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Targeting the unfolded protein response in head and neck and oral cavity cancers

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Abstract

Many FDA-approved anti-cancer therapies, targeted toward a wide array of molecular targets and signaling networks, have been demonstrated to activate the unfolded protein response (UPR). Despite a critical role for UPR signaling in the apoptotic execution of cancer cells by many of these compounds, the authors are currently unaware of any instance whereby a cancer drug was developed with the UPR as the intended target. With the essential role of the UPR as a driving force in the genesis and maintenance of the malignant phenotype, a great number of pre-clinical studies have surged into the medical literature describing the ability of dozens of compounds to induce UPR signaling in a myriad of cancer models. The focus of the current work is to review the literature and explore the role of the UPR as a mediator of chemotherapy-induced cell death in squamous cell Carcinomas of the head and neck (HNSCC) and oral cavity (OCSCC), with an emphasis on preclinical studies.

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1. Introduction

Squamous cell cancers of the head and neck, oral cavity and upper aerodigestive tract represent a significant public health concern with more than 60,000 new cases diagnosed annually in the U.S [1,2]. While early-stage disease generally harbors a good prognosis, a majority of patients continue to present with late-stage disease fostering increased morbidity and mortality. Stage I disease among OCSCC patients is associated with survival as high as 90%, a benefit that decreases five-fold by Stage IV. Curative surgical resection and adjuvant treatments burden survivors with severe aesthetic and functional deformities that are often painful and require extensive support to facilitate eating, speaking, or even breathing. With the five year survival rate quagmired at ~50%, there is a clear and urgent need to identify actionable biomarkers and new therapeutic strategies.

Improvement in therapies and outcomes for HNSCC and OCSCC has not kept pace with other preeminent cancers such as breast and prostate [3–5]. In 2006, the chimeric monoclonal EGFR antibody cetuximab (Erbix) became the first agent in several decades to gain FDA approval for late stage and metastatic HNSCC [6]. As a first line treatment, compared to platinum and 5-fluorouracil, cetuximab increased survival less than three months without significant improvement in quality of life [7,8]. A decade later, in August of 2016, the immune check point inhibitor pembrolizumab, targeted to programmed cell death 1 (PD-1), received accelerated FDA approval for HNSCC after a non-randomized multi-cohort trial (KEYNOTE-012) demonstrated an objective response rate (ORR) of 16% (28/174), which was durable for at least six months in 23 of the 28 patients [9]. A recent pooled analysis looked at the long-term results from two cohorts in the KEYNOTE-012 study and found an ORR of 18% (34/192), in which 85% of the responses lasted over 6 months, with some patients responding for over 30 months [10]. Three and six month improvements are encouraging for HNSCC and OCSCC patients while at the same time underscore the need to augment progress in survival and quality of life. Substantial strides forward have been hindered by longstanding concerns that scholarly inquiries for HNSCC and OCSCC research are underfunded relative to other malignancies [3,5]. The identification and exploitation of alternative pathways for targeted intervention remains an unmet clinical imperative.

The targeted activation of the unfolded protein response (UPR) as a selective approach to ameliorating malignancy has recently been discussed by our group and others for a wide variety of cancers [11–17]. The “UPR Hypothesis” in cancer, as discussed previously [11], is predicated on the idea that high levels of UPR biomarkers present in cancer cells (e.g., GRP78/BiP, CHOP, eIF2 α and eIF4e) (Fig. 1A) can be pharmacologically leveraged against the tumor [11] (Fig. 1B). The hypothetical basis of selectivity is that normal cells, without basal ER stress, would be able to mount an effective adaptive UPR and return to homeostasis. The preponderance of investigations into UPR manipulation in cancer are

focused on compounds that activate pro-apoptotic UPR signaling. It should be stressed, however, that none of these drugs were specifically designed to manipulate the UPR and only discovered to be UPR activators in very late pre-clinical studies or post-clinical investigations. Also, it should be noted that many of the studies identified in the current review did not examine the extent to which UPR signaling was requisite for cell death, and the identification that any given compound activates the UPR does not imply *a priori* that the mechanism of action depends on ER stress.

UPR signaling supports malignant transformation and drives tumor survival in the face of increasingly harsh microenvironmental stresses, ergo, it has been logically hypothesized that targeted UPR inhibitors might also provide an effective anticancer approach [15]. GRP78/BiP, for example, has established roles in cancer having been reported to regulate proliferation, invasion and metastasis [18,19]. Increased GRP78/BiP expression is known to provide chemoresistance and is a biomarker for poor prognosis [20–24]. GRP78/BiP inhibition could also potentially interfere with angiogenesis by limiting the expression of vascular endothelial growth factor (VEGF) [19,25,26]. Another recent study reported that siGRP78 reduced clonogenicity and the self-renewal or “stemness” of progenitor cells in pancreatic cancer cells [27]. From a pharmacological perspective, p-coumaric acid treatment could decrease GRP78/BiP expression and led to UPR-mediated cell death in colon cancer cells [28]. In consideration of other UPR targets, several potent inhibitors of the IRE1 α -XBP1 adaptive arm have been described for hematological malignancies in preclinical models however, none have made it to the clinic and a recent study reported that downregulation of IRE1-XBP1 contributed to tumor growth in a fashion that could be reversed by exogenous expression of XBP1 [29]. The primary function of the UPR is to improve the output of properly folded secretory and membrane proteins from the ER. Inhibiting GRP78/BiP and XBP1 would diminish the chaperone-mediated boost in folding productivity and could increase the burden of misfolded proteins in the lumen and exacerbate ER stress, ultimately producing the same effect as intentionally activating the UPR.

Increased UPR signaling has been demonstrated in vitro and in vivo models of HNSCC and OCSCC and represents a potential therapeutic target [11,30–34]. Increased protein demand in malignant cells, fueled by the need to synthesize membrane proteins, signaling molecules, and to produce factors that assist in immune evasion and proliferation, can overwhelm the homeostatic folding capacity of the ER and lead to a chronic UPR. Additionally, the epithelial to mesenchymal transition activates the UPR (PERK-eIF2 α) and sensitizes cells to ER stress [35]. Many studies have suggested that targeting cells with increased basal levels of UPR signaling through upregulation of pro-apoptotic pathways might be an effective therapeutic strategy [11,36–38].

The objectives of this review are two-fold: (i) to explain the activation of ER stress during homeostasis and malignancy and highlight potential of UPR activation as a therapeutic approach, and (ii) comprehensively review published preclinical and clinical examples of UPR activators that have been used as anticancer strategies in HNSCC and OCSCC models. A fundamental understanding of these propitious therapeutic approaches is important not only for basic and translational scientists, but for clinicians.

1.1. The unfolded protein response (UPR) in homeostasis and malignancy

Numerous studies have reported that principal gene transcripts and protein markers of the UPR and aberrant translation are significantly associated with HNSCC and OCSCC oncogenesis [11,39–42] (Table 1). The UPR (Fig. 2) is initiated when the demand for new proteins is outpaced by the capacity of the ER to process them. Activation of the UPR occurs when the ER transmembrane (lumen to cytosol) stress sensors PERK, ATF6 and IRE1 α are activated by the release of chaperones (PERK and ATF6) or by the binding of unfolded peptides (IRE1 α). Stress in the ER leads to the activation of two genetically distinct parallel pathways that initiate multifaceted signaling sequences to reestablish homeostasis (IRE1 α – XBP1) or induce apoptosis (PERK-ATF4-CHOP), if the challenge is persistent or robust. A hallmark of UPR activation is a transient pause in global mRNA translation that occurs upon phosphorylation of the met-tRNA binding translation initiation factor eIF2 α by PERK [43,44]. Interrupted translation affords the stressed cell a chance to marshal its resources towards the restoration of homeostatic protein folding. Protracted stress precipitates the accumulation of pro-apoptotic transcription factors such as the activation of transcription factors (ATF3, ATF4 and ATF5), CCAAT-enhancer-binding protein homologous protein (CHOP, also known as GADD153 and DDIT3), and the phosphatase growth and DNA damage 34 (GADD 34) [45,46]. CRISPR-Cas9 CHOP knock-out UMSCC23 laryngeal SCC cells [47] were resistant to ER stress [48] highlighting an integral role for CHOP in UPR-induced cell death. Whereas nuclear accumulation ATFs and CHOP activate and repress cohorts of genes that contribute to apoptosis and survival, GADD34 is directly responsible for the dephosphorylation of eIF2 α to reinitiate protein synthesis. The rate at which GADD34 dephosphorylates eIF2 α to re-establish general protein translation is critical to the re-establishment of homeostasis [45,49].

When the insulting stress to the ER is not severe or persistent, the return to homeostasis is facilitated by activation of the IRE1 α -XBP1 conduit of the UPR. As indicated above, the binding of misfolded peptides to the luminal domain of IRE1 α leads to its activation. Phosphorylation and dimerization of IRE1 α induces an endoribonuclease activity that cleaves a 26 base intron from *XBPI* transforming it into an active transcription factor that increases the level of foldases, chaperones and ER protein degradation machinery that return to the ER to increase folding output [13]. Although many questions persist regarding how the switch between adaptive and apoptotic UPR signaling occurs, it is clear that: (i) the level and duration of ATF and CHOP accumulation in the nucleus; (ii) the duration and intensity of the translational pause; and (iii) the rate at which *XBPI*-translated factors can restore folding, are key fate-determining components of the UPR.

Findings in both *in-vitro* cell lines and surgical specimens suggest that UPR-related mechanisms contribute to the unique ability of HNSCC and OCSCC cells to endure robust cellular stresses. For example, it has been observed that archived formalin-fixed paraffin-embedded (FFPE) specimens displayed significantly higher basal levels of eIF2 α and eIF4E translation factors, which facilitate the initial pause in protein synthesis and direct ribosomes to the cap structures of mRNA, respectively [39,40,43,44,50]. Similarly, glucose-regulated proteins (i.e., GRP78/BiP and GRP94) have also been recently noted to play an increased role in HNSCC [11]. Within the lumen of the ER, GRP78/BiP serves as a primary molecular

chaperone to help newly synthesized proteins attain the correct folding conformation. As the tumor milieu becomes increasingly depleted of nutrients and oxygen, cells able to tolerate the accompanying ER stress are better poised to compete for survival. These de novo protein-dependent processes are integral to tumorigenesis, angiogenesis, and apoptosis. Furthermore, increased levels of GRP78/BiP and GRP96 correlate with amplified invasiveness, aggressiveness, and increased mortality in head and neck and other cancers [21,23,24,51]. While expression of GRP78/BiP is upregulated in malignancy, its suppression has been demonstrated to sensitize malignant cells to UPR-induced apoptosis [52]. Consequently, GRP78/BiP has been proposed as a potential prognostic HNSCC and OCSCC biomarker [11,13], although further evaluation is needed.

1.2. Agents impacting the UPR

With all of these considerations in mind, manipulation of the UPR may represent a novel and selective strategy for developing HNSCC/ OCSSS targeted therapeutics. A myriad of drugs currently approved for use in clinical practice have demonstrated such activity, and are further discussed below. It should be emphasized that none of these drugs were specifically designed as UPR activators, but rather were developed with other targets/mechanisms in mind. This review will highlight clinical relevance and a need for the further development of UPR inducing compounds with increased potency for HNSCC and OCSCC.

1.3. FDA-approved compounds

1.3.1. Protease inhibitors—Protease inhibitors used to treat human immunodeficiency virus (HIV) such as nelfinavir, atazanavir, indinavir, saquinavir, ritonavir, and lopinavir have been shown to induce ER stress and activate the apoptotic arm of the UPR in HNSCC. In a recent study by Liu et al., examining the molecular effects of lopinavir and ritonavir (L/R) in FaDu hypopharyngeal and SQ20B laryngeal SCC cell lines [53] L/R was found to significantly inhibit cell growth at 25–50 μ M and induced mRNA expression of UPR genes and protein levels of CHOP, ATF-4, and XBP-1. While UPR-induced L/R did not cause significant apoptosis in the SQ20B and FaDu cells, L/R markedly increased the radiosensitivity of both cell lines [53]. UPR induction as a radiosensitizer has also been discussed extensively in brain, lung and pancreatic cancer cell lines [54–56].

1.3.2. 26S Proteasome inhibitors—Velcade (bortezomib/PS-341) is a di-peptidyl boronic acid derivative that has been characterized as a potent highly specific and reversible inhibitor of the 26S proteasome, and is currently used in the management of multiple myeloma and mantle cell lymphoma [57]. It has been reported to have antiproliferative effects in laryngeal cancer squamous cell Carcinoma [58] and a host of HNSCC and OCSCC cell lines [59–62]. Interfering with the activity of the 26S proteasome leads to the accumulation of damaged and mis-folded proteins in the ER lumen and cytosol [63], and subsequently to the generation of DNA damaging and apoptosis-inducing ROS. PS-341 treatment led to the phosphorylation of the ER membrane-resident stress kinase PERK and the accumulation of ATF4 and CHOP prior to cell death. The addition of tiron, a cell permeable superoxide scavenger, reduced ER stress to an undetectable level and prevented cell death, indicating that ROS generation is a critical component of PS-341-induced ER stress and cell death [62]. Subsequently, it was demonstrated that multiple myeloma patients

who consumed diets rich in antioxidants benefitted significantly less while on bortezomib than patients with low antioxidant diets [64]. It is also important to note that multiple myeloma patients treated with bortezomib that had low levels of XBP1 [65] or ATF3 and ATF4 [66] were characterized as poor responders in clinical studies, whereas high levels of XBP1 was a characteristic of a favorable prognosis [67]. Carfilzomib, currently approved for treatment of multiple myeloma, and the orally available second generation derivative Oprozomib (ONX 0912), have also been found to induce apoptosis in HNSCC via similar signaling patterns [68]. UPR activation was observed in eight HNSCC cell lines in vitro and was active in nude mice harboring HNSCC xenografts.

1.3.3. Disulfiram—Disulfiram (Antabuse) is a carbamoyl derivative that was FDA-approved in 1951 for treatment of alcoholism [11,69]. Disulfiram (DSF) is an inhibitor of acetaldehyde dehydrogenase that was later observed to have antineoplastic activities functioning via mechanism involving 26S proteasome inhibition, reactive oxygen species generation, and the UPR [69,70]. A high throughput screen to identify pro-apoptotic UPR activators found that disulfiram induced cell death in oral and pharyngeal squamous cell Carcinoma cells via ER stress as evidenced by CHOP and ATF4 upregulation and eIF2 α phosphorylation [71]. Using the super-oxide-specific scavenger tiron, this study also demonstrated the ability of disulfiram to induce ER stress and reduce OSCC proliferation was ROS-dependent [279]. Importantly, it has been observed that DSF can be metabolized to produce a dithiocarb-copper complex that induces the UPR, inhibits caspase 3 and induces paraptotic cell death [70]. A nation-wide population based study of Danes who remained on DSF following a diagnosis of cancer (all inclusive) revealed reduced cancer-specific mortality even among patients with metastatic disease, although no attempt to correlate this finding with the UPR was attempted, the authors did demonstrate the accumulation of CHOP and phospho-eIF2 α in cultured cells [72]. Although clinical trials employing DSF for late-stage or recurrent disease have not been encouraging, preclinical in vivo studies have found metronomic dosing at very early stages dramatically inhibited OSCC xenograft growth (unpublished observation). DSF serves as a promising UPR-inducing agent that relies on oxidative stress and the UPR to promote apoptosis in HNSCC and OSCC.

1.3.4. Celecoxib—The cyclooxygenase type 2 (COX-2) inhibitor celecoxib is an NSAID initially approved in 1999 for rheumatoid and osteoarthritis [73]. It has been hypothesized that the effects on ER stress may be independent of COX-2. The apoptotic activity of celecoxib was demonstrated in studies with the HNSCC cell line SNU-1041. Immunoblot and RT-qPCR gene expression analysis revealed dose dependent increases for transcripts of CHOP, GRP78/BiP, and XBP1 [74]. The ability of celecoxib to inhibit cell proliferation was notably hindered by transient transfection of si-*CHOP*, demonstrating a critical role for CHOP in UPR-mediated apoptosis consistent with observations in OCSCC [48]. Several in vitro and in vivo studies using human colorectal cancer cells demonstrated similar UPR-inducing effects of celecoxib prior to cell death [75,76]. It should be noted that celecoxib can lead to the upregulation of VEGF so theoretically the potential for developing drug resistance might be a confounding issue unless strategies utilizing combination therapies are considered.

1.3.5. Dasatinib—Dasatinib is a pyrimidine- and thiazole-derived tyrosine kinase inhibitor that was approved in 2006 for chronic myelogenous leukemia and Philadelphia chromosome positive acute lymphoblastic leukemia [77]. Dasatinib induced ER stress in HNSCC in an AMPK dependent manner, whereby the targeted knockdown of AMPK prevented eIF2 α phosphorylation and CHOP expression [78]. Unfortunately, a phase II study with HNSCC patients failed to demonstrate an effect on tumor growth or a clinical benefit, although p-Src was inhibited, indicating that the mechanism/s of dasatinib needs to be further elucidated [79]. It is possible that metronomic dosing of stress-inducing Dasatinib after surgical resection would provide a benefit in progression free survival.

1.4. Preclinical studies with non FDA-approved small molecules

1.4.1. HMJ-38—The antimitotic quinazolinone derivative HMJ-38 is a small molecule that was reported to increase intracellular Ca²⁺ levels, induce ER stress and initiate apoptosis in cultured Cal27 tongue SCC cells [80]. HMJ-38 treatment up-regulated CHOP, GRP78/BiP, ATF-6 α , ATF-6 β , eIF2 α , and phospho-eIF2 α (Ser51) and calpain. MTT cell viability assays revealed concentration-dependent cell death. To evaluate the role of ER stress in the antiproliferative effects HMJ-38, Lu et al., pretreated CAL 27 cells either with salubrinal (a selective inhibitor of eIF2 α dephosphorylation), calpeptin (a calpain specific inhibitor), or BAPTA (a Ca²⁺ chelator). Salubrinal prolonged the effects of UPR-associated apoptotic events by inhibiting eIF2 α de-phosphorylation, while both calpeptin and BAPTA effectively inhibited ER stress and cell death. Intraperitoneal administered HMJ-38 every other day for 20 days resulted in dramatic tumor burden reduction in BALB/c athymic mice engrafted with Cal27 cells with an acceptable toxicity profile [80]. The study was limited by the fact that only one cell line was examined however, it should be noted that the Cal27 line contains mutations in SMAD2 and SMAD4 that interfere with TGF- β signaling, a notorious mechanism of clinical chemoresistance in a variety of human cancers.

1.4.2. ML291—ML291 is a small molecular weight sulfonamidebenzamide, identified in a high throughput screening (HTS) and iterative bio-guided analog synthesis campaign. ML291 induced CHOP-dependent apoptosis in a panel of HNSCC [36,81]. In reporter cell assays there was an > 80 fold difference in the activation of a Chop-luciferase reporter vs an Xbp1-luciferase reporter and Chop-null MEF were significantly resistant to the apoptosis inducing effects of ML291. Recent studies have revealed that mice can tolerate relatively high daily doses (IP) of ML291 over a 30 day period without weight loss or obvious adverse side effects, while reducing OSCC xenograft burden (submitted).

1.4.3. Benzethonium chloride (BCI)—Benzethonium chloride is a quaternary ammonium compound that has been incorporated in a wide variety of first aid products, cosmetics and oral rinses. An intriguing feature of cationic hydrophobic detergents such as BCI is that they provide prolonged biointeraction with vital membranes such as the oral mucosa or at the site of resected tumors. Yip et al., conducted a phenotypic HTS that employed a cadre of HNSCC and non-malignant controls. BCI emerged as a compound that selectively killed HNSCC [82]. Several years later, Rayess, et al., used a HNSCC cell-based HTS and identified BCI as a compound that could kill HNSCC cells in a CHOP-dependent fashion [83], providing a UPR-supported mechanism to the selectivity previously observed.

Further in vivo studies by Yip demonstrated that a daily 5 mg/ml IP BCI bolus over the course of a week could reduce tumor burden in fairly large well-established xenografts with no obvious toxicity or harm to internal organs. Further in vivo studies are necessary to elucidate how these studies might be translated and used systemically or topically to benefit HNSCC and OCSO patients.

2. Natural products (NP)

Thirty-eight percent of the 246 FDA-approved anti-cancer compounds during the 34 years between 1981 and 2016 are natural products (NP) or derived from one [84]. NP (secondary metabolites) are organic compounds produced by a plant or organism that are not directly involved with its growth, development or reproduction. Clay tablets written in cuneiform discovered from 2600 B.C. Mesopotamia are thought to be the earliest documented use of NP's as therapeutics [85]. The ability of a variety of NP's, many of which have been employed in culture-specific medical practices for centuries, to induce ER stress and the UPR has been described. An ideal UPR-inducing NP cancer agent would be able to increase ER stress and drive malignant cell toward apoptosis and not harm healthy adjacent cells with homeostatic secretory function. It is important to note that natural products have been reported to activate the UPR through eIF2 α kinases other than PERK (i.e., GCN2) so it is clearly possible that the apoptotic UPR could be exploited to kill malignant cell without acting directly on the ER. In this section, UPR-enforcing, cytotoxic compounds with activity in head and neck or oral cavity cancers will be explored.

2.1. Cantharides

Cantharides are naturally occurring products, isolated from the chitinous shells of beetles from the genera mylabris, which are well-characterized inhibitors of PP1 and PP2A. The parent molecule cantharidin (CNT) was identified during a cell-based HTS to identify compounds able to induce a Chop-luciferase reporter [38,86]. Employed in traditional Chinese medicine for thousands of years for anticancer and other uses, cantharidin is FDA approved for topical application for dermatologic conditions including *molluscum contagiosum* [87] and *verruca vulgaris* (common wart). CNT was observed to induce UPR markers including phosphorylated eIF2 α and ATF4 and CHOP in a ROS-dependent fashion in HNSCC and MEFs [38]. A nearly identical subsequent study confirmed these findings [88]. The generation of less toxic anticancer analogs (i.e., norcantharidin and catharidic acids) remains an active area of investigation for oral cavity cancers [38,89,90].

2.2. 4-Hydroxyphenyl retinamide (4HPR)

4-Hydroxyphenyl retinamide is a synthetic retinoid that induces UPR-mediated apoptosis in HNSCC cells through increased generation of reactive oxygen species (ROS) [91]. Quantitative RT-PCR and Western blotting also demonstrated increased levels of UPR-associated mRNAs and proteins, including the HSP proteins GRP78/BiP and HSPA1A and the spliced form of XBP1. 4HPR has since undergone clinical trials for the treatment of neuroblastoma, breast cancer, and oral leukoplakia.

2.3. Borrelidin

The macrolide antibiotic borrelidin (Bor) is a well-known threonyl-tRNA synthetase (ThrRS) inhibitor derived from *Streptomyces rochei* [92]. Interference with t-RNA synthetase is hypothesized to increase ER stress and initiate the apoptotic arm of the UPR by preventing the catalysis of Thr into de novo peptides (and thus increase misfolding) [37]. Borrelidin enhanced *XBPI* splicing and increased expression of ATF4 and CHOP prior to caspase activation and cell death in a panel of HNSCC and OCSCC cell lines [37]. In these studies, CHOP accumulation and eIF2 α phosphorylation were not apparent in *Gcn2*-null cells, indicating more than one upstream kinase was responsible for the apoptotic effects of Bor, consistent with previous observations [93]. The prior study also noted that *Chop*-null MEFs were significantly resistant to the antiproliferative effects of Bor compared to wildtype littermate controls. Longstanding concerns with toxicity in normal cells and in the liver were recently somewhat assuaged by a promising in vivo breast cancer xenograft study. Significant antitumor activity was not accompanied by hepatotoxicity or other apparent negative side effects even with repeated dosing of a liposomal formulation of Bor [94]. As new analogs continue to be discovered, it will be very important to study them in vitro and in vivo models to more accurately gauge the therapeutic potential of Bor.

2.4. Lobophorin

Marine environments are teeming with biodiverse microbes that can be harvested for unique renewable enzymes and metabolites. The lobophorins are a great example of such NP's that have been isolated from the Caribbean, the South China Sea, the Costa Rican biota, and the Aviles Canyon off the Asturian coast [95–98]. Lobophorins are distant relatives of kijanimycin which is also known to have anti-inflammatory and anti-cancer activity. Although few mechanistic studies have been performed to identify potential cellular targets of this class of macrolides, an HTS campaign to identify natural products that activate the UPR at the University of Michigan Center for Chemical Genomics identified three novel lobophorins (CR 1–3) that could activate UPR and cell death in OCSCC cell lines [97]. These lobophorins selectively induced a CHOP-luciferase reporter but not an XBP-1 luciferase reporter, suggesting a bias toward apoptotic UPR signaling. Additionally, MEFs null for either *Atf4* or *Chop* were resistant compared to littermate-matched wildtype controls, implicating a critical role for the UPR in lobophorin-mediated apoptosis. Promising in vivo studies by the Fenical group administered 30 mg/kg lobophorin B (IP) to mice and found it to have anti-inflammatory properties similar to indomethacin, without toxicity [95]. Further studies are necessary to elucidate the mechanism/s by which lobophorins cause ER stress, activate the UPR and demonstrate anti-cancer activity.

2.5. Patulin

Patulin (PAT) is a water soluble polyketide lactone commonly found in apples and apple products such as jams and ciders. Mycotoxins such as PAT are secondary metabolites from certain filamentous fungi (e.g., *Penicillium expansum*) [99] that have been applied clinically despite having known toxicities in humans [100]. Patulin induces apoptosis through the mitochondrial pathway in HNSCC and human leukemia cells [86,101]. Structural similarity analysis (SSA) with citrinin congeners identified patulin as a UPR-activating agent [102].

OCSCC cells treated with PAT demonstrated dose-dependent *XBPI* splicing and increased expression of *CHOP*, *GADD34*, *ATF3*, *ATF4*, and GRP78/BiP [102]. In addition, results from this study revealed that a low dose of PAT could induce an oxidative stress that was able to overwhelm the adaptive pathway of the UPR and induce apoptosis effectively in five of six OCSCC cell lines examined, subsequently, these results were recapitulated in colon Carcinoma cells [103]. Further work has suggested that some biological PAT activity is dependent on cellular thiols and therefore, may not be sufficiently specific for cancer cells to use therapeutically [102]. The nasal administration of PAT in a clinical trial in 1944, that unsuccessfully attempted to mitigate the effects of the common cold, reported few significant adverse side effects [104], raising the intriguing notion that it might be applied to squamous cell cancers of the nasopharynx.

2.6. Celastrol

Celastrol derived from *Tripterygium wilfordii*, was initially used as an anti-inflammatory remedy, and is currently under investigation as a potential therapeutic for obesity [105,106]. This particular triterpenoid is known to activate heat shock factor 1 (HSF1) [107] and has also been found to induce apoptotic UPR signaling in OCSCC and other cancer cell types [108–112]. Fribley et al., observed increased levels of UPR-related mRNA transcripts (*CHOP*, *GADD34*, *ATF3*) and *XBPI* splicing in a panel of OCSCC cell lines exposed to celastrol [109]. The UPR-mediated cytotoxic effect of celastrol was supported by previous studies in breast, liver, and lung [108,111,112]. It is worth noting that while celastrol was found to act as a proteasome inhibitor in a variety of cancer cell lines [108,111,112], the Fribley study reported only very modest decreases in proteasome function suggesting an alternative mechanism for the induction of ER stress in OCSCC [85]. The ability of triterpenoid celastrol to promote apoptosis in OCSCC cells and other cancers highlights the novel therapeutic potential for implementing natural products as selective enforcers of the UPR [110].

2.7. Curcumin

Curcumin is a naturally occurring chemical component of the spice turmeric which is used to give curries a distinct color and flavor. Curcumin is a polyphenol derived from the rhizome of *Curcuma longa* [113] and has been used in Ayurvedic medicine for over 6000 years [114]. In modern medicine, the antioxidant and anti-inflammatory properties of curcumin have been studied for a wide-variety of pathologies [115]. A systematic review looked at curcumin as a treatment for HNSCC and found 30 studies highlighting therapeutic potential [116]. With respect to UPR in vitro, curcumin was shown to induce apoptosis through ER stress in human tongue squamous cell Carcinoma [117].

2.8. 3,3'-diindolylmethane (DIM)

Cruciferous vegetables such as broccoli, Brussels sprouts, cabbage and kale have long been known to have health benefits, despite the protests of children auteur de monde. Studies have identified the phytochemical DIM, a derivative of indolyl-3-carbinol, found in these vegetables, to be chemopreventative in oral cancer [118]. DIM also modulates natural killer cell activation and distribution in esophageal cancer patients [119]. DIM was shown to be antiproliferative in three OCSSC cell lines through a mechanism that involved the induction

ER stress and apoptosis, demonstrated by an increase in GRP78 and CHOP [120]. In a panel of three OSCC cell lines Weng et al., demonstrated that the antiproliferative effects of DIM were preceded by increased ER stress and the accumulation of proapoptotic transcripts of NOXA and PUMA, known modulators of ER stress-induced apoptosis [61,121]. Additionally they noted that DIM treatment perturbed NF κ -B, AKT, MAP Kinase and p53 signaling prior to cell death. DIM has also been shown to inhibit HDAC1, HDAC2, and HDAC3 prior to DNA damage [122]. These studies indicate that ER stress/UPR activation is likely to be only one facet of the cytotoxicity profile of DIM [123]. The more recent use of synthetic ring-substituted DIM analogs demonstrated increased potency in oral cancer cells [124] and re-kindled a determination to elucidate its therapeutic potential.

2.9. Resveratrol

The stilbenoid resveratrol is a phytoalexin found in grapes, blueberries, raspberries and mulberries that has been long studied for its chemopreventative and anticancer properties [125]. Scores of studies have been published describing the ability of resveratrol and its synthetic and naturally occurring analogs to induce ER stress-mediated cell death in a myriad of cancers. Huang and colleagues carried out a flow cytometry analysis with human nasopharyngeal Carcinoma (NPC) cells exposed to resveratrol and observed ER-stress dependent apoptosis [126]. Immunoblot studies by Chow et al., also noted increased CHOP expression and ER stress in NPCs exposed to resveratrol [127]. While both studies suggested ER stress and UPR activation as a primary mechanism of resveratrol-induced apoptosis, it is worth mentioning that the Huang study observed downregulation of chaperone GRP78/BiP with resveratrol, and Chow's group, reported no decrease in apoptosis with the transfection of siRNA to silence *CHOP*. Having used different cell lines it is difficult to make a direct comparison, but it is likely that the down-regulation of GRP78/BiP would serve to enhance ER stress (and thus death), and that the siRNA knockdown of CHOP in the subsequent study was not sufficient to prevent death. It is also possible that the expression of other ER stress-related cell death transcription factors (e.g., ATF3 or ATF4) were present in sufficient levels to overcome adaptive UPR signaling. Pterostilbene is a naturally occurring dimethylated resveratrol congener found in blueberries. Pterostilbene treatment of esophageal cancer cells cultures led to increased levels of CHOP, GRP78/BiP, ATF6, and phosphorylated PERK and eIF2 α , as well as the known UPR executioner NOXA [128]. These studies found that the addition of the general ROS-scavenging compound N-Acetyl cysteine could reduce ER stress and cell death. ROS generation is a well characterized ER stress inducer in studies with both small molecules and natural products. Further studies are needed to better understand the role that resveratrol plays in activating the UPR in cancers affecting the head and neck and oral cavity.

2.10. Alpha-momorcharin

Alpha-momorcharin (α -MMC) is a ribosome inactivating protein isolated from the seeds of the bitter melon (aka bitter gourd or balsam pear) *Momordica charantia*, varieties of which are grown throughout Asia, Africa and the Caribbean. Traditional culture-specific medicinal arts have applied extracts of the fruit as antibiotics and antimycotics, and to treat a wide range of medical conditions including cancer and diabetes [129]. α -MMC protein is known to inhibit protein synthesis by cleaving an adenine base from rRNA; it was found to inhibit

the UPR in nasopharyngeal cancer cells (thereby exacerbating ER stress) and lead to cell death [130]. Immunoblot analysis demonstrated that α -MMC down-regulated levels of key proteins involved in the UPR such as PERK, IRE1 α and CHOP, and triggered intrinsic (mitochondrial-mediated) apoptosis. The downregulation of the adaptive pathway of the UPR was shown to be a key mechanism of action for α -MMC. Although α -MMC was shown to be significantly less toxic to cultures of healthy muscle cells compared to a panel of cancers [131], the translational potential is constrained by a narrow therapeutic window observed in other cell types [132,133]. Interest in the use of α -MMC as an anticancer treatment remains strong; recent attempts to generate PEGylated analogs have reportedly preserved anti-tumor activity and ameliorated non-specific toxicities [134].

3. Conclusion

Late stage clinical trials for recurrent and metastatic HNSCC and OSCC rarely demonstrate a benefit unless the overall response is measured in weeks. The fact that many patients continue to present with very late stage disease continues to codify the designation of this cadre of malignancies as “surgeons’ disease”. The relative ease of access to lesions in the head and neck and oral cavity however, is a distinct advantage not afforded to other major cancers, and provides very high long term survival and cure rates for those who are diagnosed early. The development of adjuvant therapies with more trivial toxicities and side effects represents an urgent and unmet need for all cancers. This review focused exclusively on the use of small molecules and natural products that induce the UPR in preclinical models of HNSCC and OSCC.

Very few of the studies that were discussed employed late-stage xenograft models whereby the UPR inducing compounds were administered when the tumor burden was large. The success of UPR-inducing compounds to prevent growth and metastasis in early stage models (when tumors have been resected or are very small at the start of treatment) may provide an important clue as to how this approach might be applied clinically to afford patients the greatest opportunity for success. To this point, the UPR-inducing anti-alcoholism drug disulfiram (Antabuse) has not been successful in human clinical trials for any malignancy when given to patients with un-resectable, late stage or metastatic disease. Preclinical data with this compound raise the intriguing possibility that it might be added to other chemotherapies or biologic therapies to improve rates of recurrence and metastasis [71,135]. The fact that patients who continue to take DSF after a cancer diagnosis have a better prognosis than those who do not speaks to this point and is very encouraging. Disulfiram is very inexpensive and would be particularly attractive as part of an anticancer strategy due to the fact that, in the absence of alcohol, it has very mild side effects and can be taken at very high doses over a prolonged period of time.

The large number of compounds identified in the literature able to induce UPR in HNSCC and OSCC was surprisingly large (Table 1). The fact that none of these compounds were UPR targeted could in some cases be an artifact of the timeframe examined. ER stress observed at time points greater than 6–12 h could be a reflection of the inability of a dying cell, or one depleted of sufficient resources, to fold proteins while in the process of being dismantled. It is intriguing that such a large number of molecules targeted to such a wide

variety of cancer fragilities are able to activate the UPR. Ongoing studies to determine the ability of UPR inducers to reduce cancer burden either directly or as radio-sensitizers are greatly anticipated and will continue to shed light on this novel approach.

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Fig. 1. Overview of the protein translation during homeostasis and malignancy(A) and the UPR hypothesis (B).

Fig. 2. Overview of ER stress and the UPR highlighting the apoptotic (PERK-eIF2α-ATF4-CHOP) and adaptive (IRE1α-XBP1) axes.

Table 1

Drug/ Compound	Classification	Clinical/Preclinical Status	FDA approval	Drug Indications	HNSCC, OSCC, Tongue SCC, and Nasopharyngeal Cancer Cell Lines Studied	Other Malignancies Studied	Observed UPR Markers	References
FDA Approved Compounds								
Afinitinib	small molecule	Phase I/II/III/IV	2013	receptor tyrosine kinase inhibitor	<u>HNSCC</u> CAL-27 Detroit 562 FaDu HN6	Breast Cancer Non-Small Cell Lung Cancer	increased phosphorylation of PERK and eIF2α	Duchnowska [137] Liu [136]
Bortezomib (Velcade) (PS-341)	small molecule	Phase I/II/III/IV	2003	26S proteasome inhibitor	<u>HNSCC</u> CAL27 UMSCC-1 UMSCC-5 UMSCC-5PT UMSCC-9 UMSCC-10B UMSCC11A UMSCC-11B UMSCC-14A UMSCC-23 UMSCC74A <u>Nasopharyngeal Carcinoma</u> C666–1 HA	Acute Promyelocytic Leukemia Lymphoma Multiple Myeloma Neuroblastoma	induced caspase activation, up regulated GRP78/BiP, phospho-PERK, ATF4, CHOP, and GADD34	Fribley [62] Fribley [138] Fribley [61] Yoo [34] Boccardo [139] Miyahara [140] Granato [141] Mimura [142] Hui [143]
carfilzomib (Kyprolis)	small molecule	2nd-in-class Phase I/II/III	2012	irreversible 26S proteasome inhibitor	<u>HNSCC</u> 1483 Cal33	ALL Hematologic Malignancies Lymphoma	induced phosphorylation of PERK and eIF2α, upregulation of ATF4, and BiK, activation of caspase-3	Zang [144] Zang [145]

Drug/ Compound	Classification	Clinical/Preclinical Status	FDA approval	Drug Indications	HNSCC, OSCC, Tongue SCC, and Nasopharyngeal Cancer Cell Lines Studied	Other Malignancies Studied	Observed UPR Markers	References
Celecoxib (Celebrex)	small molecule	Phase I/II/III/IV	2005	nonsteroidal anti-inflammatory drug, COX-2 inhibitor, VEGF activator	UMSCC-1	Mantle Cell Lymphoma	upregulated GRP78/BiP, XBP1, and CHOP	Cha [74]
					UMSCC-22A	Multiple Myeloma		Huang [146]
					UMSCC-22B	Neuroendocrine Cancer		Du [75]
						Prostate Cancer		
						Small Cell Lung Cancer		
Dasatinib (Sprycel)	small molecule	Phase I/II/III/IV	2010	inhibitor of SRC-family protein-tyrosine kinase s	<u>HNSCC</u> SNU-1041	Solid Tumors	induced AMPK-dependent ER stress, depletion of intracellular Ca ²⁺ induced expression of GRP78/BiP and CHOP	Bellodi [147]
						Breast Cancer		
						Colorectal Cancer		
						Esophageal Cancer		
						Pancreatic Cancer		
Disulfiram (Antabuse)	small molecule	Phase I/II/III	1951	chronic alcoholism	<u>HNSCC</u> Ca9-22	urothelial Carcinoma	induced splicing of XBP1 mRNA induced ROS upregulated phosphorylation of eIF2α, 26S proteasome inhibitor	Lin [78]
					HSC3	Acute Lymphoblastic Leukemia		
					SAS	Chronic Myeloid Leukemia		
					<u>OSCC</u>	Lymphoblastic Lymphoma		
					UMSCC-1	Glioblastoma		Tardito [70]
Erlotinib (Tarceva)	quinazoline derivative	Phase I/II/III/IV	2013	inhibitor of EGFR tyrosine kinase activity	UMSCC-14A	Melanoma	increased spliced XBP1, p-eIF2α, ATF4, and CHOP protein accumulation	Fribley [71]
					UMSCC-23	Non-Small Cell Lung Cancer		Cen [148]
						Prostate Cancer		
					<u>HNSCC</u> Cal-27	Solid Tumors (Liver)		Fan [149]
					FaDu	Colorectal Cancer		Wang [150]
					SCC-25	Esophageal Squamous Carcinoma		Sobhakumari
						Non-Small Cell Lung Cancer		

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HDAC inhibitors (MS-275, apicidin and romidepsin)	synthetic benzamide derivative, cyclic peptide, depsipeptide respectively	Phase I/II/III	variable	HDAC inhibitor	SQ20B	Squamous Cell Lung Cancer		[151]
					<u>Nasopharyngeal Carcinoma</u>	Breast Cancer	increased expression of GRP78/BiP	Baumeister [152]
					C666–1	Kidney Cancer		Hui[143]
					HA	Non-Small Cell Lung Cancer		
Metformin (Glucophage)	small molecule	Phase I/II/III/IV	1994	antihyperglycemic (type 2 diabetes)	<u>HNSCC</u>	Bladder Cancer	up-regulation followed by a down-regulation of GRP78/BiP	Liu [153]
					Ca9–22	Breast Cancer	expression, increased expression of activated caspase-3	Martinez [154]
					HSC3	Endometrial Cancer		Minematsu [155]
					<u>SAS OSCC</u>	Medulloblastoma		Lin [78]
					KB	Melanoma		Wang [156]
						Non-Small Cell Lung Cancer		Granato [141]
						Ovarian Cancer		Moon [157]
Oprozohrib (ONX 0912)	Bioavailable derivative	Phase I/II		irreversible 20S proteasome inhibitor	<u>HNSCC</u>	Hepatocellular Carcinoma	induced phosphorylation of PERK and eIF2 α upregulation of ATF4 and BIK activation of caspase-3	Vandewynckel [158]
					1483			Zang [144]
					Cal33	Multiple Myeloma		Zang [68]
					UMSCC-1			Zang [145]
					UMSCC-22A			
Ritonavir/Lopinavir	protease inhibitor.	Phase I/II/III/IV	2015	HIV protease inhibitor	UMSCC-22B			
					<u>HNSCC</u>	Acute Myeloid Leukemia	dose-dependent increase CHOP, ATF-4, and XBP-1 mRNA levels increased mRNA expression of the UPR genes with corresponding up-regulation of protein levels	Liu [53]
					FaDu	Kaposi's Sarcoma		Kraus [159]
					SQ20B	Lymphoma of NPX		Lucia [160]
								Varna [161]
								Corona [162]

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Sorafenib (Nexavar)	small molecule	Phase I/II/III/IV	2013	multiple kinase inhibitor (cytotoxic)		Acute Myeloid Leukemia Breast Cancer Hepatocellular Carcinoma HNSCC Melanoma Non-Small Cell Lung Cancer Pancreatic Cancer Renal Cell Carcinoma Soft Tissue Sarcoma	induced splicing of XBPI, mRNA, increased CHOP and GADD34 gene expression, induced phosphorylation of eIF2α	Yi [163] Molina-Ruiz [164]
Trisenox (arsenic trioxide)	small molecule	Phase I/II/III/IV	2000	Acute Promyelocytic Leukemia	<u>Laryngeal SCC</u> Hep-2 <u>OSCC</u> HSC-3	Acute Promyelocytic Leukemia Leukemia OSCC Solid Tumors	increased the expression of GRP78/BiP, upregulation of GADD153 activation of PERK, phosphorylation of eIF2-α, CHOP Overexpression	Yang [165] Tsai [166]
Vorinostat (suberoylanilide hydroxamic acid)	small molecule	Phase I/II/III	2006	Histone Deacetylase Inhibitor		Acute Myeloid Leukemia Cutaneous T-cell lymphoma Multiple Myeloma Non-Hodgkin's Lymphoma	prolonged eIF2α phosphorylation and ER stress increased apoptosis through caspase-12 cleavages.	Suzuki [167] Duvik [168]
Synthetic non FDA Compounds								
3-Bromopyruvate	lactic acid analogue	preclinical	in vivo	hexokinase II (HKII) inhibitor	<u>Nasopharyngeal Carcinoma</u> CNE-2Z HNE1	Breast Cancer Colorectal Cancer Gastric Cancer Glioblastoma Hepatocellular Carcinoma Malignant Melanoma	increased levels of CHOP in NPC cells large increase in p-AMPK expression	Can [169] Chong [170] Chiasserini [171] Lee [172] Guo [173] Ho [174]

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4-N-1,3-diaryltriazenes	Synthetic diaryl/triazene derivative	preclinical		Triazene class of medications; antineoplastic, antimicrobial	<u>Laryngeal Cancer</u> HEp-2	Pancreatic Cancer		Altia [175]
						Prostate Cancer		Chapiro [176]
						Cervical Cancer	induced CHOP and GRP78/BiP, cleavage of PARP and procaspase-9,-8 and-3, increase in subG1 fraction	El Sayed [177]
						Colorectal cancer		Cimbora-Zovko [178]
9-hydroxy-pheophorbide- α	pheophorbide-based photosensitizer	preclinical		photodynamic therapy sensitization	<u>HNSCC</u> AMC-HN3	Pancreatic Cancer		
						Urinary Bladder Cancer		
Benzethonium Chloride	synthetic quaternary ammonium salt	preclinical		in vivo	disinfectant, cosmetics and oral rinses,	Breast Cancer	upregulated caspase-12 and CHOP expression, increased expression of downstream cascade including caspase-3, -8 and-9 increased PARP expression	Chung [180] He [179]
						<u>HNSCC</u> C666-1	increased expression of CHOP, increased levels of the spliced (active) form of XBPI, ATF3, GRP78/BiP, GADD34, DRS, and TRB3	Rayess [83] Yip [82]
BG (O6-benzylguanine)	guanine analogue	Phase I/II/III	in vivo	O(6)-methylguanine-DNA methyltransferase inhibitor	<u>HNSCC</u> SQ20b	FaDu		
						HN12		
						UMSCC23		
						Multiple Myeloma	BG + cisplatin increased, caspase-12 cleavage increased, GADD153 (CHOP) expression	Rabik [181] Tacastacas [182]
BI-D1870	small molecule	preclinical	in vitro	p90 ribosomal s6 kinase inhibitor	<u>OSCC</u> Ca922 HSC-3 SCC4 SCC9 SCC2095	Non-hodgkin Lymphoma		
						Non-small cell lung cancer		
						Ovarian Cancer		
						Soft Tissue Tumors		
						Solid Tumors		
						Breast Cancer	increased expression of GRP78/BiP, ATF6 α , and/or XBP-1 However, eIF-2 α phosphorylation was unchanged	Abdulrahman [183]
						Lung Adeno Carcinoma		Chiu [184]
						Malignant Melanoma		Davies [185]
						Medulloblastoma		Pambid [186]
						Multiple Myeloma		Shimura [187]

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Fenretinide	synthetic retinoid	Phase I/II/III		breast cancer chemopreventative agent	<u>HNSCC</u> UMSCC22A UMSCC22B	Breast cancer Ewing's sarcoma Head and Neck Leukemia Multiple myeloma Neuroblastoma Non-small cell lung cancer Ovarian cancer Pancreatic cancer Prostate cancer Small cell lung cancer	induced endoribonuclease-mediated splicing of XBP-1 mRNA, upregulated chaperone proteins including HSPA1A (HSP70), HSP 90/ HSPAC, GRP78/HSPA5/BiP, and GRP58 induced ATF3 and GADD153 (CHOP).	Theodosakis [188] Cooper [189] Kadara [91]
Glucosamine-Hydrochloride	dietary supplement	Phase I/II/III/IV	in vitro	treatment for rheumatoid arthritis and osteoarthritis	<u>OSCC</u> YD-8 YD-10B YD-38	Breast Cancer Leukemia Prostate Cancer Osteosarcoma	increased expression levels of GRP78/BiP protein	Jung [190]
MG-132	small molecule	preclinical	in vitro	proteasome inhibitor	<u>OSCC</u> Tca-8113	Prostrate Cancer	downregulated XBP1 mRNA	Chen [191] Guo [192] Li [193]
MPPa (Pyrophosphorbide-a methyl ester)	semi-synthetic cholophyll derivative	preclinical		pheophorbide-based photosensitizer	<u>Nasopharyngeal Carcinoma</u> CNE-2 HONE-1	Cervical Cancer Colorectal Cancer Glioma Lung Cancer Osteosarcoma Ovarian Cancer	calnexin expression up-regulation along with GRP78/BiP and GRP94. Increased expression and activity of caspase-3 and caspase-9	Qian [194] Pan [195] Tu [196] Huang [197] Li [198] Guelly [199] Sun [200] Marroule [201] Li [202]

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Drug/ Compound	Classification	Clinical/Preclinical Status	FDA approval	Drug Indications	HNSCC, OSCC, Tongue SCC, and Nasopharyngeal Cancer Cell Lines Studied	Other Malignancies Studied	Observed UPR Markers	References
Zn-BC-AM	synthetic Zinc II benzochlorin analog	preclinical	in vivo	porphyrin-based photosensitizer	<u>Nasopharyngeal Carcinoma</u>		upregulation of CNX, GRP78/BiP, and GRP94 increased production and activation caspase-12	Xu [203]
					CNE-2			
					HONE-1			
					<u>OSCC</u>	Malignant Melanoma1	increased expression of GRP78, GRP94, p-PERK and p-eIF2α, increased in splicing fragments of ATF4 and ATF6 increased expression of CHOP	Liu [205]
Natural non FDA Compounds 11-dehydrosimulialide (<i>Simularia leptoclados</i>)	natural product	preclinical	in vitro	antineoplastic properties	Ca9-22			Su [206]
					CAL-27			Liu [207]
					<u>Nasopharyngeal Carcinoma</u>			
					NPC-TW01	Breast cancer	upregulated GRP78/BiP, GADD34 weak activation of PERK increased activity of caspase 12, increased expression of CHOP/GADD153	Mangal [208]
Acetogenins (<i>Annonaceous</i> plants)	natural product	preclinical		antineoplastic properties		Cervical cancer		Juang [209]
						Colon cancer		
						Lung cancer		
						Ovarian cancer		
Borrelidin (<i>Streptomyces sp.</i>)	natural product	preclinical	in vitro	angiogenesis inhibitor, threonyl-tRNA synthetase inhibitor	<u>HNSCC</u>	Acute Lymphoblastic Leukemia	activated GCN2 pathway, phosphorylation of eIF2α, up regulated CHOP protein levels	Harisi [213]
					A253			
					UMSCC1	Breast Cancer		Jeney [212]
					UMSCC14A	Fibro sarcoma		Tsuchiya [210]
Cantharidin (Meloidae (Spanish fly))	natural product	Phase I/II/III	in vivo	topical wart medication	UMSCC23	Osteosarcoma		Habibi [93]
					<u>OSCC</u>			Gafluc [214]
						induced splicing of XBP1	Bladder Cancer Cells	Moss [211]
					A253	mRNA up regulated		Sidhu [37]
								Xi [38]
								Su [215]

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Drug/ Compound	Classification	Clinical/Preclinical Status	FDA approval	Drug Indications	HNSCC, OSCC, Tongue SCC, and Nasopharyngeal Cancer Cell Lines Studied	Other Malignancies Studied	Observed UPR Markers	References
Capsaicin	natural product	phase I/II/III/IV	in vivo	topical analgesia	CAL-27	phosphorylation of eIF2 α		Amantini [216] Chakraborty [217]
					HNI2	increased protein expression		
					SAS	of ATF4 and CHOP induced		
					SCC-4	caspase activation		
					UMSCC1			
					UMSCC10A			
					UMSCC10B			
					UMSCC14A			
					UMSCC14B			
					UMSCC23			
Celastrol (Tripterygium wilfordii (Thunder of God Vine) and Celastrusregeli)	natural product	preclinical		anti-inflammatory and antioxidant properties, RA, SLE, psoriasis, nephropathy and ankylosing spondylitis	<u>Nasopharyngeal Carcinoma</u>	Bladder Cancer	production of ROS increased protein expression of PARP, ATF6- α , IRE1- α , PERK, GRP78/BiP and GADD153 (CHOP) activation of caspase 12	Chen [218] Chow [219] Clark [220] Zhang [221] Lp [223] Lu [222] Thoenissen [224] Zheng [225] Fribley [109] Setty [105] Wang [106] Zhu [112]
					NPC-TW 039	Breast Cancer		
						Colon Cancer		
						Gastric Cancer		
						Multiple Myeloma		
						Non-small cell lung cancer		
						Osteosarcoma		
						Pancreatic Cancer		
						Prostate Cancer		
						Skin Cancer		
Celastrol (Tripterygium wilfordii (Thunder of God Vine) and Celastrusregeli)	natural product	preclinical		anti-inflammatory and antioxidant properties, RA, SLE, psoriasis, nephropathy and ankylosing spondylitis	<u>OSCC</u>		induced splicing of XBP1 mRNA, upregulated of UPR genes (CHOP, GADD34, ATF3, ERDJ4, HERPUD1 and p21), increased protein levels of GRP78/BiP, ATF4 and CHOP, increased ubiquitinated proteins, increased NOXA induced caspase activation	
					A-253			
					CAL27			
					FaDu			
					MSCC1			

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Curcumin (Diarylheptanoid)	natural product	Phase I/II/III/IV		anti-inflammatory properties	UMSCC14A			
					UMSCC23			
					<u>Nasopharyngeal Carcinoma</u>	Breast Cancer	phosphorylation of PERK and IRE1α, increased protein expression of CHOP, GADD34, p50-ATF6 and XBP-1	Pan [226]
					<u>CNE1</u>	Chronic Lymphocytic Leukemia		Pan [227]
					<u>CNE2</u>	Colorectal Cancer		Zheng [228]
DIM (3,3' diindolylmethane)	Phytochemical (metabolite of Indole-3-carbinol)	Phase I/II/III		recurrent respiratory papillomatosis		Endometrial Cancer		Ng [229]
						HNSCC		
						Non-Small Cell Lung Cancer		
						Osteosarcoma		
						Pancreatic Cancer		
						Prostate Cancer		
						Solid Tumors		
					<u>OSCC</u>	Breast Cancer	Akt-NF-KB, MAPK, and p53 signaling, upregulated DRS, induced expression of GRP78/BiP, IRE1α, CHOP and phosphorylation of p53 at Ser-15	Weng [123]
					<u>HEp-2</u>	Cervical Cancer		Abdelrahim [120]
					<u>HN22</u>			Kandala [230]
Emodin	natural product	preclinical		type 2 diabetes	<u>SCC9</u>	Ovarian Cancer		Shin [118]
					<u>SCC15</u>	Pancreatic Cancer		
					<u>SCC2095</u>	Prostate Cancer		
					<u>Tongue SCC</u>	Colon Cancer	oxidative stress induced p53, upregulated GRP78/BiP and CHOP	Lin [231]
					<u>SCC-4</u>			Xie [232]
Fisetin	natural product	Phase I/II	in vitro	antioxidant, anti-inflammatory, anti-invasive, anti-angiogenesis, anti-proliferation, and anti-cancer	<u>OSCC</u>	Acute Monocytic Leukemia	increased expression of GRP78/BiP, GADD153, caspase-4, ATF-6α, and ATF-6β that were associated with ER stress.	Su [233]
					<u>SCC-4</u>	Cervical Cancer		
					<u>HSC3</u>	Colon Cancer		Shih [234]
						Lung Adenocarcinoma		
						Melanoma		
						Pancreatic Cancer		
						Prostate Cancer		

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Flavanoids (flavokawain B and Tectochrysin)	natural product	preclinical		novel chemotherapeutic agent	<u>OSCC</u> HSC-3	Colon Cancer	increased expression of HSP70	Bhardwaj [235] Hseu [236] Ji [237]
Gambogenic Acid	natural product	preclinical	in vitro	inhibitor of the fibroblast growth factor receptor (FGFR) signaling pathway	<u>Nasopharyngeal Carcinoma</u> CNE-1	Breast Cancer Gastric Carcinoma Hepatocellular Carcinoma Lung Adenocarcinoma Melanoma	decreased expression of phospho-Akt	Yan [238] Chen [239] He [240] Tan [241] Wang [242] Yu [243]
GL63	(curcumin analog)	preclinical		novel chemotherapeutic agent	<u>Nasopharyngeal Carcinoma</u> CNE2	hepato cellular Carcinoma lung cancer	upregulated XBP1, ATF4, CHOP, Cox-2 inhibitor	Pan [226] Xiao [244] Xiao [245]
HMI-38	small molecule	preclinical		angiogenic suppressor	<u>OSCC</u> CAL27	Leukemia	induced DNA fragmentation, increased intracellular Ca ²⁺ , increased GRP78/BiP, p-eIF2α, CHOP and ATF6 protein accumulation induced cleavage of PARP and caspases	Lu [80]
Honokiol	Component of <i>Magnolia obovata Thunb.</i>	preclinical	in vivo	antiangiogenic, anti-inflammatory, and anti-tumor properties	<u>OSCC</u> HN22 HSC4	Breast Cancer Gastric Cancer HNSCC Lung Cancer Malignant Mesothelioma Melanoma Neuroblastoma Non-melanoma Prostate Cancer Urinary Bladder Cancer	increased ER-stress and apoptosis related proteins including CHOP cleaved PARP	Cho [246] Prasad [247]
Hydrogen Peroxide	natural product	preclinical	in vitro	strong oxidizing agent	<u>OSCC</u>	Lung Cancer	increased phosphorylation of PERK and eIF2α, increased levels of GRP78/BiP and CHOP	Min [248]

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Indole-3-Carbinol	natural product	phase I	in vivo	antineoplastic properties	HN4			Vilema-Enriquez [249]
					IHOK			
					<u>OSCC</u>	Breast Cancer	up regulation of GADD153 (CHOP) and GRP78/BIP expression in a dose-dependent manner	Weng [250]
					SCC4	Colon Cancer		Weng [251]
					SCC15	Prostate Cancer		
Interferon-Gamma	cytokine	Phase I/II/III/IV	in vitro	diagnosis of tuberculosis	SCC2095			
					<u>HNSCC</u>	Lung Cancer	enhanced phosphorylation PERK and IRE1 α	El Jamal [252]
					CLS-354	Melanoma		
					RPMI 2650			
Manumycin A (<i>Streptomyces parvulus</i>)	small molecule	preclinical	in vivo	NSAID; anti-bacterial	<u>OSCC</u>	Anaplastic thyroid cancer	CHOP, death receptor 4 (DR4), and death receptor 5 (DR5) (all related to ER stress), expression levels were significantly increased	Carey [253]
					HN22	Breast cancer		Cho [254]
					HSC4	Hepatocellular Carcinoma		Dackiw [255]
						Lymphoma		Datta [256]
						Mesothelioma		Frassanito [257]
								Hu [258]
						Ovarian cancer		Kim [259]
						Pancreatic cancer		Matsui [260]
						Prostate cancer		Pan [261]
								Sears [262]
ML-291 (sulfonamidebenzamide)	small molecule	1st-in-class chemical probe		selectively activates the apoptotic, but not the adaptive, arm of the UPR				She [263]
								Singha [264]
								Solar [265]
								Yang [266]
								Yeung [267]
								Zhou [268]
						HNSCC	induced splicing of XBP1 mRNA, upregulated CHOP and GADD34 gene expression	Flaherty [36] Flaherty [81]

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Patulin (Penicillium sp., Aspergillus sp. and Byssochlamys)	natural product	preclinical		potassium uptake inhibitor	<u>OSCC</u>	Nasopharyngeal Carcinoma	upregulation of GRP78/BIP, ATF4, CHOP, ATF3 and GADD34 gene expression, induced XBP1 mRNA splicing, upregulated CHOP protein expression	Fribley [102]
					A-253			Boussabbeh [103]
					CAL27			
					FaDu			
					UMSCC1			
Polydatin	natural product	preclinical		natural precursor of resveratrol	UMSCC14A			
					UMSCC23			
					<u>Nasopharyngeal Carcinoma</u>		increased XBP1s, ATF and CHOP protein expression, induced caspase activation	Liu [269]
					CNE			
					<u>OSCC</u>	Cervical Cancer	induced expression of CHOP and caspase-3 and PARP cleavage	Utaipan [270]
Pyrafoline D (Isomahanine; extract of Muraya koenigii)	natural alkaloid extract	preclinical	in vitro	antineoplastic properties	CLS-354	Colon Cancer		
						Leukemia		
					<u>Nasopharyngeal Carcinoma</u>	Breast Cancer	upregulation of GRP78/BIP, and CHOP mRNA increased protein levels of BIP, IRE1, p-PERK, CHOP, p-eIF2α and XBP1 induced caspase-3 and PARP cleavage	Chow [127]
					NPC-CG1	Follicular Lymphoma		Huang [126]
					NPC-TW04	Leukemia		Izquierdo-Torres [271]
Resveratrol	natural product	Phase I/II/III/IV		antioxidant, anti-inflammatory effects	NPC-TW039			Liu [272]
					NPC-TW076			
					<u>Nasopharyngeal Carcinoma</u>		increased GRP78/BIP expression, upregulated PERK and ATF6 pathways increased ROS	Lin [273]
					NPC-039			Yu [274]
					<u>OSCC</u>	Breast Cancer	increased HSP70 protein, time-dependent increase in the expression of preform caspase-4	Lee [275]
Rhein	natural product	Phase I		antibacterial agent	HSC-3	Liver Cancer		
					<u>Nasopharyngeal Carcinoma</u>	Bladder cancer	increased calpain 1, calpain 2, caspase-12, IRE-1α, IRE-1β, GADD153 (CHOP), GRP78/BIP, ATF-6α, and ATF-6 that are associated with ER stress, increased level of cleaved PARP and caspase 3	Lin [276]
					NPC-TW 039	Breast Cancer		Lin [277]
					NPC-TW 076	Colon cancer		Bhagya [278]
Solanaceae (Physalis angulata)	natural product	preclinical		antineoplastic properties		Esophageal Cancer		
Tetrandrine	natural product	preclinical		antineoplastic and antimicrobial properties				

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						Glioma Leukemia Liver Carcinoma Non small cell lung cancer OSCC Ovarian Cancer Prostate Cancer Renal Cancer		