 2014). There are three major forms of autophagy in mammalian cells: microautophagy, macroautophagy, and chaperone-mediated autophagy. All three forms deliver cytoplasmic materials to the lysosome for degradation and recycling to meet cellular energy and metabolic demands (Parzych & Klionsky, 2014). This process is characterized by the following steps: (i) induction of autophagy in response to signals; (ii) nucleation and expansion of the phagophore; (iii) phagophore membrane sealing and autophagosome formation; and (iv) autophagosome maturation, which signals docking and fusion with lysosome and results in the formation of an autolysosome (Glick et al., 2010; Wen & Klionsky, 2016). The key molecular events involved in autophagy have been schematically depicted in Figure 1.

2.1 | Role of autophagy in cancer development and progression

The role of autophagy in cancer is complex–autophagy can play both cancer-supportive and cancer-suppressive roles, and is suggested to play opposing roles in different stages of tumorigenesis. Initially, autophagy was thought to function as a tumor suppressive process as loss of autophagy-related protein genes (namely *BECN1*, *ATG5*, and *ATG12*) was noted in several different cancers, including breast, ovarian, prostate, and hepatocellular cancers (Debnath et al., 2023). Autophagy is also thought to play a suppressive role during the early stages of tumorigenesis by mediating the targeted degradation of oncogenic molecules (Chavez-Dominguez et al., 2020). Additionally, during the early stages of tumorigenesis, it serves as a mechanism to combat reactive oxygen species (ROS)-induced oxidative damage, which is heavily implicated in tumorigenesis (Lim et al., 2021).

Conversely, autophagy is reported to play a tumor-supportive role in the later stages of tumorigenesis, specifically following oncogenic activation. In the later stages, autophagy supports tumor growth by meeting the increased energy and metabolic demands of proliferating cancer cells (Debnath et al., 2023; Yun & Lee, 2018). Autophagy is also implicated in other hallmarks of cancer cells, such as migration and invasion through inhibition of anoikis, immune evasion through decreased presentation of cancer antigens, among other hallmarks of cancer (Hasan et al., 2022; Lim et al., 2021).

2.2 | Targeting autophagy as a cancer therapeutic approach

Given the dynamic role of autophagy in tumorigenesis, targeting autophagy is a promising therapeutic approach for cancer. Namely, chloroquine and its derivative hydroxychloroquine are autophagy inhibitors that are well-studied as adjuvants to conventional treatment approaches. These two drugs are classically used for the treatment of malaria and inhibit autophagy by specifically blocking autophagosome fusion with the lysosome. However, there are limitations to their use. First, the two drugs exhibit pH-related sensitivity, which results in inefficient uptake in acidic tumors, and also exhibit autophagy-independent effects, raising concerns of off-target effects (Mulcahy Levy & Thorburn, 2020; Russell & Guan, 2022). Lys05 is a chloroquine derivative that is more potent than both chloroquine and hydroxychloroquine. It accumulates more readily in the lysosome and increases lysosomal membrane permeability resulting in lysosome-dependent cell death in glioma cells (Zhou, Guo, et al., 2020) and has been reported to enhance the effect of ionizing radiation in lung cancer cells (Cechakova et al., 2019). Apart from chloroquine derivatives, other autophagy inhibitors, namely 3-methyladenine (a phosphatidylinositol 3-kinase inhibitor) and bafilomycin A1 (a V-ATPase inhibitor) have also been investigated for anticancer effects both alone or in combination with other chemotherapeutic drugs. However, their clinical translation is greatly hindered by several factors including poor

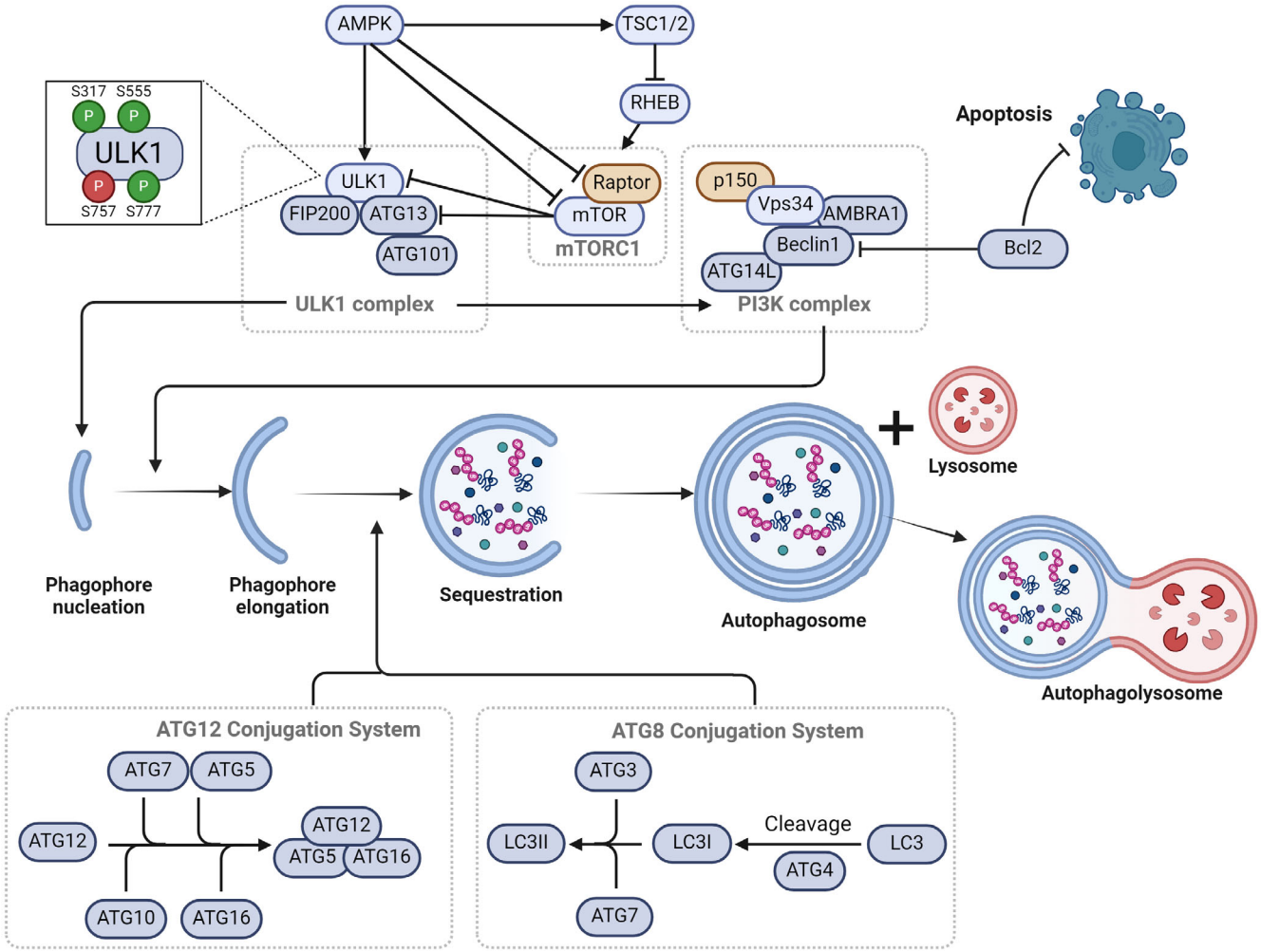

FIGURE 1 Key molecular events in autophagy. Autophagy is characterized by several steps. (i) Induction of autophagy is regulated by the mTORC1-AMPK axis. Under nutrient-rich conditions, mTORC1, a complex including mTOR and regulatory proteins, phosphorylates the Ser757 residue of ULK1 to disrupt its interaction with AMPK. Conversely, under nutrient-low conditions, mTORC1 is inactivated by AMPK via the activation of TSC1/2, and subsequent inhibition of RHEB. Additionally, AMPK inhibits mTOR, the core component of mTORC1, and Raptor, a key adaptor protein involved in the downstream effects of mTORC1. AMPK also directly activates the ULK1 complex to initiate phagophore nucleation by phosphorylating ULK1 at the Ser317, Ser555, and Ser777 residues. (ii) The ULK1 complex further activates the PI3K complex, which regulates phagophore expansion. Beclin1 in the PI3K complex serves as a point of crosstalk between autophagy and apoptosis through its interaction with Bcl-2, an anti-apoptotic protein that also inhibits autophagy. (iii) There are two conjugation systems, the ATG12 and ATG8 conjugation systems, that facilitate both the elongation and maturation of the growing phagophore membrane, allowing sequestration of ubiquitinated proteins and other cytoplasmic cargo. (iv) The phagophore eventually seals to give rise to the double-membraned autophagosome, which fuses with the lysosome to form the autophagolysosome.

bioavailability and off-target effects. Further, 3-methyladenine is not a specific inhibitor of autophagy and can in fact induce autophagy at higher concentrations (Klionsky et al., 2021); hence, its use is mainly limited to mechanistic studies.

Given the limitations of general autophagy inhibitors, more targeted approaches to autophagy inhibition are being investigated. SBI-0206965 is a ULK1 inhibitor that suppresses ULK1-mediated phosphorylation events, which are integral to autophagy induction (Egan et al., 2015). Similarly, MRT403, another ULK1 inhibitor, was recently reported to sensitize patient-derived leukemic stem cells to tyrosine kinase inhibitors (TKIs; Ianniciello et al., 2021). ATG4 is a crucial protein in macroautophagy as it regulates the cleavage of ATG8 for lipidation as well as the delipidation of ATG8 homologs during autophagosome maturation. Hence, targeting ATG4B, a homolog of ATG4, is another promising mechanism of autophagy inhibition (Yang, Li, Zhao, et al., 2021). NSC185058, an ATG4B inhibitor, was reported to inhibit the progression of osteosarcoma in vivo (Akin et al., 2014). Another ATG4B inhibitor, DC-ATG4in, was identified by high-throughput screening and was reported to inhibit the proliferation of hepatocellular carcinoma by blocking Sorafenib-induced autophagy and synergizing with Sorafenib, a protein kinase inhibitor (Xie et al., 2023).

As of May 2024, only chloroquine and hydroxychloroquine are in clinical trials for various solid and hematological cancers in

combination with other approaches (https://clinicaltrials.gov/). Although autophagy inhibition is the main approach targeting autophagy as a cancer therapeutic approach, some groups have also investigated induction/promotion of autophagy for the same. In this regard, pevonedistat (MLN4924), a NEDD8-activating enzyme, which induces autophagy by inhibiting mTOR through the HIF1-REDD1-TSC1 axis (Li, Wang, et al., 2021), is presently in clinical trials for hematological cancers in combination with other approaches (https://clinicaltrials.gov/).

3 | ER STRESS

The ER is a complex organelle integral to cell fate and homeostasis, and is the site of protein synthesis and folding, lipid synthesis, and Ca^{2+} homeostasis. Generally, protein biosynthesis in the ER is regulated through a quality control system–ER-associated degradation, which ensures that unfolded and/or misfolded proteins are degraded through the ubiquitin–proteasome pathway to avoid their potentially cytotoxic effects (Krshnan et al., 2022; Ruggiano et al., 2014). Several intrinsic and extrinsic factors can cause perturbations in the ER, which results in the accumulation of unfolded and/or misfolded proteins, and consequently, "ER stress." In cancer cells, ER stress can be attributed to the high mutation load, which can overwhelm the protein folding capacity, particularly due to increased incidence and stability of misfolded proteins as a result of mutations (Hetz & Papa, 2018). Additionally, the inherently high protein production in cancer cells due to their high proliferation rate, among other reasons, also contributes to ER stress (Almanza et al., 2019). Further, extrinsic factors, such as hypoxia and nutrient deprivation, which are characteristic of cancer cells also contribute to ER stress (Almanza et al., 2019).

The unfolded protein response (UPR) is the cellular stress response to ER stress, which aims to restore ER homeostasis. This signal transduction pathway is classified into three branches based on three ER transmembrane protein sensors that recognize unfolded and/or misfolded proteins: (i) inositol-requiring enzyme 1α (IRE1α); (ii) protein kinase R-like ER kinase (PERK); and (iii) activating transcription factor 6 (ATF6) (Almanza et al., 2019; Hetz & Papa, 2018). Under normal physiological conditions, binding immunoglobulin protein (BiP; also called GRP78) represses the UPR by binding to the luminal domains of PERK and IRE1α, preventing their dimerization and hence activation (Hetz & Papa, 2018; Oakes & Papa, 2015). Similarly, BiP binds to ATF6 and prevents its translocation to the Golgi, which is essential for ATF6 activation (Corazzari et al., 2017; Hetz & Papa, 2018). However, under ER stress, BiP functions as an allosteric regulator. Misfolded proteins bind to the substrate binding domain of BiP and release it from the ER sensors, allowing their dimerization (PERK and IRE1α) or translocation to the Golgi (ATF6) for activation of the UPR (Hetz & Papa, 2018). Similarly, BiP binds to hydrophobic stretches in unfolded proteins (Karagöz et al., 2019), and ER-localized DnaJ family members also facilitate the interaction of BiP with unfolded proteins (Pobre et al., 2019). The three branches of the UPR have been schematically depicted in Figure 2.

3.1 | Role of the UPR in cancer development and progression

The UPR governs both pro-survival and pro-death functions; hence, it is unsurprising that it plays a pro-tumorigenic role and at the same time can also be exploited as a therapeutic approach. In many cancers, the UPR is upregulated to combat ER stress caused by intrinsic stresses, and plays different roles in different stages of tumorigenesis. Given the dual roles of the UPR, its upregulation in cancers is facilitated in a manner that promotes tumor survival without triggering UPR-mediated apoptosis.

For example, IRE1α is a commonly mutated kinase in cancers; however, mutations often retain RNase activity, which facilitates X-box binding protein 1 (*XBP1*) mRNA splicing and the adaptive pro-survival responses, while not retaining RIDD and the downstream apoptotic responses (Hetz & Papa, 2018). Interestingly, XBP1s specifically mediates various pro-tumorigenic processes. XBP1s has been reported to enhance autophagy as a pro-survival mechanism to meet energy demands by binding to *BECN1* promoter, thereby enhancing Beclin-1 expression (Oakes, 2020). Furthermore, XBP1s reportedly forms a complex with hypoxia-inducible factor 1α (HIF-1α), a transcription factor induced during hypoxia, to facilitate transcription of its downstream gene targets (Madden et al., 2019; Siwecka et al., 2019). Consistently, XBP1s has also been implicated in angiogenesis through upregulation of vascular endothelial growth factor (VEGF), a classical HIF-1α target gene, and interleukin (IL)-6 and IL-8 (Hetz & Papa, 2018; Oakes, 2020).

The PERK–ATF4 pathway also upregulates VEGF expression (Corazzari et al., 2017) and reportedly promotes antioxidant responses to combat hypoxia-induced oxidative stress (Madden et al., 2019; Siwecka et al., 2019). The IRE1α–XBP1s and PERK–ATF4 pathways have been implicated in epithelial–mesenchymal transition (EMT), a key event during the invasion and metastasis of cancer cells (Madden et al., 2019; Oakes, 2020). Interestingly, several existing chemotherapeutic drugs, including cisplatin, tunicamycin, methotrexate, 5-fluorouracil, sorafenib, doxorubicin, among others, have been reported to induce ER stress resulting in UPR activation. However, this has been implicated in chemoresistance, specifically through UPR-mediated activation of adaptive autophagy and BiP/GRP78-mediated inhibition of apoptosis (Avril et al., 2017).

3.2 | Targeting the UPR as a cancer therapeutic approach

Targeting of the UPR for cancer treatment involves two approaches, both of which overload the UPR, ultimately inducing ER stress-mediated apoptosis: (i) induction of ER stress or (ii) inhibition of one of the main components of the UPR (Cole et al., 2019; Li et al., 2011; Ojha & Amaravadi, 2017; Wang, Law, et al., 2018). Consistently, in this section, we have discussed anticancer drugs that target UPR components, including PERK, IRE1α, and BiP/GRP78 inhibitors.

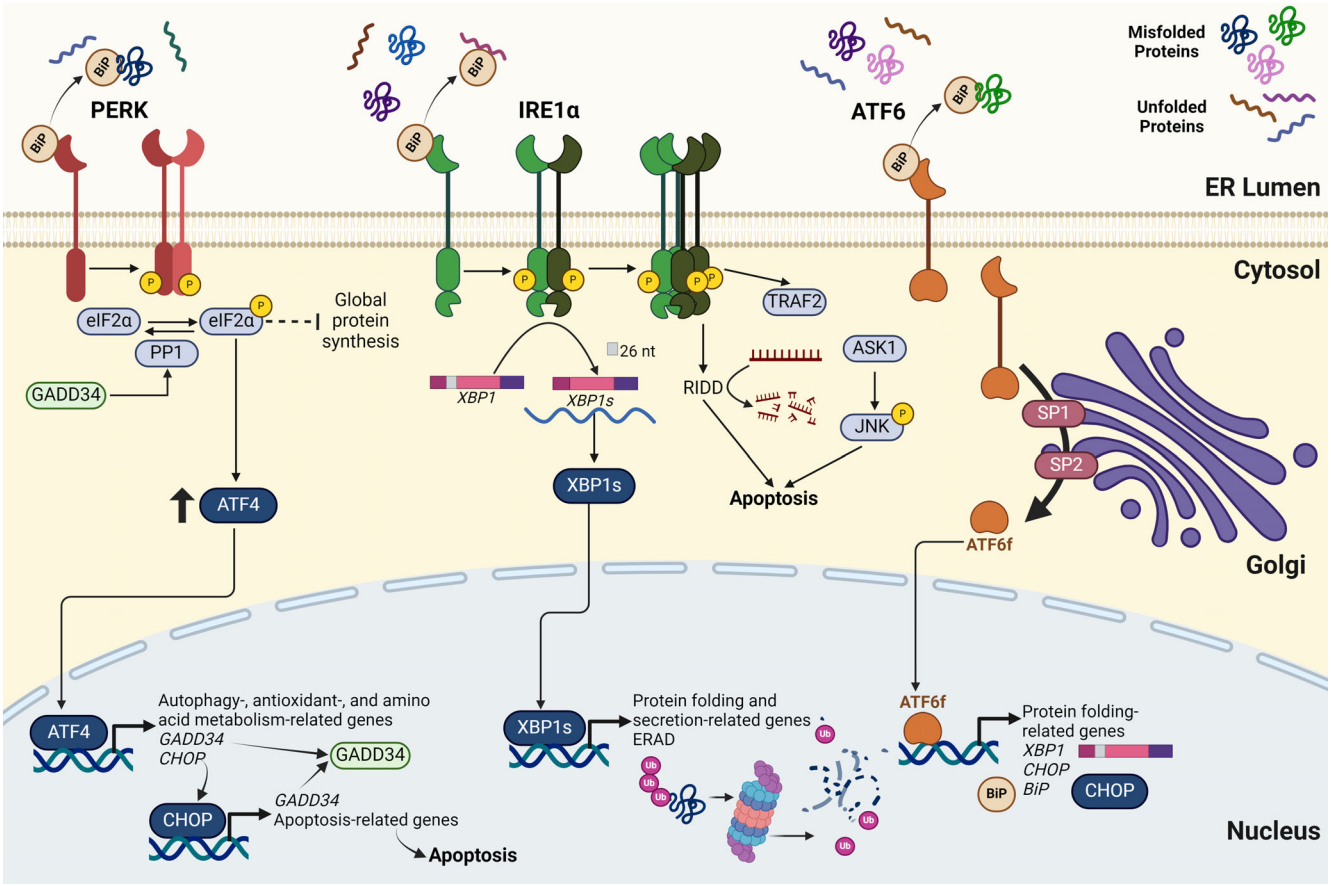

FIGURE 2 The ER stress sensors PERK, IRE1α, and ATF6. The UPR is triggered in response to ER stress, which is characterized by the accumulation of unfolded and/or misfolded proteins. Under normal conditions, the UPR sensors, PERK, IRE1α, and ATF6, are associated with BiP. However, during ER stress, BiP preferentially binds to unfolded and/or misfolded proteins, dissociating from these sensors and facilitating their activation. (i) PERK branch: Upon BiP disassociation, PERK dimerizes and undergoes autophosphorylation, subsequently, phosphorylating eIF2α, which inhibits global protein synthesis. Phosphorylated eIF2α upregulates ATF4, which induces the expression of autophagy-, antioxidant-, and amino acid metabolism-related genes as well as *GADD34*, and *CHOP*. GADD34 inhibits eIF2α phosphorylation, while CHOP induces the expression of apoptosis-related genes. (ii) IRE1α branch: Upon BiP disassociation, IRE1α dimerizes, undergoes autophosphorylation, and splices *XBP1* mRNA to produce *XBP1s* mRNA. XBP1s induces the expression of protein folding, secretion-, and ERAD-related genes. Constituent IRE1α activation facilitates its oligomerization, which induces apoptosis through RIDD and activation of JNK pathway. (iii) ATF6 branch: Upon BiP disassociation, ATF6 translocate to the Golgi, where SP1 and SP2 proteolytically cleave it to release ATF6f, a transcription factor. ATF6f induces the expression of protein folding-related genes, and other UPR components, including *XBP1*, *CHOP*, and *BiP*. ERAD, ER-associated degradation; RIDD, regulated IRE1-dependent decay.

GSK2606414 was the first reported selective inhibitor of PERK (Axten et al., 2012) and its anticancer activity has been reported against pancreatic cancer (Li, Ge, et al., 2022), leukemic (Zhang et al., 2017), neuroblastoma (Rozpędek et al., 2017), and colorectal cancer (CRC) (Rozpędek et al., 2017) cells. Despite promising results in in vitro studies, its clinical use is limited due to associated toxicities. On the other hand, HC-5404-FU, first reported in 2021, is another selective PERK inhibitor (Calvo et al., 2021) that is presently being tested in a Phase I clinical trial (NCT04834778; https://clinicaltrials.gov/). Recently, HC-5404-FU was reported to sensitize renal cell carcinoma cells to VEGF receptor TKIs (Stokes et al., 2023), which further highlights that this PERK inhibitor is a promising anticancer agent.

As mentioned earlier, the IRE1α arm of the UPR mediates both adaptive and proapoptotic responses through *XBP1* mRNA splicing and RIDD, respectively. Hence, inhibitors of its RNase domain, which can inhibit *XBP1* mRNA splicing to inhibit the adaptive responses, and consequently increase apoptotic signaling, are the main focus area of research. Consistently, several IRE1α kinase inhibitors have demonstrated anticancer activity against hematological cancers in preclinical studies, including toyocamycin, STF083010, A106, MKC-3946 IRE1, 4μ8C IRE1, and 3-methoxy-6-bromosalicyl-aldehyde (Raymundo et al., 2020; Wang, Law, et al., 2018; Wiese et al., 2022). Presently, ORIN1001, a first-in-class IRE1α inhibitor formerly known as MKC8866, is undergoing Phase 1/2 clinical testing for advanced solid tumors alone or in combination with paclitaxel for relapsed refractory metastatic breast cancer (NCT03950570; https://clinicaltrials.gov/) (Rimawi et al., 2023). Although not a specific IRE1α kinase inhibitor, Sunitinib is a multi-target TKI that is also known to target the IRE1α

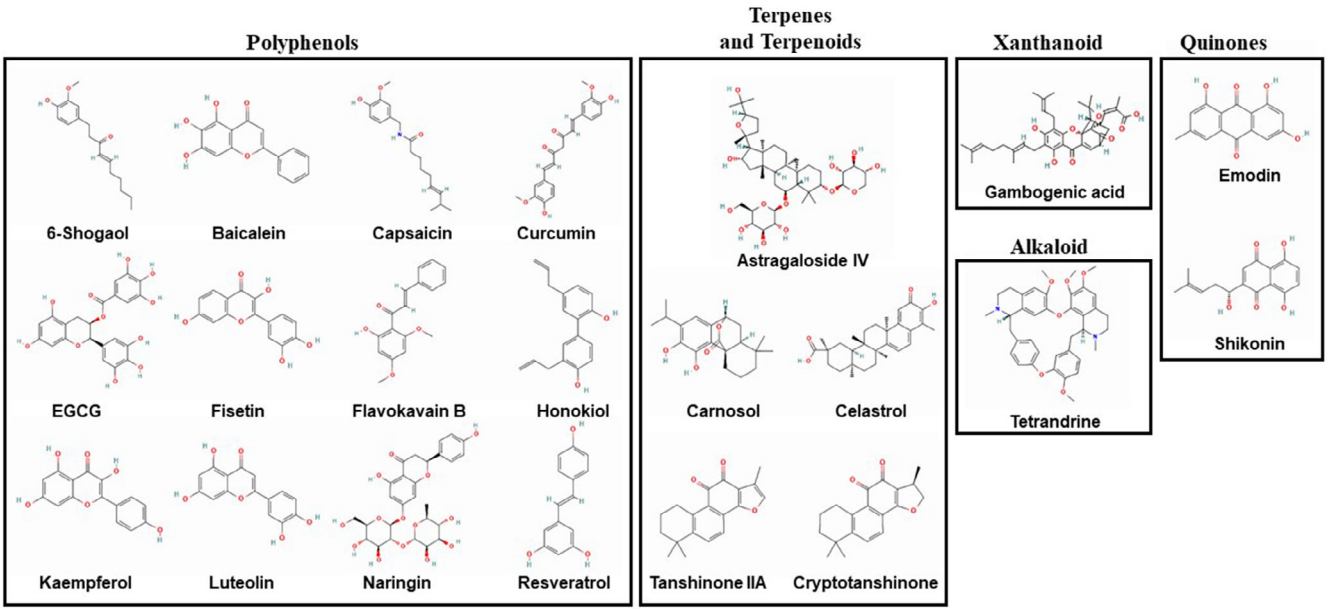

FIGURE 3 Chemical structures of phytochemicals that exert their anticancer effects through induction of autophagy and ER stress discussed in the review. Structures were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/).

kinase domain, and is FDA approved for pancreatic neuroendocrine tumors, imatinib-resistant gastrointestinal stromal tumors, and advanced renal cell carcinoma (Blumenthal et al., 2012).

BiP/GRP78 is a central regulator of ER stress as it inactivates the UPR sensors by binding to them under physiological conditions. Interestingly, GRP78 is upregulated in various cancers, and downregulation of GRP78 has hence been proposed as a therapeutic approach for cancer. In fact, several natural and synthetic compounds downregulate GRP78 in in vitro studies. GRP78 antibodies PAT-SM6 and Bold-100 showed potent anticancer activity in animal models and have been tested in clinical trials. Bold-100 is presently being tested in a Phase 2 clinical trial (NCT04421820; https://clinicaltrials.gov/) involving three countries and has reported promising findings, resulting in orphan drug designation for gastric and pancreatic cancers (Hernandez & Cohen, 2022; Raymundo et al., 2020).

4 | PHYTOCHEMICALS THAT MODULATE AUTOPHAGY AND/OR ER STRESS

Plant-based cancer therapeutics is one of the oldest branches of cancer therapeutics, specifically, the use of phytochemical compounds or their derivatives. For example, vinca alkaloids were first isolated from Madagascar periwinkle (*Catharanthus roseus*; syn. *Vinca rosea*) in the 1950s and two natural vinca alkaloids, vinblastine and vincristine, are used to this day for the treatment of solid cancers as well as hematological and lymphatic cancers (Martino et al., 2018). The continuing interest in phytochemicals as anticancer drugs has led to the investigation and characterization of numerous phytochemical compounds in preclinical studies. Moreover, various other phytochemicals are also in different stages of clinical trials for other cancers (Choudhari et al., 2019).

In the present review, we have comprehensively reviewed phytochemicals with demonstrated anticancer activity that can be attributed to the induction of autophagy and/or ER stress. In the coming sections, various phytochemical compounds have been grouped and discussed based on their chemical class (Figure 3). It is important to note that the phytochemicals discussed in the text are not exhaustive and others, less extensively studied are mentioned in Table 1.

4.1 | Polyphenolic compounds

Polyphenols are a broad and diverse class of phytochemicals and several polyphenols have been studied extensively for their biological effects including anticancer effects. In this section, polyphenolic phytochemicals have been classed into polyphenolic amides, stilbenoids, flavonoids, lignans, curcuminoids, and gingerols. Other polyphenols including methyl gallate, guangsangon E, among others, have been listed in Table 1.

4.1.1 | Polyphenolic amides

Capsaicin is a polyphenolic amide that accounts for the sensation of burning and heat in chili peppers of the *Capsicum* genus. In recent years, numerous studies have investigated capsaicin as both a chemopreventive and an anticancer agent. Its anticancer effects have been characterized in numerous cancers both in vitro and in vivo (Adetunji et al., 2022). However, clinical trials have shown limited antiproliferative efficacy.

ER stress has been implicated as a mechanism underlying the observed anticancer effects of capsaicin. Activation of the PERK-

TABLE 1 Phytochemicals that exert anticancer effects through induction of autophagy and/or ER stress.

Phytochemical[a]	Cancer type[b]	Effect on autophagy	Effect on ER stress	Effect on Apoptosis	ROS involvement	In vivo	Ref
Methyl gallate (Polyphenol; *Euphorbia teheranica*)	CRC (HCT116)	ROS-induced autophagy[c]	Upregulation of PERK, phospho-PERK, eiF2α, Grp78, and CHOP	• DNA damage • P53-mediated apoptosis	+	N/E	(Notaro et al., 2023)
Guangsangon E (Polyphenol; *Morus alba*)	Nasopharyngeal (CNE1), NSCLC (A549)	• Facilitated dissociation of Beclin-1 from Bcl-2 • ER stress-mediated autophagy • Autophagic cell death	• ROS-dependent ER stress • Increased cytoplasmic calcium levels • Upregulation of GRP78, IRE1α, and ATF4	ROS-mediated apoptosis	+	+ (A549 xenografted mice)	(Shu et al., 2021)
Sophoridine (Alkaloid; *Sophora alopecuroides*)	Hepatocellular (HepG2 and MHCC-97H)	–	• Upregulation of ATF3 • Pro-death ER stress	Induction of ATF3-mediated ferroptosis	+	+ (HepG2 xenografted mice)	(Tian et al., 2023)
Corynoxine (Alkaloid; *Uncaria rhynchophylla*)	Pancreatic (Panc-1 and Patu-8988)	N/E	• Upregulation of GRP78, ATF4, ATF6, CHOP, p-EIF2α, p-PERK, p-IRE1, and p-JNK • Increased cytoplasmic calcium levels • ROS-dependent ER stress	• ER stress-mediated apoptosis through CHOP • ROS-dependent apoptosis through p38 activation	+	+ (Panc-1 xenografted mice)	(Wen et al., 2022)
(+)-Bornyl p-Coumarate (Monoterpene; *Piper betle*)	Melanoma (A2058 and A375)	Induction of autophagic cell death	Upregulation of GRP78, p-PERK, p-eIF2α, ATF6, ATF4 and CHOP	• Loss of mitochondrial membrane potential • ER stress-mediated apoptosis through CHOP • Activation of intrinsic apoptosis pathway	N/E	N/E	(Wu et al., 2020)
Kalantuboside B (Steroid; *Kalanchoe tubiflora*)	Melanoma (A2058)	ROS-dependent cytoprotective autophagy	–	• ROS-dependent apoptosis • Upregulation of ERK pathway	ER stress-mediated Caspase 12-dependent apoptosis	+ (A2058 xenografted mice)	(Hseu et al., 2019)
2β-Methoxy-2-deethoxyphantomolin (EM-2) (Sesquiterpene; *Elephantopus mollis*)	Hepatocellular (Huh-7)	Inhibition of autophagy through inhibition of lysosome maturation	Upregulation of p-IRE1α, p-eIF2α, ATF4, and Bip	ER stress-mediated apoptosis through activation of the JNK pathway	N/E	N/E	(Yang, Li, Hou, et al., 2021)
	TNBC (MDA-MB-231 and SKBR3)	Inhibition of autophagy	Upregulation of p-PERK, p-eIF2α, ATF6, and Bip	ER stress-mediated apoptosis	+	+ (SKBR3 xenografted mice)	(Li et al., 2023)

(Continues)

TABLE 1 (Continued)

Phytochemical[a]	Cancer type[b]	Effect on autophagy	Effect on ER stress	Effect on Apoptosis	ROS involvement	In vivo	Ref
Dehydrodiisoeugenol (Polyphenol; *Myristica fragrans*)	CRC (HCT 116 and SW620)	Inhibition of autophagic flux	Upregulation of BiP, Ero1-Lα, PERK, eIF2α, p-eIF2α, IRE1α, XBP-1 s, and CHOP	–	N/E	+ (HCT116 and SW620 xenografted mice and patient-derived xenograft mice)	(Li, Zhang, et al., 2021)
Demethylzeylasteral (Triterpenoid monomer; *Tripterygium wilfordii*)	Prostate (DU145 and PC3)	Induction of cytoprotective autophagy without increased autophagic flux	Upregulation of p-PERK, PERK, BiP, and IRE1α	• Caspase 3-dependent apoptosis • Autophagy-mediated apoptosis • ER stress-mediated apoptosis • Increased intracellular Ca^{2+} levels	+	N/E	(Yang, Zhang, He, et al., 2021)
2α, 3α, 24-thrihydroxyurs-12-en-24-ursolic acid (TEOA) (Triterpenoid; *Actinidia eriantha*)	Pancreatic (PANC1 and SW1990)	• Autophagic cell death via ROS-dependent inhibition of mTOR/p70S6k signaling pathway • ROS-dependent autophagy	N/E	Induction of apoptosis	+	N/E	(Yang, Li, Hu, et al., 2021)
Cardamonin (Polyphenol; *Amomum subulatum*)	Ovarian (SKOV3)	Induction of autophagy through mTOR inhibition via downregulation of Raptor[c]	N/E	Caspase 3-dependent apoptosis	N/E	N/E	(Shi, Niu, et al., 2018)
		Induction of autophagy through mTOR inhibition and AMPK activation[c]	N/E	N/E	N/E	N/E	(Shi, Zhao, et al., 2018)
		• Induction of autophagy through mTOR inhibition[c] • DAP1 negatively regulates autophagy	N/E	N/E	N/E	N/E	(Nie et al., 2020)
Daurisoline (Alkaloid; *Menispermum dauricum*)	Hepatocellular (HepG2 and SMMC-7721)	Decreased autophagic flux	Enhances cisplatin-mediated apoptosis	N/E	N/E	+ (HepG2 xenografted mice)	(Xue & Liu, 2021)
	Esophageal (EC1 and ECA109)	N/E	• Upregulation of p-eIF2α and ATF4 • ROS-dependent ER stress	• ER stress-mediated apoptosis through CHOP • Noxa-dependent intrinsic apoptosis	+	+ (ECA109 xenografted mice)	(Yuan et al., 2022)

TABLE 1 (Continued)

Phytochemical[a]	Cancer type[b]	Effect on autophagy	Effect on ER stress	Effect on Apoptosis	ROS involvement	In vivo	Ref
Physapruin A (Steroid; *Physalis peruviana*)	Breast (MCF7), TNBC (MDA-MB-231)	ROS-dependent cytoprotective autophagy	N/E	Inhibition of autophagy augmented apoptosis	+	N/E	(Yu et al., 2022)
		N/E	• Upregulation of IRE1α, ATF6, PERK, and BIP • ROS-dependent ER Stress	ER stress-mediated apoptosis	+	N/E	(Yu et al., 2023)
Bacoside A (Triterpene glycoside; *Bacopa monnieri*)	Glioma (U251 and U87)	Induction of autophagy[c]	–	• Increased expression of proapoptotic Bax and cleaved caspase-9 • Decreased expression of anti-apoptotic protein Bcl-2	–	N/E	(Liu, Ji, et al., 2023)
δ-Tocotrienol (Tocotrienol; *Amaranthus cruentus*)	Prostate (PC3 and DU145)	ER stress-mediated cytoprotective autophagy	Upregulation of p-eIF2α, ATF4, CHOP, and IRE1α	• Induction of paraptosis • ER stress-mediated apoptosis	N/E	N/E	(Fontana et al., 2019)
		Induction of autophagy[c] and mitophagy	N/E	• Increased mitochondrial Ca^{2+} levels • Induction of paraptosis	+	N/E	(Fontana et al., 2020)
α-Mangostin (Xanthone; *Garcinia mangostana*)	TNBC (MDA-MB-231)	Induction of cytoprotective ER stress-dependent autophagy	• Upregulation of CHOP, PERK, IRE1α, and ATF6 • Induction of cytoprotective ER stress	Inhibition of ER stress and autophagy enhanced apoptosis	–	N/E	(Huang et al., 2019)
	Osteosarcoma (143B and Saos-2)	N/E	Upregulation of CHOP, PERK, and ATF6	ER stress-mediated apoptosis through inactivation of the Wnt/β-catenin pathway	+	+ (143B xenografted mice)	(Yang, Zhou, Dong, & Ren, 2021)
6-Gingerol (Polyphenol; *Zingiber officinale*)	NSCLC (A549)	Induction of cytotoxic autophagy through inhibition of USP14-mediated deubiquitination of Beclin-1	N/E	Autophagy-dependent ferroptosis	+	+ (A540 xenografted mice)	(Tsai et al., 2020)
	Prostate (PC3, LNCaP, and DU145)	• Cytoprotective autophagy (PC3 and LNCaP) • Autophagic cell death (DU145)	N/E	Induction of ferroptosis	+	N/E	(Liu et al., 2022)

(Continues)

TABLE 1 (Continued)

Phytochemical[a]	Cancer type[b]	Effect on autophagy	Effect on ER stress	Effect on Apoptosis	ROS involvement	In vivo	Ref
Zerumbone (Sesquiterpene; *Zingiber zerumbet*)	Hepatocellular (HepG2/C3A)	N/E	Upregulation of IRE1α	ER stress-mediated apoptosis	N/E	N/E	(Rondina et al., 2022)
Tanshinone I (Diterpene; *Salvia miltiorrhiza*)	Hepatocellular (HepG2 and Huh7)	Inhibition of p53-DRAM-mediated autophagy	ROS-dependent ER stress	ER stress-mediated apoptosis	+	N/E	(Liu & Liu, 2020)
	Ovarian (A2780 and Skov3)	Induction of autophagic cell death through inhibition of the PI3K-AKT–mTOR pathway	N/E	Caspase 3-mediated apoptosis	N/E	+ (A2780 xenografted mice)	(Zhou, Jiang, et al., 2020)
	Glioblastoma (U87)	Cytoprotective autophagy	Upregulation of CHOP and eIF2α	AKT-mediated apoptosis	+	N/E	(Jian et al., 2020)

Note: –, not involved; CRC, colorectal cancer; N/E, not explored in the study; NSCLC, non-small cell lung cancer; ROS, reactive oxygen species.
[a]Phytochemical class and plant source are mentioned in brackets.
[b]Only human cancer cell lines were considered.
[c]The cytoprotective or pro-death nature was not clarified; only abstract was available for (Fontana et al., 2020) (Bacoside A).

eIF2α-ATF4 and the IRE1α-XBP1s pathways was reported in capsaicin-treated oral squamous cancer cells (Huang et al., 2021). Downstream of ER stress, ER stress-mediated autophagy (Huang et al., 2021) was reported in these cancer cells. In the context of autophagy, both pro-survival and pro-death autophagy were reported. Cytoprotective autophagy as a survival mechanism was reported to be induced by capsaicin in osteosarcoma (Wang, Deng, et al., 2018) and melanoma (Chu et al., 2019) cells. Whereas, other studies reported autophagy as a pro-death mechanism in oral squamous cell cancer (Chang et al., 2020; Huang et al., 2021), melanoma (Islam et al., 2021), renal cancer (Que et al., 2022), and thyroid cancer (Wu, Xu, et al., 2022) cells. Inhibition of the PI3K-AKT–mTOR pathway (Islam et al., 2021; Wu, Xu, et al., 2022), ROS induction (Islam et al., 2021), AMPK activation (Que et al., 2022), increased ULK1 acetylation via the tNOX-SIRT1 axis (Chang et al., 2020; Islam et al., 2021), and downregulation of ribophorin II (Huang et al., 2021) were reported as mechanisms underlying capsaicin-mediated autophagy. The contrasting results on cytoprotective autophagy versus autophagic cell death can be attributed to numerous factors including cellular context, threshold, among others. Nonetheless, it is important to note that under specific conditions autophagy can trigger other forms of cell death, such as apoptosis, further highlighting the adaptive aspect of this physiological process (Klionsky et al., 2021).

Other reported effects of capsaicin include decreased stemness (downregulation of OCT4A) (Wu, Xu, et al., 2022), inhibition of EMT (Que et al., 2022), and G0/G1 cell cycle arrest (Wang, Deng, et al., 2018). However, contrasting results were also noted; for example, in contrast to Que et al. (2022) who reported that capsaicin decreased EMT, Amantini et al. (2016) reported increased EMT as a consequence of capsaicin-induced cytoprotective autophagy. These findings are in line with our existing understanding of autophagy and EMT–different pathways activated downstream of autophagy differentially regulate EMT induction and repression (Chen et al., 2019). This highlights the need for in-depth investigations into the downstream effects of phytochemical-induced autophagy in the context of different cancers, especially for facilitating clinical translation.

4.1.2 | Stilbenoids

Resveratrol (3,4′,5 tri-hydroxystilbene) is a stilbenoid that is found in plants of over 34 families, encompassing 100 species, with red grapes (*Vitis vinifera* L.) being the most common source of extraction (Tian & Liu, 2020). The anticancer activity of resveratrol is well established and induction of ER stress has been implicated as one of the main mechanisms of its cytotoxic effects across various cancers, including neuroblastoma (Sun et al., 2023), melanoma (Heo, Kim, et al., 2018), breast (Bian et al., 2022), and lung (Bian et al., 2022) cancers. Resveratrol induces ER stress through different mechanisms including ROS induction (Heo, Kim, et al., 2018; Sun et al., 2023), ER calcium depletion (Selvaraj et al., 2016), impairment of protein glycosylation, and ceramide accumulation. With respect to modulation of UPR components, resveratrol increased the expression of Grp78/Bip (Sun

et al., 2023), and activated different UPR sensors: PERK in melanoma (Heo, Kim, et al., 2018) and ATF6α in ovarian cancer cells (Gwak et al., 2016). Additionally, resveratrol induced ER stress-mediated apoptosis through upregulation of the proapoptotic factor CHOP (Gwak et al., 2016; Heo, Kim, et al., 2018), activation of p38MAPK (Bian et al., 2022; Heo, Kim, et al., 2018), and upregulation of sirtuin 1 (Bian et al., 2022). Resveratrol also induced DNA damage (Bian et al., 2022), mitochondrial dysfunction (Bian et al., 2022), and senescence (Bian et al., 2022) in an ER stress-dependent manner. Resveratrol has also been reported to induce autophagy in neuroblastoma (Sun et al., 2023).

It is noteworthy to mention that resveratrol exerted synergistic effects with the conventional chemotherapeutic drug cisplatin in gastric cancer cells (Ren et al., 2020) through the induction of ER stress. Recently, Önay Uçar et al. (2023) and Li, Zhang, et al. (2022) reported that the effects of resveratrol can be enhanced by depletion of heat shock proteins (Hsp27, Hsp60, Hsp70, or Hsp90) and knockdown of lncRNA H19, respectively, to further modulate ER stress in glioblastoma and gastric cancer cells, respectively.

4.1.3 | Flavonoids

Flavonoids represent one of the most diverse classes of polyphenols and phytochemicals in general. Based on their chemical structures, flavonoids are further classified into different subclasses. In the present review, flavanols, flavones, flavonols, flavanones, and chalcones have been discussed.

Flavanols

Epigallocatechin gallate (EGCG), a flavanol, specifically a catechin, is found abundantly in green tea (*Camellia sinensis*) and has been studied extensively for its biological effects against a variety of health conditions, including obesity, metabolic syndrome, and cancer. Its anticancer effects have been characterized in multiple cancer types both in vitro and in vivo (Gan et al., 2018). EGCG has also been investigated in combination with various other chemotherapeutic drugs (Gan et al., 2018).

With respect to induction of autophagy, EGCG was reported to synergize with gefitinib (an epidermal growth factor receptor [EGFR] TKI) (Meng et al., 2019) to induce autophagy in CRC and NSCLC cells. Modernelli et al. (2015) reported that in prostate cancer (PC3) cells, EGCG antagonizes bortezomib (a proteasome inhibitor) to promote cytoprotective autophagy and downregulate ER stress induction by decreasing the expression of eIF2α, BIP, and CHOP, thereby protecting prostate cancer cells from bortezomib cytotoxicity. Cytoprotective autophagy was also reported to be induced by EGCG in CRC cells, conferring resistance to TRAIL-induced apoptosis as a result of decreased expression of death receptors (Kim, Moon, & Park, 2016). In contrast to Modernelli et al. (2015), Wu, Xu, et al. (2022) and Wu, Gou, et al. (2022) reported that EGCG in combination with irinotecan (a topoisomerase I inhibitor) induces BiP-mediated endoplasmic reticulum stress in CRC cells (Wu, Gou, et al., 2022). The underlying reason for this contrasting finding is unclear and can perhaps be attributed to different molecular targets in the combination approach. This further highlights a gap in phytochemical research with respect to the elucidation of the exact molecular targets of these compounds.

An analog of EGCG, 4-(S)-(2,4,6-trimethylthiobenzyl)-EGCG, has been reported to exhibit better effects than the parent compound in melanoma cells (Xie et al., 2017). Specifically, it was more effective in inducing cell death and selectively induced ROS in cancer cells and not in normal cells. Additionally, it suppressed tumor growth in vivo. The mechanisms underlying its effects included ROS-dependent autophagy through AMPK activation, and induction of ER stress through upregulation of IRE1α, p-eIF2α, and CHOP.

Flavones

Luteolin (3′,4′,5,7-tetrahydroxyflavone) is a flavone, a class of flavonoid compounds, which is found in several dietary plants including celery (*Apium graveolens*), Broccoli (*Brassica oleracea var. italica*), Bell pepper (*Capsicum annuum*), among others. It exhibits various biological effects including anti-inflammatory, antioxidant, and anticancer effects, which have been reported in various types of solid organ cancers both in vitro and in vivo. Activation of autophagy and ER stress has been reported to be involved in the anticancer effects of luteolin (Imran et al., 2019). Luteolin induced autophagy via the SGK1-FOXO3a-BNIP3 axis in triple-negative breast cancer (TNBC) cells (Wu, Lin, et al., 2023) and p53-dependent autophagy in CRC cells (Yoo et al., 2022). In metastatic colon cancer cells, luteolin induced MEK/ERK-dependent cytoprotective autophagy, and the inhibition of the MEK/ERK signaling pathway using PD0325901 (a MERK inhibitor) induced apoptosis (Potočnjak et al., 2020). As stated previously, phytochemical-based induction of cytoprotective autophagy requires deeper studies to determine the underlying mechanisms, and highlights the need for combination approaches when considering the clinical translation of phytochemicals. With respect to ER stress, luteolin was reported to induce ER stress in hepatocellular carcinoma in p53 null, but not in p53 wild-type cells (Lee & Kwon, 2019), and ROS-dependent ER stress in glioblastoma cells through the PERK-eIF2α-ATF4-CHOP pathway (Wang, Wang, et al., 2017).

Baicalein (5,6,7-trihydroxy-2-phenyl-4H-1-benzopyran-4-one) is another flavone that was originally isolated from roots of Chinese skullcap (*Scutellaria baicalensis*) and is an active ingredient of traditional Chinese and Japanese herbal formulations. Its anticancer effects have been demonstrated both in vitro and *in vivo* for several cancers with various underlying molecular mechanisms including autophagy and ER stress (Morshed et al., 2023). Several mechanisms of baicalein-mediated induction of autophagy have been reported in various types of cancers, including: mTOR inhibition in breast (Yan et al., 2018) and gastric (Li, Hu, et al., 2020) cancer cells; AMPK activation in glioma (Liu, Ding, et al., 2019) cells; and AKT inhibition in gastric (Li, Hu, et al., 2020; Qiao et al., 2019) and undifferentiated thyroid (Wang, Qiu, & Qin, 2019) cancer cells. Both ERK activation and inhibition have been reported as the underlying mechanism for Baicalein-induced autophagy, in ovarian cancer (Wang, Xu, et al., 2017) and undifferentiated thyroid cancer (Wang, Qiu, & Qin, 2019) cells,

respectively, suggesting cancer type-specific effects, perhaps reflecting the role of the ERK pathway in the cancer type. Noteworthy, baicalein induced cytoprotective autophagy in CRC (Phan et al., 2020) as the inhibition of autophagy enhanced baicalein-mediated apoptotic cell death. In combination assaya, baicalein increased sensitivity of gastric cancer cells to cisplatin (Li, Hu, et al., 2020) and of TNBC cells to doxorubicin (Hua et al., 2023).

Flavonols

Fisetin (3,3′,4′,7-tetrahydroxyflavone) is a flavonol, which is characterized by a CA 3-hydroxyflavone backbone, and this class of polyphenols are distinct from flavanols. It is found in a wide variety of edible plants including strawberry (*Fragaria* × *ananassa*), apple (*Mallus* spp.), and persimmon (*Diospyros* spp.), among others. With respect to the anticancer effects of fisetin, antiproliferative, antiangiogenic, and antimetastatic effects have been reported (Zhou, Huang, et al., 2023). In oral cancer cells, fisetin increased ROS and intracellular Ca^{2+} levels, and induced apoptosis through the ER stress-associated ATF6-CHOP pathway (Su et al., 2017). In NSCLC cells, fisetin induced ER stress through activation of the MAPK pathway, which resulted in activation of all three arms of the UPR, the IRE1α-XBP1s, ATF6-CHOP, and PERK-eIF2α-CHOP pathways, and hence, downstream induction of ER stress-mediated apoptosis (Kang et al., 2016). With respect to autophagy, in hepatocellular cancer cells, fisetin was reported to mediate its anticancer effects through inhibition of autophagy (Sundarraj et al., 2021). In contrast, in oral squamous (Park et al., 2019) and pancreatic (Jia et al., 2019) cancer cells, fisetin induced cytoprotective autophagy since its inhibition increased fisetin-mediated cell death.

Kaempferol (3,4′,5,7-tetrahydroxyflavone) is another flavonol that has been extensively studied for its biological effects against various diseases, including cardiovascular diseases, neurodegenerative diseases, obesity, and cancer. It is found in numerous plants including dietary plants, such as capers (*Capparis spinosa*), cruciferous vegetables (*Brassica oleracea*; cabbage, kale, cauliflower, etc.), *Aloe vera*, among others. Its anticancer effects have been explored extensively against various cancer types (Amjad et al., 2022) and induction of autophagy is a primary mechanism of the anticancer effects of kaempferol. Mechanisms underlying kaempferol-mediated autophagy include AMPKα activation in gastric cancer cells (Kim, Lee, et al., 2018), ULK1 activation in gastric cancer cells (Kim, Lee,- et al., 2018), AKT inhibition in NSCLC cells (Wang et al., 2023), and mTOR inhibition in NSCLC cells (Wang et al., 2023). Involvement of the ER response was noted in gastric cancer cells through activation of the IRE1 pathway (Kim, Lee, et al., 2018), in ovarian cancer cells through activation of the IRE1α, ATF6-CHOP, and PERK-eIF2α-CHOP pathways (El-Kott et al., 2020), and in melanoma cells through the eIF2α-CHOP pathway (Heo, Lee, et al., 2018). ER stress-mediated autophagy was reported in gastric cancer cells as autophagy was induced by IRE1α-JNK1-mediated disruption of Bcl-2-Beclin-1 (Kim, Lee, et al., 2018). ER stress-mediated cell death was reported through the IRE1-JNK-CHOP pathway in gastric cancer cells (Kim, Lee, et al., 2018) and eIF2α-CHOP-mediated activation of the intrinsic apoptotic pathway in melanoma cells (Heo, Lee, et al., 2018). Additionally, ROS involvement has been reported in kaempferol-induced autophagy in melanoma cells (Heo, Lee, et al., 2018) and ER stress in breast cancer cells (Nandi et al., 2023).

Kaempferol has also been explored in combination with other drugs. It synergized with docetaxel to induce autophagy and the combination was more efficient than each drug alone in prostate cancer both in vitro and in vivo (Zhou, Fang, et al., 2023). Additionally, the combination of kaempferol and verapamil (a calcium channel blocker) induced ROS-dependent autophagy in breast cancer cells (Nandi et al., 2023), increased sensitivity to cisplatin in ovarian cancer cells (El-Kott et al., 2020), and synergized with cisplatin and paclitaxel in gastric cancer cells (Kim, Lee, et al., 2018).

Flavanones

Naringin (flavanone-7-O-glycoside) is a flavanone, a class of aromatic ketones, and is found commonly in citrus fruits, such as grapefruits, oranges, lemons, and accounts for the bitter taste in citrus juices. Various biological effects of naringin have been reported including antioxidant, anti-inflammatory, anti-osteoporotic, and anticancer effects (Chen et al., 2016). In cervical cancer cells, naringin induced ER stress through the p-eIF2α-CHOP pathway to induce ER stress-mediated apoptosis (Chen et al., 2020). In ovarian cancer cells, naringin induced ER stress-mediated apoptosis through the PERK-CHOP pathway and inhibited autophagy through activation of the PI3K-AKT–mTOR pathway (Zhu et al., 2023). However, in gastric cancer cells, Xu et al. (2021) reported that naringin induced autophagy by suppressing the PI3K-AKT–mTOR pathway. Later, Raha et al. (2020) further reported that naringin induced ROS-dependent autophagy as well as lysosomal membrane permeabilization and cathepsin D release, which induced ERK1/2-p38-dependent autophagic cell death.

In combination therapy, Albayrak et al. (2021) reported that naringin in combined with tunicamycin (ER stress inducer) and BAY 11-7082 (NF-κB inhibitor) induced mitochondrial apoptosis through ROS-dependent activation of the PERK-eIF2α-ATF4-CHOP pathway in CRC cells. Additionally, the combination of naringin and cisplatin was shown to be more effective than either drug alone in ovarian cancer cells (Zhu et al., 2023).

Chalcones

Flavokavain B (or flavokawain B; 2′-hydroxy-4′,6′-dimethoxychalcone), isolated from the Kava plant (*Piper methysticum*), is a flavokavain that belongs to the class of chalcones/chalconoids, which are phenolic compounds characterized by an α, β-unsaturated ketone backbone. Of the three identified flavokavains, flavokavain B exhibits more potent anticancer effects compared to flavokavains A and C (Abu et al., 2013). Flavokavain B induced ER stress in glioma cells, through activation of the eIF2α-ATF4-CHOP pathway (Wang, Qi, et al., 2018). Autophagy is also involved in the anticancer effect of flavokavain B. Various mechanisms of autophagy induction were reported, including inhibition of the PI3K-AKT–mTOR pathway (He et al., 2018; Hseu, Chiang, et al., 2020; Wang, Qi, et al., 2018), AMPK activation (He et al., 2018), and dysregulation of Beclin-1 and Bcl-2

interaction (Hseu, Chiang, et al., 2020). Cytoprotective autophagy was reported in flavokavain B-treated glioma (Wang, Qi, et al., 2018) and thyroid (He et al., 2018) cells, since inhibition of autophagy improved cell death in both studies. Additionally, the combination of flavokavain B with doxorubicin or cisplatin was more efficient in inducing cell death in gastric cancer both in vitro and in vivo (Hseu, Lin, et al., 2020). While flavokavain C has also been reported to induce ER stress and CHOP-mediated apoptosis in CRC cells (Phang et al., 2016), to the best of our knowledge, as of May 2024, there have been no reports on flavokavain A with respect to autophagy and/or ER stress induction.

4.1.4 | Lignans

Honokiol is a lignan, a class of phenolic compounds that are considered precursors to phytoestrogens. Honokiol was isolated from *Magnolia* species and is widely used in traditional Japanese medicine. Various biological effects of honokiol have been reported including neuroprotective, antioxidant, antimicrobial, cardioprotective, anti-inflammatory, and anticancer effects (Rauf et al., 2021). Autophagy and ER stress have both been implicated in the anticancer effects of honokiol. Increased BiP and intracellular Ca^{2+} levels were noted in osteosarcoma cells (Huang et al., 2018). With respect to the specific sensors of the UPR activated by honokiol, activation of the PERK-eIF2α-CHOP pathway was reported in lung cancer cells (Zhu, Xu, et al., 2019) and activation of the PERK and IRE1α sensors in melanoma cells (Chiu et al., 2019). Downstream of ER stress induction, CHOP-mediated apoptosis was reported in lung cancer (Zhu, Xu, et al., 2019) and melanoma cells (Chiu et al., 2019) cells. Interestingly, honokiol-induced ER stress downregulated HDAC3 expression through inhibition of the NFκBp65-CEBPβ pathway in gastric cancer cells, which consequently led to the inhibition of EMT (Wu, Jan, et al., 2023). Similarly, honokiol-induced ER stress inhibited EMT in melanoma cells through suppression of the MITF and β-catenin pathways (Chiu et al., 2019). Honokiol was also reported to induce autophagy-mediated apoptosis in neuroblastoma cells (Lin et al., 2019), and osteosarcoma cells (Huang et al., 2018). In the latter cancer type, activation of the ERK1/2 pathway was implicated in autophagy induction (Huang et al., 2018).

4.1.5 | Curcuminoids

Curcumin is a linear diarylheptanoid, a class of polyphenols also referred to as curcuminoids. Curcumin is the main active component of turmeric (*Curcuma longa*) extract, which has long been used in traditional Chinese and Indian medicine for various conditions. In fact, curcumin is one of the most well-studied phytochemicals with respect to its anticancer activity both in vitro and in vivo, and is also being investigated in Phase I and II clinical trials for solid and hematological cancers (Tomeh et al., 2019).

Curcumin was reported to induce autophagic cell death in glioblastoma cells (Lee et al., 2020), whereas it induced cytoprotective autophagy in breast cancer cells (Akkoç et al., 2015) and laryngeal cancer cells (Wan et al., 2017). Inhibition of autophagy in the latter two cell types increased curcumin-mediated apoptosis. Similarly, the curcumin derivative tetrahydrocurcumin was shown to induce autophagy as a pro-death mechanism in NSCLC cells through inhibition of the PI3K-AKT–mTOR pathway (Song et al., 2018). Other curcumin derivatives also induced pro-death autophagy through AMPK activation, such as PAC (5-Bis (4-hydroxy-3-methoxybenzylidene)-N-methyl-4-piperidone) in oral cancer cells (Semlali et al., 2021). On the other hand, WZ35 (1-(4-hydroxy-3-methoxyphenyl)-5-(2-nitrophenyl) penta-1,4-dien − 3-one), another synthetic curcumin derivative, inhibited YAP-mediated autophagy to promote apoptosis in hepatocellular carcinoma cells (Wang, Zhu, et al., 2019).

Curcumin was shown to induce ROS-dependent ER stress in CRC cells (Huang et al., 2017), cervical cancer cells (Kim, Kim, et al., 2016), and prostate cancer cells (Lee et al., 2015). Curcumin was also shown to induce cell death through CHOP-mediated apoptosis in papillary thyroid cancer cells (Zhang, Cheng, et al., 2018). Several curcumin derivatives were reported to exert their anticancer effects through ROS-dependent ER stress, such as WZ37 in head and neck squamous cell carcinoma cells (Zhang, Lin, et al., 2020) and B2 (2E,2′ E)-3,3′-(1,4-phenylene)bis (1-(2-chlorophenyl)prop-2-en-1-one) in NSCLC cells (Wei et al., 2022).

4.1.6 | Gingerols

Gingerols and shogaols, which are the dehydrated products of gingerols, are the main bioactive constituents of fresh and dry ginger (*Zingiber officinale*), respectively. The anticancer activity of 6-gingerol and 6-shogaol has been extensively studied. Some studies suggested that 6-shogaol is more potent and effective as an anticancer phytochemical than 6-gingerol (Kou et al., 2018). The anticancer effects of 6-gingerol seem to depend mainly on induction of autophagy, as listed in Table 1.

Various biological activities of 6-shogaol including anti-inflammatory, antioxidant, neuroprotective, cardioprotective, and anticancer activities have been reported. In contrast to 6-gingerol, 6-shogaol has been reported to modulate various signaling pathways including those regulating autophagy and ER stress in various types of cancer (Kou et al., 2018). 6-shogaol induced ROS-dependent autophagy and ER stress through the activation of ATF6, eIF2α, and IRE1α in hepatocellular cancer cells (Wu et al., 2015). In addition, 6-shogaol was reported to induce ER stress through inhibition of 26S proteasome and ER stress-mediated paraptosis in TNBC and NSCLC cells (Nedungadi et al., 2018).

The role of 6-shogaol-induced autophagy seems complex. In cervical cancer cells, 6-shogaol induced cytoprotective autophagy through inhibition of the PI3K-AKT–mTOR pathway, and the inhibition of autophagy increased ROS-dependent apoptosis in 6-shogaol-treated cells (Pei et al., 2021). On the other hand, Bawadood et al.

(2020) reported that 6-shogaol suppressed autophagy through inhibition of the Notch pathway in breast cancer cells (MCF7 and T47D). These studies highlight the importance of investigating the context-dependent role of cellular processes and the context-dependent effects of phytochemicals. In combination approaches, 6-shogaol was shown to enhance the effect of 5-fluorouracil, FOLFIRI (5-fluorouracil + irinotecan), FOLFOX (5-fluorouracil + oxaliplatin), and FOLFOXIRI (5-fluorouracil + oxaliplatin + irinotecan) in CRC cells through induction of autophagy and apoptosis (Woźniak et al., 2020). In hepatocellular cancer cells, the combination of 6-shogaol and TRAIL enhanced ROS-dependent TRAIL-induced apoptosis by inhibiting autophagic flux (Nazim & Park, 2018).

4.2 | Terpenes and terpenoids

4.2.1 | Diterpenes

Carnosol is a phenolic diterpene that was originally isolated from Sage (*Salvia carnosa*) and has since been identified in various other herbs including rosemary (*Rosmarinus officinalis*), basil (*Ocimum basilicum*), and thyme (*Thymus vulgaris*). The anticancer activity of carnosol has been demonstrated in various types of cancers in vitro and in vivo (O'Neill et al., 2020). However, only few reports have attributed autophagy and/or ER stress to its anticancer effects. ROS-dependent autophagy in response to carnosol treatment was reported in TNBC cells (Al Dhaheri et al., 2014) and in osteosarcoma cells (Lo et al., 2017). Further, in TNBC cells, carnosol was reported to induce Beclin-1-independent autophagy, which preceded apoptosis (Al Dhaheri et al., 2014). Later, carnosol was reported to induce activation of p38, which further activated the UPR and induced proteasome-dependent degradation of mTOR (Alsamri et al., 2022). Both p38 activation and ER stress-mediated mTOR degradation were implicated in carnosol-mediated autophagy in TNBC cells (Alsamri et al., 2022). Interestingly, carnosol also induced proteasome-dependent degradation of other proteins in TNBC cells, including STAT3 (Alsamri et al., 2019), PCAF (Alsamri et al., 2021), and p300 (Alsamri et al., 2021). Additionally, activation of the PERK-ATF4-CHOP pathway induced CHOP-mediated apoptosis in carnosol-treated TNBC cells (Alsamri et al., 2022).

Tanshinones, represent the main active ingredients of the dried roots of Red sage (*Salvia miltiorrhiza*), a plant widely used in traditional Chinese medicine (TCM) for various conditions. More than 40 tanshinones have been identified thus far, of which tanshinone I, tanshinone IIA, dihydrotanshinone, and cryptotanshinone are the most well-characterized with respect to their anticancer effects (Jiang et al., 2019). The anticancer effects of tanshinone I and isocryptotanshinone are listed in Table 1.

Tanshinone IIA was reported to induce autophagy in leukemia (Zhang, Geng, et al., 2019), oral squamous cell carcinoma (Qiu et al., 2018), CRC (Qian et al., 2023), osteosarcoma (Yen et al., 2018), and renal cell carcinoma (Kim et al., 2022) cells. Except in prostate cancer cells (Li et al., 2016), tanshinone IIA-induced autophagy was generally described as a pro-cell death mechanism. The mechanisms underlying tanshinone IIA-induced autophagy include inhibition of the PI3K-AKT–mTOR pathway in glioma (Ding et al., 2017), leukemia (Zhang, Geng, et al., 2019), oral squamous cell carcinoma (Qiu et al., 2018), and osteosarcoma (Yen et al., 2018), and activation of the MEK–ERK-mTOR pathway in CRC (Qian et al., 2020) cells.

Regarding ER stress, tanshinone IIA inhibited the growth of pancreatic cancer xenografts through induction of ER stress via the PERK-eIF2α, IRE1α, and ATF6-CHOP pathways (Chiu & Su, 2017). Tanshinone IIA also induced ER stress and activated the PERK-ATF4-CHOP pathway in NSCLC cells, and synergized with TRAIL to increase apoptosis in TRAIL-resistant NSCLC cells (Kim, Kang, et al., 2016).

Cryptotanshinone, another diterpene, activated the PERK sensor of the UPR, induced ER stress-mediated autophagy and -apoptosis in CRC cells (Fu et al., 2021). Similarly, another study showed that cryptotanshinone induced ER stress and increased intracellular Ca^{2+} levels in CRC cells (Wang, Zhang, et al., 2020). The same study also reported that inhibition of calpain improved cryptotanshinone-induced p53-dependent apoptosis (Wang, Zhang, et al., 2020). Cryptotanshinone induced autophagy in oral squamous cell carcinoma cells (Jiang et al., 2023).

4.2.2 | Triterpenoids

Astragaloside IV is a triterpenoid that is the main bioactive component of Mongolian milkvetch (*Astragalus mongholicus*) extract, a plant used in traditional Mongolian and Chinese medicine. Various biological effects of astragaloside IV have been reported including hepatoprotective, neuroprotective, antidiabetic, and anticancer effects (Zhang, Wu, et al., 2020). Studies suggest that astragaloside IV exerts its anticancer effect mainly through modulation of autophagy. It induced pro-death autophagy through the TGF-β/Smad signaling pathway in vulvar squamous cell carcinoma cells (Zhao et al., 2018), and through the PTEN-PI3K-AKT signaling via IDO1 inhibition in uterine leiomyoma cells (Qiu et al., 2022). Similarly, it induced pro-death autophagy in cervical cancer cells (Xia et al., 2020); however, the mechanism underlying the induction of autophagy was not clarified. Intriguingly, astragaloside IV acts as an inhibitor of autophagy when used in combination approaches in NSCLC cells (Lai et al., 2020; Li, Li, et al., 2022; Liu, Chen, et al., 2023). Indeed, the inhibition of autophagy by astragaloside IV was implicated in sensitization of NSCLC to cisplatin (Lai et al., 2020) and bevacizumab (Li, Li, et al., 2022) and in the potentiation of the anticancer effects of propofol (Liu, Chen, et al., 2023). Mechanistically, astragaloside IV was able to reverse bevacizumab-mediated inhibition of the mTOR–AKT pathway (Li, Li, et al., 2022). As for the modulation of ER stress, only Lai et al. (2020) reported that astragaloside IV induced ER stress to sensitize NSCLC cells to cisplatin; however, the underlying pathways were not explored.

Celastrol (also known as tripterine), is an active component of thunder god vine (*Tripterygium wilfordii*) root extract, commonly used

in TCM. It has been reported to exhibit anticancer effects against various cancer types including solid and homological tumors (Shi et al., 2020). Celastrol induced cytoprotective autophagy in glioma (Liu, Zhao, et al., 2019) and CRC cells (Zhang, Wu, et al., 2022) since the inhibition of autophagy by 3-methyladenine promoted apoptosis. The inhibition of the AKT–mTOR pathway was implicated in celastrol-mediated autophagy in the former cancer type (glioma) (Liu, Zhao, et al., 2019). Celastrol also promoted lipophagy, a selective form of autophagy that maintains lipid homeostasis, and inhibited EMT in clear cell renal cell carcinoma cells (Zhang, Zhu, et al., 2021). Depending on the cancer type, celastrol-induced ER stress plays either a pro-survival or pro-death role (Chen et al., 2018; Ren et al., 2017). In hepatocellular carcinoma cells, celastrol induced ER stress-mediated apoptosis through the PERK-eIF2α-ATF4-CHOP pathway (Ren et al., 2017). Conversely, the activation of the PERK pathway in osteosarcoma cells was reported to be rather cytoprotective (Chen et al., 2018). In fact, GSK2656157 (PERK inhibitor) increased celastrol-mediated apoptosis and autophagy in osteosarcoma cells (Chen et al., 2018). In combination assays, celastrol synergized with erastin (a ferroptosis inducer) to induce autophagy and mitophagy, a selective form of autophagy that recycles damaged mitochondria, in NSCLC cells (Liu, Fan, et al., 2021).

4.3 | Xanthonoid

Gambogenic acid is a xanthonoid, a class of polyphenolic compounds with a xanthone backbone, commonly isolated from Gamboge tree (*Garcinia hanburyi*). Gambogenic acid has been explored along with other xanthonoids for its anticancer activity. In prostate cancer cells, gambogenic acid induced ROS-dependent cytoprotective autophagy since the inhibition of autophagy increased apoptosis induction through activation of the JNK pathway (Wu, Wang, et al., 2023). Gambogenic acid was also reported to induce pro-death ER stress in CRC cells by downregulating Aurora A leading to the activation of the PERK-eIF2α-ATF4 and IRE1α pathways (Liu, Xu, et al., 2021). Additionally, gambogenic acid was shown to induce ROS-dependent ER stress and Noxa-mediated apoptosis, downstream of activation of IRE1α-JNK in CRC cells (Zhao et al., 2020).

4.4 | Quinone derivatives

4.4.1 | Naphthoquinones

Shikonin (5,8-dihydroxy-2-[(1R)-1-hydroxy-4-methyl-3-pentenyl]-1,4-naphthoquinone) is a 1,4-naphthoquinone analog that is found in the dried roots of purple gromwell (*Lithospermum erythrorhizon*), a plant used in traditional Japanese medicine. It exhibits a range of biological properties including antimicrobial, anticancer, and anti-inflammatory effects, among others (Yadav et al., 2022). Shikonin is a potent inducer of autophagy; however, depending on the cancer type, both cytoprotective and pro-death autophagy have been reported. Wang, Mayca Pozo, et al. (2020) reported that shikonin induced cytoprotective autophagy in TNBC, NSCLC, and pancreatic cancer cells. In gastric cancer cells, shikonin induced ROS-dependent cytoprotective autophagy, and its inhibition enhanced ROS-dependent pyroptosis, a caspase 1-dependent programmed cell death (Ju et al., 2023). Similarly, in melanoma cells, shikonin also induced ROS-dependent cytoprotective autophagy through p38 activation and its inhibition enhanced apoptotic cell death (Liu, Kang, et al., 2019). In bladder cancer cells, inhibition of shikonin-induced cytoprotective autophagy augmented ROS-dependent necroptosis (Liu, Liu, et al., 2023). Shikonin was also reported to induce pro-death autophagy in hepatocellular carcinoma (Zhang, Shang, et al., 2022), testicular cancer (Yao et al., 2020), CRC (Zhu, Zhao, et al., 2019), and renal cancer (Tsai et al., 2021) cells. In hepatocellular carcinoma, shikonin induced autophagic cell death through inhibition of the PI3K-AKT–mTOR pathway (Zhang, Shang, et al., 2022), while in renal cancer cells through ROS-dependent activation of p38 (Tsai et al., 2021).

As for ER stress, shikonin has been reported to induce ROS-dependent ER stress in adult T cell leukemia/lymphoma (Boonnate et al., 2023), CRC (Qi et al., 2022), and melanoma (Liu, Kang, et al., 2019) cells. Shikonin was also reported to induce ER stress-mediated apoptosis through activation of the PERK-eIF2α-CHOP axis in 5-FU-resistant CRC cells (Piao et al., 2022), CRC cells (Qi et al., 2022), and melanoma cells (Liu, Kang, et al., 2019). Additionally, the IRE1α-JNK pathway has been implicated in shikonin induced ER stress-mediated apoptosis in adult T cell leukemia/lymphoma cells (Boonnate et al., 2023) and CRC cells (Qi et al., 2022). Moreover, shikonin has been reported to sensitize wild-type EGFR NSCLC cells to EGFR TKIs erlotinib and gefitinib (Li et al., 2018) and osimertinib (Hu et al., 2020), through ROS-dependent ER stress, which enhanced EGFR TKI-mediated apoptosis.

4.4.2 | Anthraquinone

Emodin (1,3,8-trihydroxy-6-methylanthraquinone) is an anthraquinone analog that is the active component of several medicinal herbs used in traditional Chinese and Japanese medicine, including Chinese rhubarb (*Rheum palmatum*), Asian knotweed (*Reynoutria japonica*), and *Aloe vera*, among others. It has been demonstrated to exhibit a wide range of biological effects including antimicrobial, anti-inflammatory, antidiabetic, neuroprotective, and anticancer effects, the latter of which is mediated through modulation of various pathways including autophagy and ER stress (Dong et al., 2016). Emodin has been reported to induce ER stress and CHOP-mediated apoptosis through the PERK-eIF2α-CHOP pathway in CRC cells (Cheng & Dong, 2018).

Emodin-induced autophagy was generally described as a mechanism of cell death. Emodin induced ROS-dependent autophagy through inhibition of the AKT–mTOR pathway in NSCLC cells (Shen et al., 2020). ROS-dependent autophagy was also reported in CRC cells (Wang, Luo, et al., 2018). In hepatocellular carcinoma cells, emodin induced autophagy through inhibition of the PI3K-AKT–mTOR pathway, which further inhibited EMT via autophagy-mediated

degradation of Snail and β-catenin (Qin et al., 2022). Emodin was also shown to mediate its cytotoxic effects through induction of autophagy in pancreatic cells (Du et al., 2019); however, the molecular mechanism underlying the induction of autophagy was not investigated. Conversely, emodin was also reported to induce cytoprotective autophagy and reverse adriamycin resistance in breast cancer cells (Cheng et al., 2021).

In combination approaches, emodin exhibited synergistic effects with gemcitabine in NSCLC cells (Shen et al., 2020). It also synergize with carfilzomib (a proteasome inhibitor) in multiple myeloma cells to increase ROS production, autophagy, and apoptosis (Hsu et al., 2022).

4.5 | Alkaloid

Tetrandrine is a bis-benzylisoquinoline alkaloid present in extracts of plants from the moonseed family (Menispermaceae) including *Stephania tetrandra*, which is used extensively in TCM. It acts as a calcium channel blocker with various biological effects including antidiabetic, antimicrobial, anti-inflammatory, and anticancer effects (Bhagya & Chandrashekar, 2016). Tetrandrine induced autophagy in TNBC (Guo & Pei, 2019), hepatocellular carcinoma (Zhang, Liu, et al., 2018), and gastric cancer (Bai et al., 2018) cells. Inhibition of the PI3K-AKT–mTOR pathway was implicated in tetrandrine-induced autophagy in TNBC (Guo & Pei, 2019) and gastric cancer (Bai et al., 2018) cells. Downstream of autophagy, tetrandrine inhibited EMT in hepatocellular carcinoma cells through autophagy-mediated degradation of Wnt2a and MA1 (Zhang, Liu, et al., 2018). Tetrandrine was also reported to induce an ROS-dependent ER stress associated with an increase of intracellular Ca^{2+} levels which consequently induced CHOP-mediated apoptosis in nasopharyngeal carcinoma cells (Lin et al., 2016; Liu et al., 2017). Similarly, tetrandrine was reported to induce ER stress and apoptosis through the eIF2α-ATF4-CHOP pathway in liposarcoma cells (Samsuzzaman & Jang, 2022). Tetrandrine also sensitized nasopharyngeal cancer cells to irradiation, through induction of autophagy (Wang, Yao, et al., 2020). Interestingly, and in contrast to the above studies, tetrandrine sensitized EGFR mutant lung adenocarcinoma cells to gefitinib (an EGFR TKI) by inhibition of autophagy through lysosomal inhibition (Sato et al., 2019).

Other alkaloids that exert their anticancer effects through induction of autophagy (graveoline), through induction of ER stress (sophoridine and corynoxine) or induction of both autophagy and ER stress (daurisoline) have been listed in Table 1.

5 | PLANT EXTRACTS

Given the rising popularity of phytochemicals as anticancer drugs, it is unsurprising that plant extracts widely used in traditional/folk medicine are being investigated for their anticancer activity. In particular, in recent years, there has been growing evidence supporting the therapeutic use of alternative traditional medicines, particularly TCM, for cancer therapeutics (Yadav et al., 2022). Specifically, plant extracts, which are at the heart of traditional medicine including TCM, are rich in bioactive constituents that exhibit a variety of pharmacological activities, including antioxidant, anti-inflammatory, and anticancer activities (Zhang, Qiu, et al., 2021). Hence, this line of research, that is, investigating the anticancer activity of traditionally used plant extracts, is of paramount importance as it directs the isolation and characterization of bioactive compounds with potential clinical applications for cancer treatment (Sasidharan et al., 2011). Indeed, several chemotherapeutic agents that are presently used in clinical practice have been identified through such means, including camptothecin and its derivatives, vinca alkaloids, among others. Several others, such as, resveratrol, curcumin, and berberine have undergone evaluation in multiple clinical trials to assess their safety, efficacy, and clinical applicability against various cancer types (McCubrey et al., 2017).

With regards to TCM, plant extracts and herbal formulas/concoctions have been employed in China and other East Asian countries as adjunct therapy to treat cancer-associated symptoms. Notably, Bu-zhong-yi-qi-tang (Hochuekki-to in Japanese, or Bojungikki-Tang in Korean), a concoction of seven traditional herbs, is commonly prescribed by traditional Chinese physicians and was reported to reduce the mortality hazard ratio of patients with lung cancer, reduce chronic cancer-related fatigue, and increase infiltration of lymphocytes in tumors (Zhang, Qiu, et al., 2021). Similarly, Shi-quan-da-bu-tang (Juzentaiho-to in Japanese, or Sipjeondaebo-tang in Korean), a concoction of 10 traditional herbs, is also prescribed in South Korea for chronic cancer-associated fatigue and was reported to reduce chemotherapy-associated adverse events (Zhang, Qiu, et al., 2021). In the present review, we have focused on plant extracts that have roots in traditional medicine, and not herbal concoctions. Within this category, we have specifically highlighted plant extracts that exhibit anticancer activity through modulation of autophagy and/or ER stress (Table 2).

There are, however, limitations to the use of herbal concoctions and plant extracts. The exact mechanisms of actions and molecular targets of these concoctions and extracts are often not known, and cannot be realistically elucidated owing to the diversity of bioactive constituents. Further, the composition of these concoctions and plant extracts, and hence their clinical effects, can vary drastically as environmental factors, such as temperature, nutrient availability, salinity, environmental stress, altitude, soil composition, and light intensity, among others, can greatly affect the biosynthesis and accumulation of phytochemical compounds (Li, Kong, et al., 2020). Hence, the lack of standardization in this regard greatly hinders the clinical translation of traditional herbal concoctions and plant extracts. Nonetheless, they serve as reservoirs of phytochemical compounds with potent anticancer activities. Therefore, we would like to emphasize the need for researchers to focus on the identification of the active fractions of herbal concoctions and plant extracts, and further the identification of promising bioactive constituents using approaches such as UV–visible spectroscopy, high-performance liquid chromatography-mass spectrometry, and liquid chromatography with tandem mass spectrometry (Altemimi et al., 2017).

TABLE 2 Plant extracts that exhibit anticancer activity through modulation of autophagy and/or ER stress.

Plant name	Traditional medicine	Plant part	Solvent	Cancer type[a]	Anti-cancer effects	ROS involvement	Ref
Garcinia dulcis (Mundu)	Thailand, Indonesia, Philippines, Vietnam	Flower	Acetone	Glioblastoma (A172)	• ER stress-mediated autophagy • S and G2/M phase cell cycle arrest	–	(Siangcham et al., 2022)
Elsholtzia stachyodes (Spiked mint)	TCM, North-east India	Aerial parts	Ethanol	Leukemia (U937 and K562)	• ER stress • G1 phase cell cycle arrest • UPR-mediated Autophagy • Apoptosis	+	(Kulaphisit et al., 2023)
Cnidium officinale Makino	TCM, Korean Peninsula, Japan	n/s	Ethanol	Multiple myeloma (U266), lymphoma (U937)	• ROS-dependent apoptosis • ER stress-mediated apoptosis	+	(Cha et al., 2018)
Salvia miltiorrhiza (Red sage)	TCM, Korean Peninsula, Japan	n/s	Ethanol	Multiple myeloma (U266), lymphoma (U937)	• ROS-dependent apoptosis • ER stress-mediated apoptosis	+	(Kim, Song, et al., 2018)
Origanum majorana (Marjoram)	Mediterranean, Turkey, Cyprus, Western Asia, Arabian peninsula	Leaves	Ethanol	CRC (HT-29 and CaCo-2)	• Autophagy-mediated apoptosis • DNA damage	–	(Benhalilou et al., 2019)
Zingiber officinale (Ginger)	TCM, Indian Subcontinent, Japan, South East Asia	Rhizome	Ethanol	TNBC (MDA-MB-231), NSCLC (A549)	• ER stress • Paraptosis • DNA Damage • Mitochondrial dysfunction	+	(Nedungadi et al., 2021)
Euterpe oleracea Mart. (Açai)	Brazil	Seed	Hydroalcoholic	Breast (MCF7)	• Autophagy	+	(Silva et al., 2021)
			n/s	Breast (MCF7)	• ROS-dependent autophagy	+	(Da Silva et al., 2022)
			Oil	CRC (CaCo-2 and HCT-116)	• ROS-dependent autophagy • ROS-dependent apoptosis	+	(Da Silva et al., 2023)
Cichorium (Chicory grass)	TCM, South Africa, Eastern Europe	Whole grass	Ethyl acetate	CRC (HCT116 and SW620)	• ROS-dependent autophagy • Apoptosis	+	(Wen et al., 2019)
Ficus carica (Fig)	TCM, Indian Subcontinent	Fruit	Ethanol	Pancreatic (Panc-1 and QGP-1)	• Autophagy • ROS-dependent apoptosis • ROS-dependent senescence • Lipid peroxidation • Decreased mitochondrial membrane potential	+	(Ou et al., 2022)
Buddleja officinalis (Pale butterfly bush)	TCM, Korean Peninsula, Vietnam	Flower	Ethanol	Head and neck (FaDu)	• ER stress-mediated autophagy • Apoptosis • Autophagy	+	(Cho et al., 2018)

(Continues)

TABLE 2 (Continued)

Plant name	Traditional medicine	Plant part	Solvent	Cancer type[a]	Anti-cancer effects	ROS involvement	Ref
Quercus infectoria galls (Aleppo oak)	Indian Subcontinent	n/s	Aqueous	CRC (CT-26 and HT-29)	• Caspase-dependent Apoptosis • ROS-dependent autophagy • ROS accumulation	+	(Zhang, Wang, et al., 2020)
Artemisia vulgaris (Mugwort)	TCM, Indian Subcontinent	Aerial parts	Methanol	CRC (HCT-15)	• ROS-dependent autophagy • ROS-dependent decrease in mitochondrial membrane potential	+	(Lian et al., 2018)
Malus pumila Miller cv. *Annurca* (Annurca apple)	Levant	Fruit	Phenol	TNBC (MDA-MB-231)	• ROS-dependent G2/M phase cell cycle arrest • ROS-dependent apoptosis • ROS-dependent autophagy	+	(Martino et al., 2019)
Terminalia bellirica (Baheda)	TCM, Indian Subcontinent	Seed	Aqueous	Oral squamous cell (Cal33)	• ROS-dependent apoptosis • Autophagy	+	(Patra et al., 2020)
Artemisia kruhsiana Besser (Alaska wormwood)	Russia	Leaves	Methanol	Prostate (PC-3)	• Apoptosis • Autophagy	+	(Lee et al., 2021)
Dendrobium denneanum	TCM	n/s	Ether	NSCLC (A549)	• ER stress • Apoptosis • Autophagy	+	(Zhang, Li, et al., 2019)
Paeonia suffruticosa (Tree peony)	TCM	Root bark	Aqueous	Pancreatic (AsPC1)	• ROS-dependent ER stress • ER stress-mediated autophagy • ER stress-mediated mitophagy • ER-mediated apoptosis	+	(Liu et al., 2018)
Galenia africana (Kraalbos)	Southern Africa	Leaves	Ethanol	Breast (MCF-7), TNBC (MDA-MB-231)	• DNA damage • Autophagy-mediated apoptosis • Apoptosis • Necroptosis • S and G2/M cell cycle arrest	+	(Mohamed et al., 2020)
Solanum xanthocarpum (Yellow-fruit nightshade)	TCM, Indian Subcontinent	Leaves	Aqueous	Nasopharyngeal (C666-1)	• Autophagy • ROS-dependent Apoptosis • DNA Damage	+	(Zhang, Wang, et al., 2018)

TABLE 2 (Continued)

Plant name	Traditional medicine	Plant part	Solvent	Cancer type[a]	Anti-cancer effects	ROS involvement	Ref
Zingiber officinale (Java Ginger)	TCM, Indian Subcontinent, Japan, Korean Peninsula, Southeast Asia	Rhizome	n/s	Cervical (SiHa)	• Autophagy-mediated apoptosis • Apoptosis • Decreased mitochondrial membrane potential	+	(Nath et al., 2023)
Momordica charantia (Bitter melon)	TCM, Indian Subcontinent, Turkey	Fruit	Aqueous	Oral (Cal27 and JHU022)	• ER stress • ROS-dependent apoptosis • Inhibition of glycolysis	+	(Sur et al., 2019)
Polyalthia longifolia (False Ashoka)	Indian Subcontinent	Leaves	Ethanol	Prostate (PC3, DU145, C4-2, and PC3M-LUC-C6)	• G1/S phase cell cycle arrest • ER stress-mediated apoptosis	−	(Afolabi et al., 2019)
Taraxacum mongolicum (Dandelion)	TCM, Europe	Whole plant	Aqueous	Cervical (HeLa)	• S phase cell cycle arrest • ER stress	−	(Lin, Liu, et al., 2022)
			Aqueous	Breast (MCF7 and ZR-75-1), TNBC (MDA-MB-231)	• Decreased mitochondrial membrane potential • ER stress-mediated apoptosis	−	(Lin, Chen, et al., 2022)
Drimia maritima (Sea onion)	Indian Subcontinent, Egypt	Bulb	Methanol	Breast (MCF7), TNBC (MDA-MB-468)	• ER stress • Decreased mitochondrial membrane potential • Mitochondria-mediated apoptosis	+	(Hamzeloo-Moghadam et al., 2018)
Urtica dioica (Stinging nettle)	TCM, Europe	Leaves	Methanol	NSCLC (H1299, A549, H460 and H322)	• DNA damage • G2/M phase cell cycle arrest • ER stress-mediated apoptosis	−	(D'Abrosca et al., 2019)
Leonurus japonicus (Oriental motherwort)	TCM, Japan, Korean Peninsula	Whole plant	Ethanol	Acute myeloid leukemia (U937 and THP-1)	• Decreased mitochondria membrane potential • ROS-dependent apoptosis • ER stress	+	(Park et al., 2022)
Rhododendron luteum (Honeysuckle azalea)	TCM	Leaves	DMSO	Cervical (HeLa)	• S phase cell cycle arrest • ER stress • Apoptosis	+	(Turan et al., 2022)

Abbreviations: CRC, colorectal cancer; ER, endoplasmic reticulum; n/s, not specified; NSCLC, non-small cell lung cancer; ROS, reactive oxygen species; TCM, Traditional Chinese Medicine; TNBC, triple-negative breast cancer.

[a]Only studies performed in human cancer cell lines were considered in this review.

6 | INTERPLAY BETWEEN AUTOPHAGY AND ER STRESS

Autophagy and ER stress are both response processes to cellular stress with complex interplay between the two. In the present review, we identified six phytochemicals, carnosol, capsaicin, cryptotanshinone, guangsangon E, kaempferol, and δ-tocotrienol, that induce ER stress-mediated autophagy (Figure 4a). This finding is in line with the existing literature on the interplay between autophagy and ER stress, as the UPR is a well-known regulator of autophagy (Figure 4b).

All three UPR sensors regulate autophagy in different ways: (i) PERK-eIF2α-ATF4-CHOP upregulates transcription of autophagy genes; (ii) IRE1α-XBP1s induces the expression of Beclin-1; (iii) ATF6 induces the expression of DAPK1, which phosphorylates Beclin-1 (Kwon et al., 2023). In fact, knockdown of any one of the UPR sensors, PERK, IRE1, or ATF6 impairs the induction of autophagy (Rashid et al., 2015). With respect to the underlying mechanism, the UPR sensors induce autophagy through inhibition of the mTOR–AKT pathway, and activation of the AMPK pathway. In the PERK arm, ATF4 upregulates the expression of *SESN2*, *DDIT3*, and *DDIT4*, of which SESN2 and DDIT3 are negative regulators of mTORC1. DDIT4 further upregulates TRIB3, which is a negative regulator of AKT. On the other hand, IRE1α activation stimulates RPS6KA3, which activates AMPK, and consequently, the ULK1 complex. AMPK activation is also facilitated by PERK and ATF6, which activate AMPK via DDIT3-mediated ATP depletion (Rashid et al., 2015). The interplay between autophagy and ER stress also extends to a specialized form of autophagy called ER-phagy, in which the autophagosome fuses with damaged ER to restore ER homeostasis through interaction between ER-phagy receptors and LC3 (Kwon et al., 2023; Rashid et al., 2015). Further, there is also evidence to the effect that the UPR regulates other forms of selective autophagy, specifically in mitophagy through AFT4-mediated PARK2 expression (Rashid et al., 2015).

With respect to the six phytochemicals that induced ER stress-mediated autophagy, different pathways were implicated. Capsaicin upregulated the expression of TRIB3, which was concomitant with upregulation of p-eIF2α, suggesting the involvement of the PERK arm (Huang et al., 2021). The IRE1α arm was implicated in the anticancer activity of kaempferol (Kim, Lee, et al., 2018) and guangsangon E (Shu et al., 2021) as knockdown of IRE1α or use of a selective IRE1α inhibitor (4μ8c) impaired autophagy induction. More specifically, IRE1α-JNK1-mediated disruption of Bcl-2-Beclin-1 was noted as the underlying mechanism in ER stress-mediated autophagy in kaempferol-treated cells (Kim, Lee, et al., 2018). In contrast, carnosol induced ER stress-mediated activation of p38, which regulated proteasome-dependent degradation of mTOR, which in turn induced autophagy (Alsamri et al., 2022). The specific underlying mechanisms were not clarified for cryptotanshinone (Fu et al., 2021) and δ-

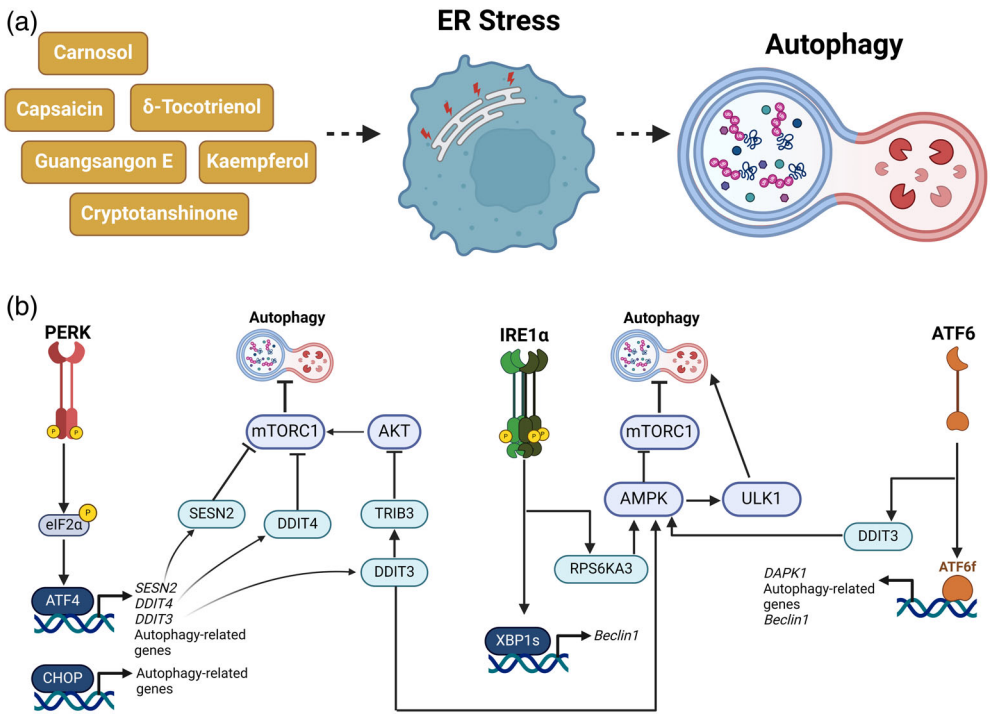

FIGURE 4 Interplay between ER stress and autophagy: ER stress-mediated autophagy. (a) The phytochemicals carnosol, capsaicin, cryptotanshinone, guangsangon E, kaempferol, and δ-tocotrienol induced ER stress-mediated autophagy. (b) All three UPR sensors regulate autophagy. The PERKe-eIF2α-ATF4-CHOP axis upregulates transcription of autophagy gene. In this axis, ATF4 also upregulates the expression of SESN2, DDIT3, and DDIT4. SESN2 and DDIT3 are negative regulators of mTORC1, while DDIT4 upregulates TRIB3, which is a negative regulator of AKT. PERK also activates AMPK via DDIT3. The IRE1α-XBP1s axis induces Beclin-1 and IRE1α activates RPS6KA3, which in turn activates AMPK, and consequently the ULK1 complex. ATF6 induces DAPK1, and also activates AMPK via DDIT3.

tocotrienol (Fontana et al., 2019); however, ER stress-mediated autophagy was confirmed using ER stress inhibitors 4-phenyl butyric acid and/or salubrinal.

7 | LIMITATIONS TO CLINICAL TRANSLATION, FUTURE DIRECTIONS, AND CONCLUDING REMARKS

As is evident from the studies discussed herein, the anticancer effects of various phytochemicals have been well characterized in preclinical studies. However, the clinical translation of a vast majority of the discussed phytochemicals is greatly hindered due to inherent limitations.

One of the biggest limitations to the use of phytochemicals is their context-dependent effects in different cancers, at times even with respect to modulation of the same pathway/cellular process. For example, as was noted multiple times in this review, the same phytochemical can induce both cytoprotective autophagy and autophagic cell death under different cellular contexts. In the present review, we noted studies that reported induction of cytoprotective autophagy or autophagic cell death in cancer-specific manners by the following phytochemicals: 6-gingerol, capsaicin, celastrol, curcumin, emodin, shikonin, and tanshinone IIA (Figure 5). This phenomenon is of concern given that cytoprotective autophagy can serve as a tumor-supportive mechanism (Debnath et al., 2023; Yun & Lee, 2018). While the use of autophagy inhibitors is one approach to circumvent this limitation, to date, no autophagy inhibitor has been approved for use in cancers, further highlighting the existing gaps in cancer therapeutics (Mohsen et al., 2022). In contrast to this, we only came across two studies that reported cytoprotective ER stress, which was in celastrol-treated osteosarcoma cells (Chen et al., 2018) and α-Mangostin-treated TNBC cells (Huang et al., 2019). This perhaps speaks to the tight regulation of ER homeostasis, such that external factors that cause perturbations in the same greatly skew the UPR towards apoptosis. It also suggests that focusing on phytochemicals that induce ER stress over autophagy may present a more promising avenue for clinical translation.

Another concerning limitation to the clinical translation of phytochemicals is the lack of deep mechanistic studies identifying their molecular targets. While many studies have explored the specific pathways that were activated or inhibited to induce the reported anticancer effects, the direct molecular targets of a vast majority of phytochemicals have not been identified. The absence of clarity in this regard raises the concern of off-target effects. Moreover, it also hampers clinical translatability as it hinders informed decision-making by

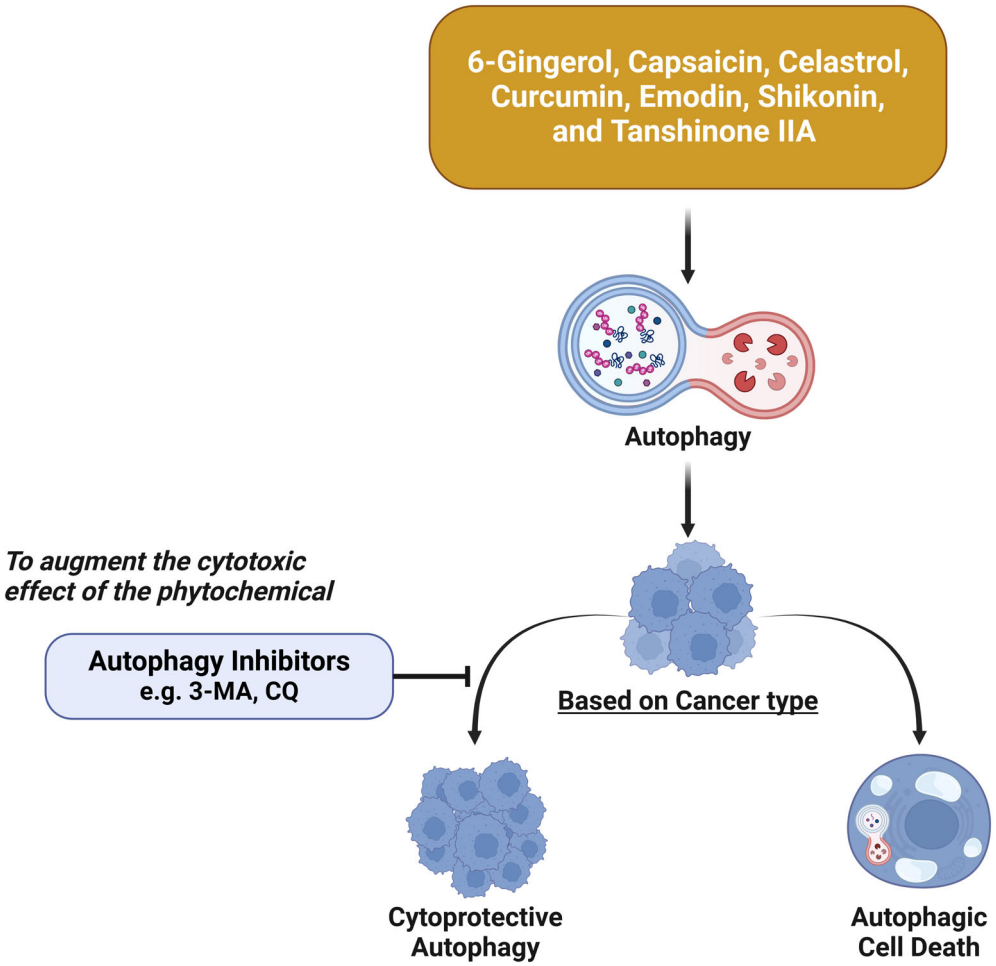

FIGURE 5 Phytochemicals induce cytoprotective autophagy or autophagic cell death in a cancer specific manner. Phytochemicals can induce autophagy as either a survival mechanism, that is, cytoprotective autophagy or as a cell death mechanism, that is, autophagic cell death, under different contexts, including cancer type. In cancer types where a phytochemical induces cytoprotective autophagy, the use of autophagy inhibitors, such as 3-MA and CQ, can augment phytochemical-induced cell death through other mechanisms, such as apoptosis. For example, curcumin induces autophagic cell death in breast and laryngeal cancer cells. On the other hand, it induces cytoprotective autophagy in esophageal cancer and glioblastoma cells. In these two cancer cell types, inhibition of autophagy enhances apoptosis. 3 MA, 3-methyladenine; CQ, chloroquine; EGCG, epigallocatechin gallate.

clinicians about treatment options for patients, taking into consideration their genetics or tumor profile/subtypes. Hence, elucidating the molecular targets of phytochemicals is of paramount importance to eventually enable personalized treatment approaches for cancer patients. It is, therefore, our suggestion that researchers should consider employing computational modeling for initial screening of molecular targets, which can further be validated using genetic approaches and/or chemical inhibitors (Tabana et al., 2023).

Tying into the same limitation, there is also a lack of studies investigating the effects of these phytochemicals on the broader landscape of tumors, that is, the tumor microenvironment and tumor resident and infiltrating immune cells. It is important to clarify whether these phytochemicals promote anti-tumor immune responses or hinder the same, or worse, enhance tumor immune evasion as an off-target effect. Further, multimodal treatment approaches present the best clinical outcomes and hence more emphasis is needed on combination approaches. In this regard, some studies reviewed herein reported on combination approaches: EGCG with gefitinib (an EGFR TKI) in CRC and NSCLC cells (Meng et al., 2019) and irinotecan (a topoisomerase I inhibitor) in CRC cells (Wu, Gou, et al., 2022), kaempferol with docetaxel in prostate cancer cells (Zhou, Fang, et al., 2023), verapamil (a calcium channel blocker) in breast cancer cells (Nandi et al., 2023), and with cisplatin and paclitaxel in gastric cancer cells (Kim, Lee, et al., 2018), naringin with tunicamycin (ER stress inducer) and BAY 11-7082 (NF-κB inhibitor) in CRC cells (Albayrak et al., 2021) and cisplatin in ovarian cancer cells (Zhu et al., 2023), flavokavain B with doxorubicin or cisplatin (Hseu, Lin, et al., 2020), 6-shogaol with FOLFIRI, FOLFOX, and FOLFOXIRI in CRC cells (Woźniak et al., 2020), celastrol with erastin (a ferroptosis inducer) in NSCLC cells (Liu, Fan, et al., 2021), and emodin with gemcitabine in NSCLC cells (Shen et al., 2020) and carfilzomib (a proteasome inhibitor) in multiple myeloma cells (Hsu et al., 2022). It is important to note here that some of the reported combination approaches are not clinically translatable at present; verapamil is not FDA approved for any solid organ or hematological cancers, and tunicamycin and BAY 11-7082 have no approved FDA indications and are used rather for experimental purposes. We hence suggest that the focus with respect to combination approaches be with approved and clinically used agents to facilitate clinical translation.

Additionally, it is important to explore sensitization effects to clinically used chemotherapeutic drugs, given that chemoresistance is a major clinical concern. Herein, we reviewed that baicalein increased sensitivity to cisplatin in gastric cancer cells (Li, Hu, et al., 2020) and to doxorubicin in TNBC cells (Hua et al., 2023), kaempferol increased sensitivity to cisplatin in ovarian cancer cells (El-Kott et al., 2020), astragaloside IV increased sensitivity of NSCLC to cisplatin (Lai et al., 2020) and bevacizumab (Li, Li, et al., 2022). Nonetheless, more emphasis is needed on these fronts, especially in in vivo studies and in combination to existing chemotherapeutic regimens as well as immunotherapy approaches. Additionally, there is also a need to explore the contribution of other programmed cell deaths, such as pyroptosis, ferroptosis, and necroptosis, in the anticancer activity of phytochemical compounds. Herein, we reviewed that 6-gingerol induced ferroptosis in NSCLC (Tsai et al., 2020) and prostate cells (Liu et al., 2022), and shikonin in combination with autophagy inhibitors induced ROS-dependent necroptosis in bladder cancer cells (Liu, Liu, et al., 2023) and ROS-dependent pyroptosis in gastric cancer cells (Ju et al., 2023). Exploration of other forms of cell deaths would further aid in understanding the molecular mechanisms underlying the effects of phytochemical compounds, directing clinical translation and personalized treatment approaches.

The clinical translation of phytochemicals is also limited by common issues concerning bioavailability, pharmacokinetics, and adverse effects. For example, while resveratrol has been investigated in Phase 1/Phase 2 clinical trials for various cancers (https://clinicaltrials.gov/), its clinical translation has been vastly limited due to concerns about adverse effects (at high doses), bioavailability (although the same has been improved with micronized resveratrol SRT501), pharmacokinetics, among others (Ramírez-Garza et al., 2018). While of use of alternate delivery platforms are being explored to combat these issues, these platforms are still far from being clinically applicable and represent another direction of research in phytochemical-based cancer therapeutics that needs to be emphasized (Lagoa et al., 2020).

In summary, in the present review, we explored the contribution of autophagy and ER stress in the anticancer effects of various phytochemical compounds. While induction of ER stress does represent a promising avenue of cancer therapeutics, the induction of cytoprotective autophagy is a cause of concern that can hinder the clinical translation of the concerned phytochemicals. Nonetheless, phytochemicals represent a promising avenue for cancer therapeutics, with great scope of research in this field.

AUTHOR CONTRIBUTIONS

Mazoun Al Azzani: Conceptualization; writing – original draft; writing – review and editing. **Zohra Nausheen Nizami:** Conceptualization; writing – original draft; writing – review and editing. **Rym Magramane:** Writing – original draft; writing – review and editing. **Mohammed N. Sekkal:** Writing – review and editing. **Ali H. Eid:** Writing – review and editing. **Yusra Al Dhaheri:** Writing – review and editing. **Rabah Iratni:** Conceptualization; writing – original draft; writing – review and editing.

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The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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