

Review

Parthenolide as Cooperating Agent for Anti-Cancer Treatment of Various Malignancies

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Abstract: Primary and acquired resistance of cancer to therapy is often associated with activation of nuclear factor kappa B (NF- κ B). Parthenolide (PN) has been shown to inhibit NF- κ B signaling and other pro-survival signaling pathways, induce apoptosis and reduce a subpopulation of cancer stem-like cells in several cancers. Multimodal therapies that include PN or its derivatives seem to be promising approaches enhancing sensitivity of cancer cells to therapy and diminishing development of resistance. A number of studies have demonstrated that several drugs with various targets and mechanisms of action can cooperate with PN to eliminate cancer cells or inhibit their proliferation. This review summarizes the current state of knowledge on PN activity and its potential utility as complementary therapy against different cancers.

Keywords: parthenolide; herbal medicines; cancer treatment; NF- κ B; multimodal therapy; synergistic effect; cancer stem-like cells

1. Introduction

Parthenolide (PN) is a sesquiterpene lactone derived from leaves of the medicinal plant feverfew (*Tanacetum parthenium*). It contains an α -methylene- γ -lactone ring and epoxide group, which are able to interact with nucleophilic sites of biological molecules (Figure 1) [1]. For centuries, PN has been used as a herbal medicine with regard for its anti-inflammatory and anti-migraine properties, as reviewed extensively [2–4]. Recently, the anticancer potential of PN has attracted great attention. PN, and its 1000-fold more soluble in water synthetic derivative, dimethylamino-parthenolide (DMAPT; Figure 1), were subjects of many preclinical in vitro and in vivo studies, performed on cancer cells from hematological malignancies and solid tumors [5–50].

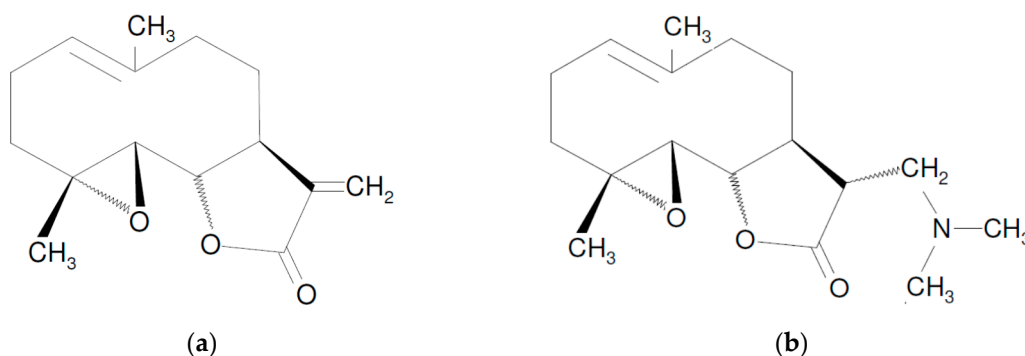


Figure 1. (a) Chemical structure of parthenolide (PN), a sesquiterpene lactone from *Tanacetum parthenium*, and (b) Chemical structure of dimethylamino-parthenolide (DMAPT), a synthetic, water-soluble derivative of PN.

A distinctive feature of PN is its ability to induce cell death in cancer cells while sparing normal ones [12,22]. Moreover, PN significantly reduces the viability of both the bulk population of cancer cells and the cancer stem-like cell subpopulation [14,17,22,39–46]. PN has been reported to trigger a robust apoptosis in primitive CD34⁺ cell population from acute myelogenous leukemia (AML) specimens while sparing normal hematopoietic cells [22] and can induce cell death in primitive chronic myelogenous leukemia (CML) cells through reactive oxygen species [46]. PN has been shown to reduce the frequency of ABCB5⁺ melanoma cells in melanospheres [14], induce oxidative stress, mitochondrial dysfunction and necrosis of breast cancer stem-like cells [17] and target prostate cancer CD44⁺ cells [44].

2. Mechanisms of PN Action

The mechanisms of PN-induced anticancer activity are complex. PN predominantly acts via the inhibition of nuclear transcription factor-kappa B (NF- κ B) (Figure 2, Section 1) [1,13,23,51]. NF- κ B is constitutively active in many types of cancer and controls expression of genes important for tumor growth, angiogenesis, and metastasis [52–55]. Elevated activity of NF- κ B may have essential effects on sensitivity of cancer cells to therapy and has been attributed to development of drug resistance [56–58]. PN inhibits the activity of the upstream kinases of I κ B complex (IKK) precluding degradation of the two NF- κ B regulatory proteins, I κ B- α and I κ B- β [51], and/or it directly alkylates the NF- κ B/p65 subunit at Cys38 and Cys120 residues (Figure 2, Section 1) [59].

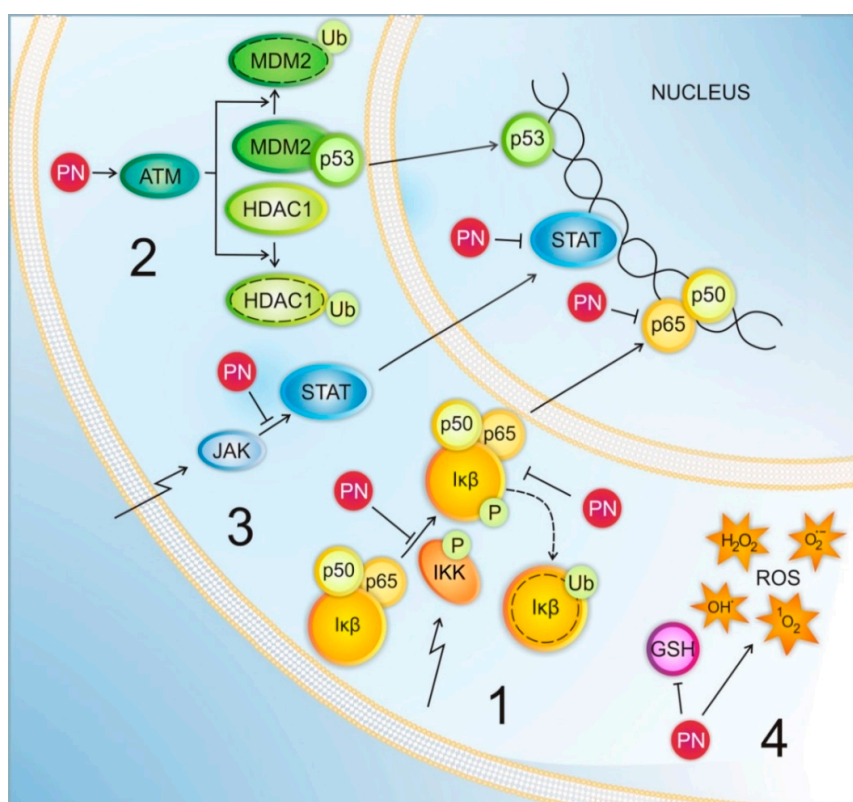


Figure 2. Selected mechanisms of anticancer activity of parthenolide (PN). (1) Inhibition of nuclear factor kappa B (NF- κ B) signaling either through interaction with I κ B kinase (IKK) or directly with p65 subunit results in the downregulation of antiapoptotic gene transcription; (2) Degradation of the mouse double minute 2 homolog (MDM2) and depletion of histone deacetylase 1 (HDAC1) regulate activity of p53 and increase cancer cells sensitivity to therapy; (3) Inhibition of signal transducer and activator of transcription protein 3 (STAT3) phosphorylation prevents its dimerization, nuclear translocation and STAT3-dependent gene expression; (4) Reduction of cellular level of glutathione (GSH) and reactive oxygen species (ROS) accumulation induce oxidative stress.

Suppressed NF- κ B activation is correlated with sustained c-Jun N-terminal kinase (JNK) activation followed by tumor necrosis factor α (TNF- α)-mediated cell death of cancer cells [60]. PN-induced JNK activation can be also independent of NF- κ B inhibition [61]. PN can modify the activity of p53 along two mechanisms, both involving ataxia telangiectasia mutated (ATM) serine/threonine kinase (Figure 2, Section 2). It can occur either by promoting the ubiquitination and degradation of the mouse double minute 2 homolog (MDM2), a p53 negative regulator, or by depletion of histone deacetylase 1 (HDAC1) through proteasomal degradation (Figure 2, Section 2) [20,21]. Inhibition of HDAC1 activity by PN might also reduce the level of M isoform of microphthalmia-associated transcription factor (MITF-M) [23]. Furthermore, PN also is an effective inhibitor of signal transducer and activator of transcription (STAT) proteins. By blocking STAT3 phosphorylation on Tyr705, PN prevents STAT3 dimerization, its nuclear translocation, and STAT3-dependent gene expression (Figure 2, Section 3) [6,29,33]. Inversely, PN does not interfere with the phosphorylation of STAT6 but inhibits its DNA-binding activity [62]. PN suppresses the activity of ubiquitin-specific peptidase 7 (USP7) and WNT/ β -catenin signaling [63]. Oxidative stress may also contribute to the therapeutic effects of PN. PN-induced apoptosis is preceded by the decrease of the levels of intracellular thiols, including both free glutathione (GSH) and protein thiols, and generation of reactive oxygen species (ROS) (Figure 2, Section 4) [7,38,64]. Besides induction of apoptosis, PN can also generate ROS-mediated autophagy [19,37]. α -methylene- β -lactone moiety of PN that is highly reactive with intracellular thiols has been found to be indispensable for the inhibitory effect of PN on tubulin carboxypeptidase [65,66], which might reverse the accumulation of abnormal deetyrosinated tubulin observed in cancer cells. PN has been reported to be an effective DNA hypomethylating agent acting as inhibitor of DNA methyltransferase 1 (DNMT1) expression and activity [67].

However, PN also induces undesirable, cellular protective responses that likely reduce its overall cytotoxicity and may limit its clinical application, such as activation of nuclear factor erythroid 2-related factor 2/antioxidant response elements (Nrf2/ARE) pathway. Induction of phase II detoxification/antioxidant enzymes and their transcriptional targets e.g., heme oxygenase 1 results in increased resistance to oxidative damage [39,68]. In melanoma cells, PN increases the level of phosphorylated extracellular signal-regulated kinase (ERK1/2) [23,69], which is associated with upregulation of connective tissue growth factor (CTGF) expression [69], involved in melanoma cell migration and invasion [70]. This unfavorable effect could be blocked by trametinib, an inhibitor of mitogen-activated protein kinase 1/2 (MEK1/2) [69].

Impact of PN on important signaling pathways in cancer development provided a basis for the studies combining approved drugs and PN in various types of cancers. This review presents a wide range of approved drugs and experimental compounds that have been reported to cooperate with PN.

3. Parthenolide in Combination with Anticancer Agents

3.1. Parthenolide Combined with Tubulin-Directed Agents

Taxane diterpenoid anticancer agents such as docetaxel (Taxotere) and paclitaxel (Taxol) have shown a significant potency against many tumor types including metastatic breast cancer, advanced ovarian cancer, non-small-cell lung cancer (NSCLC), prostate cancer and Kaposi's sarcoma [71–73]. Paclitaxel and docetaxel arrest cells at the G2/M phase of cell cycle and induce cell death by stabilizing microtubules and interfering with microtubule disassembly during cell division [74,75]. Major weakness of using taxanes in cancer therapy is the development of drug resistance, which has been associated with the activation of NF- κ B [76–78].

Several studies involving multiple experimental approaches and diverse cancers suggest that PN might be used in combination with taxanes to enhance anticancer effects. Effective dose of paclitaxel necessary to induce cytotoxic effect in human NSCLC cell lines was markedly reduced by PN [79]. PN precluded NF- κ B nuclear translocation and activation as well as BCL-XL up-regulation caused by paclitaxel in human lung cancer cell lines sensitive (A549, NCI-H446) and resistant (A549-T24) to

paclitaxel [80]. Most likely, this effect was derived from reduced BCL-XL induction via PN-mediated modulation of the NF- κ B/I- κ B kinase (IKK) signal cascade (Figure 2, Section 1) [79]. Inhibition of NF- κ B by PN promoted cytochrome c release, activation of caspase-3 and -9 and inhibition of transcription of several anti-apoptotic proteins, including c-IAP1 and BCL-XL [79,80]. Co-treatment of A549 cells with PN and paclitaxel resulted in activation of the intrinsic pathway of apoptosis in contrast to mitochondria-independent apoptosis induced by paclitaxel used alone [80]. Likewise, in A549 tumor mice xenografts PN increased the efficacy of paclitaxel [81]. Combination of drugs caused a greater inhibition of the tumor growth compared with paclitaxel alone, while PN alone was unable to suppress tumor development [81]. Combination therapy was also accompanied with decreased angiogenesis and significant increase in the life span of xenograft mice and was well-tolerated [81]. Additional benefits were gained from co-encapsulation of PN with paclitaxel in mixed micelles, which increased the anticancer activity against paclitaxel sensitive and resistant NSCLC cell lines and caused significantly higher cell death than drugs used in solution [82].

Activated NF- κ B also protected breast cancer cells against paclitaxel. PN increased the sensitivity of these cells to paclitaxel and enhanced paclitaxel-induced apoptosis by inhibition of constitutive NF- κ B DNA binding activity (Figure 2, Section 1). In MDA-MB-231 cells, it was associated with reduced manganese superoxide dismutase (Mn-SOD) expression [76]. In gastric cancer cells the combined treatment of paclitaxel and sub-lethal dose of PN significantly increased apoptosis compared with the cells treated with paclitaxel alone [34]. The PN/paclitaxel combination significantly elongated survival of mice in the peritoneal dissemination model. PN also enhanced chemosensitivity to paclitaxel [34].

Docetaxel in combination with PN induced apoptosis in breast cancer cells, reduced the colony formation capacity and expression of a prometastatic gene, CXCL8, and an antiapoptotic gene, GADD45 β 1 [83]. Mice bearing MDA-MB-231 cell xenograft treated with this drug combination showed remarkably enhanced survival associated with reduced lung metastases in comparison with animals treated with each drug alone or untreated animals [83]. PN also increased the in vivo efficacy of docetaxel in a xenograft of androgen-independent prostate cancer mouse model. Docetaxel in combination with PN decreased tumor growth more efficiently compared with control xenografts and xenografts treated either with docetaxel or with parthenolide alone [32]. On the other hand, in androgen-dependent LNCaP prostate cancer cells exerting low basal NF- κ B activity, PN blocked docetaxel- and 2-methoxyestradiol-mediated apoptosis [84]. Thus, combination of antimitotic drugs with NF- κ B inhibitors can have antagonistic effects.

Vinorelbine, a semi-synthetic vinca alkaloid, induces cytotoxicity by disruption of microtubule assembly and is approved for the treatment of advanced breast cancer and NSCLC [85,86]. Both PN and vinorelbine inhibited proliferation in human breast cancer cell lines MCF7 and MDA-MB-231, but vinorelbine was less effective in side-population (SP) cells that represent cancer stem-like cells than in non-SP cells [87]. By using vinorelbine in combination with PN, the proliferation of SP cells was significantly inhibited. In the MCF7 xenografts in mice, stealth liposomal vinorelbine together with stealth liposomal PN produced a strong inhibitory effect in breast tumors [87].

3.2. Parthenolide Combined with TRAIL

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a cytokine considered as a promising anticancer agent as binding of TRAIL to its receptors, death receptor 4 (DR4) and death receptor 5 (DR5) initiates apoptosis in various cancer cell types without affecting normal cells [88,89]. However, various cancers develop resistance toward TRAIL [89,90]. Co-treatment with PN is considered as capable to overcome resistance to TRAIL [6,25,61,91].

TRAIL used in combination with PN significantly inhibited cell proliferation and induced apoptosis in TRAIL-resistant and TRAIL-sensitive human colorectal cancer cells (CRC) [25,91]. Synergistic effect was associated with upregulation of DR5 protein and its cell surface expression, deregulation of BCL-2 family members, increase in p53 level, release of cytochrome c to cytosol and activation of caspases [25,91]. Similar effects were observed in human hepatocellular carcinoma (HCC) cells lines [6].

The expression of death receptors DR4 and DR5 either at the protein or mRNA levels as well as their surface localization were increased in PN-treated HCC cell lines. Probably, this is a consequence of an inhibitory effect exerted by PN on the activation of JAK proteins resulting in decreased level of phosphorylated STAT proteins (Figure 2, Section 3) [6]. Co-treatment of HCC cell lines with PN and TRAIL induced apoptosis along extrinsic pathway, and this was associated with the activation of both caspases-8 and -3, whereas a mitochondrial pathway was not involved [6]. In contrast, PN-induced TRAIL sensitization did not alter the expression of death receptor in breast cancer cells, but activation of JNK was necessary for this process [61]. TRAIL used in combination with PN induced apoptosis in TRAIL-resistant MDA-MB-231 cells [61]. PN induced TRAIL-dependent cleavage of Bid and XIAP degradation that was associated with increased caspase-3 activity and poly (ADP-ribose) polymerase (PARP) cleavage, whereas activity of caspase-8 was not affected [61].

3.3. Parthenolide Combined with Anti-Inflammatory Drugs

NF- κ B and cyclooxygenase (COX) are activated or overexpressed in several cancers, including pancreatic cancer [92,93]. Nonsteroidal anti-inflammatory drug (NSAID) sulindac, a COX inhibitor, suppressed the growth of pancreatic cancer cells [94].

Sulindac in combination with PN lowered the threshold for apoptosis and synergistically inhibited proliferation of pancreatic carcinoma cells. The PN/sulindac combination cooperatively targeted the NF- κ B pathway, which was observed as increased level of I κ B α protein, and decreased NF- κ B transcriptional activity compared with either agent used alone [94]. Moreover, sulindac combined with DMAPT exerting higher bioavailability than PN, might mediate their antitumor effects by altering cyclin D1 levels, also in a xenograft model of human pancreatic cancer [95]. DMAPT combined with sulindac delayed or prevented progression of premalignant pancreatic lesions in the developmental mouse model of pancreatic cancer, in which tumors are formed de novo. The percentage of normal pancreatic ducts was significantly increased by the DMAPT/sulindac combinations compared with placebo [96].

Celecoxib, a COX-2 inhibitor/NSAID used in combination with DMAPT prevented from adjacent organs invasion and metastasis in an in vivo model of pancreatic cancer. It was related to decreased prostaglandin E2 and prostaglandin E2 metabolite levels and reduced NF- κ B activity [97]. PN decreased the effective dose of NS398, a COX-2 inhibitor that was used for growth inhibition of human hepatocellular carcinoma cells [98]. The combination of PN and NS398 more efficiently induced G1 cell cycle arrest, decreased cyclin D1 levels and inhibited NF- κ B DNA-binding and transcriptional activities than the single agents. Drugs used in combination inhibited phosphorylation of the NF- κ B-inhibitory protein I κ B α and increased total I κ B α levels [98].

Balsalazide is a colon-specific prodrug of 5-aminosalicylate used in the treatment of inflammatory bowel disease [99]. Inhibition of NF- κ B activity is one of the several mechanisms of reduction of inflammatory responses by balsalazide [100,101]. PN and balsalazide produced synergistic anti-proliferative effects and induced apoptosis through the mitochondrial pathway in human colorectal carcinoma cell line and colitis-associated colon cancers (CAC) [100,101]. The combination of balsalazide and PN markedly suppressed the nuclear translocation of NF- κ B, p65 and I κ B α phosphorylation, NF- κ B binding to DNA and expression of NF- κ B targets [100,101]. Combined treatment of a CAC murine model resulted in a regain of body weight and suppressed carcinogenesis [100,101].

3.4. Parthenolide Combined with Hormonal Agents

Tamoxifen, a nonsteroidal selective estrogen receptor antagonist, is commonly used in the treatment of recurrent estrogen receptor- α -positive (ER+) breast carcinoma [102]. A major problem of this therapy is a primary resistance and acquired resistance induced by drug [102]. Inhibition of NF- κ B may also be useful for the treatment of ER+ breast cancers that have acquired resistance to antiestrogen therapy. MCF7/HER2 and BT-474 breast cancer cell lines overexpressed the oncogenic receptor tyrosine kinase, HER2/ErbB2, which activates NF- κ B and diminishes the responsiveness to

tamoxifen [103]. Tamoxifen used in combination with PN suppressed activity of NF- κ B- and activator protein 1 (AP-1) and increased nuclear receptor co-repressor (NCoR) binding to the promoter of ER encoding gene [104,105].

NF- κ B inhibition by PN (Figure 2, Section 1) synergistically restored sensitivity of resistant breast cancer cells to 4-hydroxytamoxifen (4HT), and further sensitized drug-naïve cells to 4 HT [106]. In primary ER+ solid tumors, tamoxifen with PN generated significant tumor responses that were estrogen-independent [107].

Steroidal antiestrogen fulvestrant (Faslodex) stimulates degradation of the ER, prevents receptor dimerization, and inhibits estrogen-dependent gene transcription [108]. Resistance to this drug is also connected with enhanced expression and activity of NF- κ B [109].

MCF7/LCC9, antiestrogen-resistant breast cancer cell line was insensitive to fulvestrant, while PN efficiently inhibited proliferation of these cells. The combination of these drugs caused a 4-fold synergistic reduction of proliferation [110]. PN also restored sensitivity to anti-androgen therapy in a xenograft hormone refractory prostate cancer model (androgen-independent prostate cancer line CWR22Rv1 xenograft model). In mice treated with the combination of anti-androgen bicalutamide and PN, tumor volume was smaller than in controls and in mice treated with single agents and had a slower rate of proliferation [32].

Dehydroepiandrosterone (DHEA) is a naturally occurring adrenal steroid, a precursor of sex steroids such as androgen and estrogen. Among a variety of additional, beneficial effects of DHEA is inhibition of the NF- κ B signaling pathway [111]. Combined treatment of DHEA and PN efficiently inhibited growth and function of AtT20 corticotroph tumor cells both in vitro and in vivo. In vitro, DHEA and PN had inhibitory effects on pro-opiomelanocortin and NF- κ B-dependent gene expression. Combined administration of DHEA and PN in mice with xenografts of AtT20 cells significantly reduced tumor growth and survivin expression, decreased corticosterone levels in plasma and eliminated the malnutrition induced by tumor growth [112].

3.5. Parthenolide Combined with Anthracyclines

Doxorubicin (Dox), isolated from *Streptomyces peucetius*, is a potent anticancer agent and a treatment of first choice for many cancers, but is not highly effective against melanoma in vitro and in vivo [113,114]. However, its efficacy was substantially increased when it was combined with PN. Dox caused pro-survival effects including NF- κ B activation and stimulation of the ATP-binding cassette sub-family B member-5 (ABCB5) transporter expression. PN markedly lowered Dox-induced NF- κ B activity and reduced expression of matrix metalloproteinase-9 (MMP9) [36]. PN also synergized with Dox against malignant glioblastoma cell lines [115].

A similar effect was observed in human colon cancer cells after treatment with PN and disaccharide analog of Dox, sabarubicin (MEN-10755) [116]. As Dox caused an early pro-survival NF- κ B activation, sensitivity of HCT-116 cells to drug-induced apoptosis was low. Inhibition of NF- κ B by PN (Figure 2, Section 1) increased sabarubicin-induced cell death [116].

In human breast cancer cells, PN prevented the development of resistance to mitoxantrone and doxorubicin by inhibition of overexpression of proteins involved in the protection against oxidative stress, e.g., manganese superoxide dismutase (MnSOD) and other proteins that support the survival of cancer cells and favor drug resistance, including heat-shock proteins 70 (HSP70), BCL-2 and P-glycoprotein [117].

3.6. Parthenolide Combined with Alkylating Agents

Dacarbazine (DTIC), an alkylating agent, is used for the treatment of metastatic melanoma [118]. PN in combination with DTIC synergistically reduced the number of viable melanoma cells and abolished the baseline and DTIC-induced vascular endothelial growth factor (VEGF) secretion [26], however, the mechanisms of the synergy between these drugs remain unclear.

Temozolomide (TMZ) and radiotherapy are used for the treatment of glioblastoma multiforme (GBM), the most malignant brain tumor in adults [119]. While orally administered temozolomide provides survival benefits for GBM patients, the overall clinical prognosis is unsatisfactory due to intrinsic or acquired resistance to TMZ [120]. It has been shown that high expression of the DNA repair enzyme O6-methylguanine-DNA methyltransferase (MGMT) is responsible for resistance to TMZ in GBM cells [121]. Anti-apoptotic activity of NF- κ B has also been reported as being associated with resistance to TMZ [122], and NF- κ B was found to play a major role in regulation of MGMT [123]. Inhibition of NF- κ B activity by PN (Figure 2, Section 1) reduced the expression of MGMT and restored sensitivity to temozolomide in LN18 and T98G glioma cell lines [124]. PN in combination with temozolomide more efficiently inhibited tumor growth and prolonged median survival in human T98G xenograft-bearing severe combined immunodeficiency (SCID) mice than these drugs used as single agents [124].

Cisplatin is a chemotherapeutic drug used since late 1970s to treat numerous cancers [125,126]. Cisplatin and other platinum-containing drugs crosslink with the purine bases on the DNA causing DNA damage and affecting DNA repair mechanisms, which results in apoptosis of cancer cells. PN markedly enhanced the sensitivity of human lung cancer cells to oxaliplatin, an analog of cisplatin, by inhibiting NF- κ B activation (Figure 2, Section 1) and inducing apoptosis [127]. PN synergistically increased the anticancer effect of cisplatin in both apoptotic and sub-apoptotic concentrations in GBM rat and human cell lines, overcoming cisplatin resistance in GBM rat cells, probably through NF- κ B inhibition [115]. PN could also reverse cisplatin resistance of human gastric carcinoma cells [27]. In the cisplatin resistant human gastric cancer cell line, PN and cisplatin demonstrated time- and concentration-dependent cytostatic effects, and a synergy between PN and cisplatin was demonstrated [27]. Cisplatin acted synergistically *in vitro* and *in vivo* also with PN-based compound ACT001 (dimethylamino-micheliolide) [128]. In human GBM cell line, combination of cisplatin and ACT001 increased the apoptosis and reduced cell migration and invasion more efficiently than each drug alone. In the mouse xenograft model, inhibition of tumor growth was significantly enhanced by combined treatment in comparison to single agent treatment. Synergy between ACT001 and cisplatin was related to the inhibition of the plasminogen activator inhibitor-1 (PAI-1)/PI3K/protein kinase B (AKT) pathway [128].

PN has been reported to act as an epigenetic drug inhibiting both HDAC1 [20] and DNMT1 [67]. In combination with 5-aza-2'-deoxycytidine, an inhibitor of DNMT1, PN synergistically reduced growth and induced apoptosis of medulloblastoma-derived cells [129].

3.7. Parthenolide Combined with Antimetabolites

Ganciclovir (a synthetic analogue of 2'-deoxy-guanosine), an antiviral medication could be use in Burkitt lymphoma (BL) therapy, because Epstein-Barr virus (EBV) is present in cancer cells of almost all patients with endemic variant of BL. Elevated NF- κ B levels in EBV-positive BL cells inhibit lytic replication cycle of the latent EBV [130]. Treatment with PN inhibited proliferation of Raji cell line and led to apoptosis via the mitochondrial pathway. Moreover, inhibition of RelA/p65 activity by PN induced EBV lytic replication. Ganciclovir significantly augmented cytotoxic effect of PN in Raji cells [28].

Thus, 5-fluorouracil (5-FU) is an important element of chemotherapy in many types of cancer [131]. It blocks DNA synthesis by inhibition of thymidylate synthase. PN can overcome 5-FU resistance in human colorectal cancer cells [132]. Combination of these drugs synergistically induced apoptosis through the mitochondrial pathway in human colorectal cancer cells. Moreover, intra-peritoneal injection of PN and 5-FU resulted in inhibition of tumor growth and induction of apoptosis in the mouse CRC xenograft model [132]. PN reversed the 5-FU resistance also in hepatic carcinoma resistant cells [133]. Most recently, 23 conjugates of parthenolide and 5-FU were evaluated in hepatocellular carcinoma cell line [134], and one of these conjugates exerted improved anticancer activity when compared with PN alone.

Gemcitabine, a synthetic pyrimidine nucleoside prodrug, is used in the treatment of a wide variety of tumors e.g., lung, breast, ovarian and pancreatic cancer [135]. It has been shown that gemcitabine can induce NF- κ B activity in human pancreatic cancer cell lines, which can diminish its clinical efficacy [136]. DMAPT, when used in combination with gemcitabine, revoked NF- κ B induction in pancreatic cancer cells and intensified gemcitabine's anti-proliferative effect [136]. In a mouse model of pancreatic cancer, DMAPT and gemcitabine co-treatment increased the percentage of normal ducts and decreased the percentage of intraepithelial neoplasia-2 lesions [96].

3.8. Parthenolide Combined with Histone Deacetylase Inhibitors

The antitumor activity of histone deacetylase inhibitors (HDACIs) has been related to their ability to generate accumulation of hyperacetylated histones and alter gene transcription [137]. HDACIs can downregulate the expression of oncoproteins, induce differentiation, cell cycle arrest and apoptosis, and some of them are under clinical development [137–139]. As several HDACIs have been shown to induce NF- κ B activity leading to cytoprotective effects, NF- κ B inhibitors such as PN can potentiate apoptosis induced by HDACIs [140–142]. Moreover, it has been reported that PN also specifically depletes HDAC1 protein (Figure 1, Section 2) [20].

Valproic acid, an antiepileptic drug with well documented pharmacokinetics and toxicity profiles exerted an HDAC-inhibitory activity in cancer cells like neuroblastoma or teratocarcinoma [143]. As a single agent, it had slight growth-inhibitory activity in cultured cancer cells but induced the NF- κ B transcriptional activity [142]. PN markedly synergized with valproic acid to induce apoptosis in esophageal cancer cells, NSCLC cells and malignant pleural mesothelioma cells [142].

Suberoylanilide hydroxamic acid (SAHA, vorinostat), an HDACI with a high therapeutic potential has been shown to act synergistically with PN in a triple-negative breast cancer cell line (Figure 3) [144]. SAHA/PN combination decreased the intracellular GSH level and mitochondrial membrane potential, released cytochrome c, activated caspase-3 and apoptosis more potently than each drug alone [144]. These two drugs used in combination induced epigenetic changes such as hyperacetylation of histones H3 and H4 as the result of SAHA-induced inhibition of HDAC and down-regulation of DNMT1 induced by PN. They caused depletion of GSH, increased expression of the tumor suppressor genes p21 and p27 and reduced the Bcl-2 and p65 level. Moreover, combined treatment reduced the prosurvival effects observed in single-drug treatments: induction of autophagy by SAHA and induction of AKT/mammalian target of rapamycin (mTOR)/nuclear factor erythroid 2-related factor 2 (NRF2) pathway by PN [144].

PN cooperated synergistically with SAHA and another pan-histone deacetylase inhibitor LBH589 also in acute myeloid leukemia (AML) cells [11]. PN inhibited HDACI-induced IKK and RelA phosphorylation and stimulated MKK7-dependent activation of stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK) pathway [11]. It leads to apoptosis in multiple AML cell lines, transduced hematopoietic cells with leukemia-initiating cell characteristics and primary AML blasts, while sparing normal hematopoietic progenitors. A series of parthenolide-SAHA hybrids were synthesized and tested for their anti-cancer properties [145]. The most active hybrid showed several times higher activity against AML cells than PN or SAHA alone and induced apoptosis through mitochondria pathway [145].

In some cases, co-treatment with PN and HDACI could have negative effects. It has been demonstrated that trichostatin A, the reversible HDAC inhibitor, promoted acetylation of NF- κ B/p65 subunit [146]. Co-treatment of human colon adenoma cells with trichostatin A and PN significantly inhibited the trichostatin A-induced cellular levels of acetyl NF- κ B/p65 and decreased NF- κ B/p65 binding to the promoter of putative tumor suppressor gene, stanniocalcin-1 (STC1) [147].

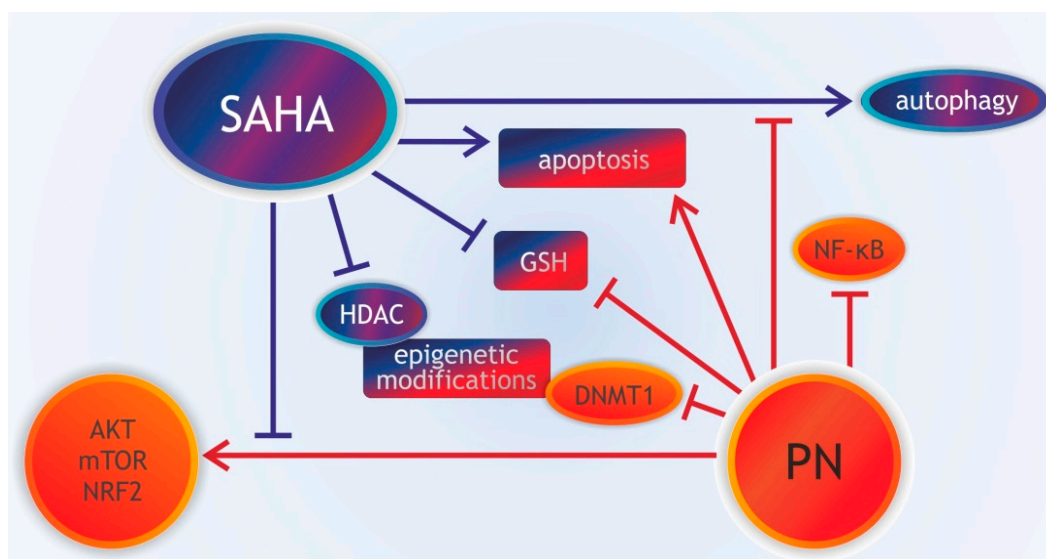


Figure 3. Schema summarizing synergistic effects of suberoylanilide hydroxamic acid (SAHA) and parthenolide PN in triple-negative breast cancer cells prepared based on Carlisi et al., [144]. SAHA (histone deacetylase 1 inhibitor, HDACIs) and PN used in combination lead to several epigenetic modifications as SAHA induces hyperacetylation of histones H3 and H4 and PN downregulates DNA methyltransferase 1 (DNMT1). These modifications, together with reduced glutathione (GSH) depletion induced by combined treatment with SAHA and PN, trigger apoptosis. While PN restrains pro-survival autophagy that is induced by SAHA, SAHA prevents cytoprotective effects of PN on AKT/mammalian target of rapamycin (mTOR)/nuclear factor erythroid 2-related factor 2 (NRF2) pathway. SAHA does not influence the inhibitory effect of PN on nuclear factor kappa B (NF- κ B) activity.

3.9. Parthenolide Combined with mTOR Inhibitors

Inhibitors of the phosphoinositide 3-kinases (PI3K)/mTOR pathway have been shown to synergize with PN in selective eradication of primary human AML cells [39,148]. The combination of PN and PI3K inhibitor wortmannin or the mTOR inhibitor, rapamycin (sirolimus) and rapamycin analog, temsirolimus exhibited synergistic toxicity against AML stem cells. These effects were manifested both in vitro with patient specimens and in vivo using murine xenotransplantation models of AML [39,148].

Ciclopirox, an antifungal agent, used for the treatment of mycoses, has shown an antitumor activity attributed also to inhibition of mTOR [149]. Similarly, to other mTOR inhibitors, ciclopirox significantly enhanced the ability of PN to target acute myeloid leukemia by inhibiting the PN-induced activation of mTOR. Ciclopirox and PN acted synergistically to eradicate bulk and leukemia stem cells [149].

3.10. Parthenolide Combined with Retinoids

All-trans retinoic acid (Tretinoin, ATRA) induces remission in a majority of acute promyelocytic leukemia patients [150]. ATRA forced promyelocytic leukemia cells to differentiate and inhibited their proliferation [151]. PN increased ATRA-induced HL-60 cell differentiation into a granulocytic lineage involving activation of PKC, ERK2, JNK and PI3-K and downregulation of asparagine synthetase expression [152,153]. Close association between enhancement of cell differentiation and inhibition of NF- κ B DNA-binding activity by PN was shown [152].

Fenretinide, a synthetic retinoid with antineoplastic activities, induced the activation of NF- κ B during apoptosis [154]. Sublethal dose of PN effectively enhanced the fenretinide-induced apoptosis in hepatoma cells [154].

Vildagliptin, an inhibitor of dipeptidyl peptidase-4 is used clinically as an anti-hyperglycemic drug in the treatment of type 2 diabetes mellitus [155]. High throughput combination drug screen

revealed that vildagliptin synergistically enhanced anti-leukemic activity of PN in primary AML samples including the stem cell fraction [41]. Vildagliptin used in combination with PN decreased the viability and clonogenic growth of AML cells, whereas spared normal human peripheral blood stem cells. Synergy between drugs was not related to vildagliptin's primary target dipeptidyl peptidase 4. Enhancement of parthenolide's activity was mediated by inhibition of dipeptidyl peptidase-8 and dipeptidyl peptidase-9 by vildagliptin [41].

3.11. Parthenolide Combined with Inducers of Reactive Oxygen Species (ROS)

Arsenic trioxide (ATO), a well-known environmental toxicant, has been approved for the treatment of certain types of leukemia [156]. PN increased cytotoxicity of arsenic trioxide in cell lines representing various hematological malignancies (EL-4, Jurkat and HL-60 cells) [9]. Addition of buthionine sulfoximine, an irreversible inhibitor of γ -glutamylcysteine synthetase that reduces intracellular GSH levels, increased efficacy of treatment. The glutathione content and intracellular ATP levels were reduced, and induction of oxidative stress was observed. Lymphocytes from healthy donors were mostly resistant to this treatment [9]. Most recently, significant increase in the cytotoxicity of arsenic trioxide by PN was confirmed in adult T-cell leukemia/lymphoma cell lines [157]. Combination therapy with arsenic trioxide and PN generated reactive oxygen species, inhibited growth, and induced apoptosis via the mitochondrial pathway also in human pancreatic carcinoma cell lines [158]. In pancreatic carcinoma xenografts in nude mice PN/ATO treatment inhibited tumor growth more efficiently than either drug alone [158].

Okadaic acid is a lipophilic polyether produced by several marine dinoflagellates. It acts by inhibiting serine/threonine protein phosphatases [159]. Okadaic acid/PN treatment effectively induced apoptosis, increased ROS levels and reduced GSH level in human retinoblastoma Y79 cells [160]. These two compounds at subtoxic doses acted together to induce a tumor suppressor PTEN, p53 activation and decreasing phospho-AKT and phospho-MDM2 levels [160].

3.12. Parthenolide Combined with Other Drugs

Abnormal activation of FMS-like tyrosine kinase 3 (FLT3) is observed in AML patients [161]. FLT3 selective inhibitor SC-203048 in combination with PN synergistically inhibited AML growth and increased cell apoptosis [162].

Heat-shock proteins (HSP) are often overexpressed in human solid tumors and hematological malignancies [163]. HSP90 inhibitor, geldanamycin induced changes in the apoptosis-related protein levels, loss of the mitochondrial transmembrane potential, formation of reactive oxygen species, nuclear damage, and cell death in the human epithelial ovarian carcinoma cell lines [164]. PN enhanced geldanamycin-induced apoptosis by increasing activation of the caspase-8- and Bid-dependent pathway and the mitochondria-mediated apoptosis leading to the activation of caspase-9 and caspase-3. The stimulatory effect of PN on the formation of reactive oxygen species (Figure 2, Section 4) was probably crucial for this combined action [164].

The main mechanism of PN action in cholangiocarcinoma (CC) was also probably associated with oxidative stress, caused by GSH depletion and ROS generation [24]. Simultaneously, during induction of apoptosis by PN in CC cells, heme oxygenase-1 was highly expressed, which could cause cell resistance to chemo-oxidative stress [165]. Protein kinase C-alpha inhibitor Ro317549, which blocked heme oxygenase-1 expression through downregulation and inhibition of nuclear translocation of Nrf2, enhanced PN-mediated apoptosis. The combination of PN and Ro317549 also efficiently inhibited tumor growth in a subcutaneous tumor model [165].

Actinomycin-D is a cyclic polypeptide antibiotic that binds to DNA and prevents elongation of RNA chain by inhibiting RNA polymerase II [166]. A phase 2 clinical trial has shown that actinomycin-D could be an effective drug in the pancreatic cancer treatment; however, it has substantial dose-limiting toxic side effects [167]. Actinomycin-D combined with DMAPT synergistically enhanced cell death of pancreatic cancer cells and may provide an effective treatment at lower doses [168].

Most cancer cells remain in a highly proliferating state because they lost the ability to mature into non-replicating adult cells. Certain cancers may be treated with agents that induce terminal differentiation [169]. Thus, $1\alpha,25$ -dihydroxyvitamin D₃ has been shown to potently initiate differentiation of promyelocytic leukemia cell into a monocytic lineage. Pretreatment of these cells with PN strongly potentiated the $1\alpha,25$ -dihydroxyvitamin D₃-induced cell differentiation via the inhibition of NF- κ B activity (Figure 2, Section 1), although PN alone did not induce cell differentiation [170].

Lactacystin, an inhibitor of proteasome activity in combination with PN led to activation of the caspase cascade and synergistically increased the apoptotic fraction of the p53-deficient, drug-resistant mouse leukemia L1210 cell (Y8) [171].

Nowadays, feverfew supplements containing at least 0.2% PN are broadly available and can be purchased in the form of capsule, tablet, or liquid extract. It has been demonstrated that PN together with other constituents of feverfew, flavonoids (apigenin and luteolin) in feverfew extract might have moderate to weak synergistic effects on the inhibition of growth of human breast cancer cells and human cervical cancer cells [172].

4. Parthenolide in Combination with Radio- and Thermo-therapy

4.1. Parthenolide Combined with Radiotherapy

Radiotherapy is currently used to treat localized tumors such as cancers of the skin, brain, breast, and prostate, but it is delimited by side effects and late complications resulting from high-dose radiation and development of resistance [173]. The acquired radio-resistance involves several mechanisms, including the activation of NF- κ B. Ionizing radiation has been reported to activate NF- κ B in both in vitro and in vivo models [174,175]. Furthermore, constitutive activity of NF- κ B may be responsible for the intrinsic radioresistance of cancer cells [30]. Treatment with PN is considered as the possibility to decrease therapeutic doses of radiation and reduces radiation toxicity to surrounding cells.

Inhibition of constitutive and radiation-induced NF- κ B activity by PN (Figure 2, Section 1) sensitized prostate cancer cells to X-ray, inhibited expression of superoxide dismutase 2 (SOD2) gene and split-dose repair and activated the PI3K-AKT pathway [176,177]. PN also mediated intense oxidative stress in these cells by enhancing ROS generation and attenuating antioxidant protection by activation of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and downregulation of MnSOD and catalase. When PN was used with radiation, further increase of ROS levels was observed in prostate cancer cells [35]. Contrarily, PN increased GSH level and reduced radiation-induced oxidative stress in normal prostate epithelial cells PrEC [35].

Treatment with DMAPT decreased proliferation and enhanced radiation-induced cell death in NSCLC cells [178,179] and human prostate cancer cells [180]. DMAPT increased the efficiency of single and fractionated X-ray treatment through inhibition of a constitutive and radiation-induced NF- κ B activity and inhibition of DNA double-strand break repair [178–180]. NF- κ B inhibition reduced homologous recombination, nonhomologous end joining and downregulated ionizing radiation-induced DNA repair biomarkers [178]. DMAPT significantly decreased tumor growth in A549 lung cancer tumor xenografts and PC-3 prostate tumor xenografts in nude mice, compared with xenografts treated with either DMAPT or radiation alone [179,180].

Treatment of whole-body X-irradiation of Transgenic Adenocarcinoma of the Mouse Prostate (TRAMP) mice with a normal immune system with PN or DMAPT prior to combination of low and high doses, protected normal tissues from a radiation-induced apoptosis [31]. Both drugs induced radiosensitivity in TRAMP prostate tissue, particularly in areas with higher grade prostatic intraepithelial neoplasia lesions [31].

Osteosarcoma is a primary malignant bone tumor, commonly demonstrates significant radioresistance and high metastatic potential [181]. In osteosarcoma, human and murine cell line, resistance to radiotherapy has been associated with NF- κ B activity [182,183]. Pretreatment with PN synergistically suppressed cell proliferation and potentiated apoptosis induced by ionizing radiation

in osteosarcoma cells. Moreover, both the overall population of cancer cells and the CD133+ stem-like cell subpopulation were affected. This effect was connected to the ability of PN to induce oxidative stress [182]. PN with irradiation treatment inhibited osteosarcoma tumor growth in mice more effectively compared to PN or irradiation alone [183]. PN enhanced X-ray sensitivity of radiation resistant CGL1 (HeLa hybrid) cells [30]. Treatment with PN induced stabilization of p53, blocked cell cycle and caused inhibition of split-dose repair [30].

4.2. Parthenolide Combined with Thermotherapy

Hyperthermia has shown promising therapeutic outcomes as an element of combined therapy to treat human cancers [184–186]. Elevated body temperature causes immune system activation and can alter the physiology of cancer cells by activating heat shock proteins, induction protein unfolding, enhancing oxygenation of the tumor microenvironment and blood flow to the tumor [184–186], but cancer cells can develop thermo-resistance or thermotolerance similar to radiotherapy and chemotherapy [185].

PN and elevated temperature used in combination caused significant sensitization of the human lung adenocarcinoma A549 cells to apoptosis. Synergistic thermo-enhancement effects on induction of apoptosis and cell cycle arrest in G2/M were due to the direct suppression of NF- κ B activity (Figure 2, Section 1) [187,188]. PN was also an effective thermo-sensitizing agent for human prostate cancer therapy [189]. Treatment of human prostate cancer androgen-independent cell lines with PN prior to hyperthermia significantly increased apoptosis and caused G2/M cell cycle arrest with the participation of the mitogen-activated protein kinase (MAPK) cascade [189].

5. Conclusions and Perspectives

PN, when used alone, has been identified in preclinical studies as an effective agent against many types of cancer and has been proposed to increase the sensitivity of cancerous cells to chemotherapy and radiotherapy (Table 1). Multimodal therapies that include PN seem to be an interesting conception to simultaneously eliminate different cancer subpopulations, including cancer stem-like cells and provide more complete eradication of the malignancy. PN and other naturally derived agents (e.g., curcumin, betulin, withanolides, lactoferrin) when administered with the standard platinum and etoposide treatments led to a complete regression of advanced small lung cell carcinoma and the patient remains in full remission more than 7 years, while the median survival with the standard treatments alone is 9–10 months from the time of diagnosis [190]. While a wide array of biological activity and low toxicity make PN a promising drug with multi-pharmacological potential, its bioavailability is unsatisfactory, which limits its clinical application in anticancer therapy. A lot of effort has been made to overcome its instability in both acidic and basic conditions and improve its solubility and bioavailability [191–199]. Several new water-soluble PN derivatives have been designed, synthesized and their activity has been evaluated in vitro and in vivo [43,47,193–202]. Better solubility and higher anticancer activity have been recently obtained with PN derivatives prepared through the aza-Michael addition of nitrogen-containing anticancer drugs such as cytarabine and melphalan [200]. PN and some of PN-based anti-cancer candidates have been clinically tested (Table 2).

Table 1. Chemotherapeutics investigated in combination with parthenolide (PN) and its derivatives in different types of cancer.

Co-Treatment with PN	Main Mechanism of Action	In Vitro Cell Line (PN Concentration)	In Vivo Model (PN Dose)	References
Leukemias				
1 α ,25-dihydroxyvitamin D3	differentiation inducer	human HL-60 (0.625–10 μ M)	–	[170]
ATO (arsenic trioxide)	reactive oxygen species inducer	human Jurkat, human HL-60, human K-562 (10 μ M)	–	[9]
ATRA (all-trans retinoic acid)	differentiation inducer	human HL-60 (0.25–10 μ M)	–	[152,153]
ciclopirox	mTOR inhibitor translation initiation factor eIF5A inhibitor	human Kasumi-1, human primary AML specimens (2.5–10 μ M)	–	[149]
SC-203048	FLT3 selective inhibitor	–	human THP-1 in athymic BALB/c nude mice (10 μ g/kg 7x each 2nd day)	[162]
lactacystin	proteasome inhibitor	murine L1210 (Y8) (5 μ M)	–	[171]
rapamycin/ temsirolimus	mTOR inhibitors	human primary AML specimens (5 μ M)	human primary AML cells in NOD/SCID mice (100 mg DMAPT/kg 3x daily)	[39]
SAHA (suberoylanilide hydroxamic acid) LBH589	pan-histone deacetylase inhibitor	human U-937, human HL-60, human NB4, human MV-4-11, human MOLM-13(3–8 μ M)	–	[11]
vildagliptin	dipeptidyl peptidase IV inhibitor	human TEX, human OCI-AML2 (2.5–5 μ M)	–	[41]
wortmannin	PI3Ks inhibitor	human primary AML specimens (2.5–10 μ M)	–	[39]

Table 1. Cont.

Co-Treatment with PN	Main Mechanism of Action	In Vitro Cell Line (PN Concentration)	In Vivo Model (PN Dose)	References
Breast Cancers				
4HT (4-hydroxytamoxifen)	selective estrogen receptor modulator	human MCF7/RR, human MCF7/LCC1, human MCF7/LCC9 (0.5 μ M)	–	[106]
docetaxel	microtubules stabilizer	human HBL-100, human MDA-MB-231 (0.5–5 μ M)	human MDA-MB-231 in female nude mice (40 mg/kg daily)	[83]
doxorubicin mitoxantrone	topoisomerase II inhibitor	human MDA-MB-231 (1–10 μ M)	–	[117]
faslodex (fulvestrant)	estrogen receptor down-regulator	human MCF7/LCC9 (0.6 μ M)	–	[110]
paclitaxel (Taxol)	microtubules stabilizer	human MDA-MB-231 (0.1–5 μ M)	–	[76]
SAHA	pan-histone deacetylase inhibitor	human MDA-MB-231 (2.5–25 μ M)	–	[144]
tamoxifen	selective estrogen receptor modulator	human MCF7, human MCF7/HER2, human BT-474 (1–50 μ M)	–	[103–105,107]
TRAIL (tumor necrosis factor-related apoptosis-inducing ligand)	apoptosis inducer	human MDA-MB-231 (1–5 μ M)	–	[61]
vinorelbine	microtubule assembly blocker mitosis inhibitor	human MCF7, human MDA-MB-231 (0.5–10 μ M)	human MCF7 in female BALB/c nude mice (10 mg/kg 5th and 8th day after inoculation)	[87]

Table 1. Cont.

Co-Treatment with PN	Main Mechanism of Action	In Vitro Cell Line (PN Concentration)	In Vivo Model (PN Dose)	References
Colorectal Cancers				
5-fluorouracil	thymidylate synthase inhibitor	human SW620 (10 µM)	human SW620 in nude mice (2.5 mg/kg 3x weekly)	[132]
balsalazide	anti-inflammatory agent	human HCT116, human SW480, human HT-29 (5–10 µM)	azoxymethane-induced CAC in BALB/c female mice (2 mg/kg 3x weekly)	[100,101]
sabarubicin	topoisomerase II inhibitor	human HCT116 (10–20 µM)	–	[116]
TRAIL	apoptosis inducer	human HT-29, human HCT116 (10 µM)	–	[91]
trichostatin A	histone deacetylase inhibitor	human HT-29 (10 µM)	–	[147]
Thoracic Cancers				
oxaliplatin	inter- and intra-strand DNA cross-linker	human A549 (10–500 µM)	–	[127]
paclitaxel (Taxol)	microtubules stabilizer	human A549, H446, human A549-T24, human H460 (5 µM)	human A549 and H460 in athymic nude mice (5 mg/kg 3x weekly)	[79,81,82]
valproic acid	histone deacetylase inhibitor nitric oxide synthase inhibitor	human TE2, human TE12, human H322, human H460, human H513, human H211 (20–30 µM)	–	[142]
Pancreatic Cancers				
actinomycin-D	RNA polymerase inhibitor	human PANC-1 (3–24 µM DMAPT)	–	[168]
ATO	reactive oxygen species inducer	human PANC-1, human BxPC-3 (2.5–5 µM)	human PANC-1 in athymic nude mice (0.8 mM/25 µL 2x weekly)	[158]

Table 1. Cont.

Co-Treatment with PN	Main Mechanism of Action	In Vitro Cell Line (PN Concentration)	In Vivo Model (PN Dose)	References
celecoxib	COX-2 inhibitor	–	cancer induced in hamster by N-nitroso bis(2-oxopropyl) amine (20–40 mg DMAPT/kg daily)	[97]
gemcitabine	ribonucleotide reductase inhibitor	human BxPC-3, human PANC-1, human MIA PaCa-2 (1–10 μ M DMAPT)	–	[136]
sulindac	prostaglandin synthesis inhibitor	human BxPC-3, human PANC-1, human MIA PaCa-2 (2.5–10 μ M)	–	[94]
Melanomas				
DTIC (dacarbazine)	DNA alkylator	human A-375, patient derived melanoma (3–24 μ M)	–	[26]
doxorubicin	topoisomerase II inhibitor	human A-375, human 1205Lu, patient derived melanoma (10–24 μ M)	–	[36]
Hepatomas				
5-fluorouracil	thymidylate synthase inhibitor	human BEL-7402 (5–100 μ M)	–	[133]
fenretinide	reactive oxygen species inducer	human Hep 3B, human SK-HEP-1 (4 μ M)	–	[154]
NS398	COX-2 inhibitor	human Hep 3B, human Hep G2, human PLC (5 μ M)	–	[98]
Ro317549	protein kinase C-alpha inhibitor	human Choi-CK, human Cho-CK, human JCK1, human SCK (10–40 μ M)	human Choi-CK and human SCK in BALB/cByJ-Hfh11 ^{null} nude mice (2.5 mg/kg daily)	[165]
IIITRAIL	apoptosis inducer	human Hep 3B, human Hep G2, human SK-HEP-1 (15 μ M)	–	[6]
Brain Malignancies				
5-aza-2'-deoxycytidine	DNA methyltransferase 1 inhibitor	human Daoy, human D283 Med (2–5 μ M)	–	[129]

Table 1. Cont.

Co-Treatment with PN	Main Mechanism of Action	In Vitro Cell Line (PN Concentration)	In Vivo Model (PN Dose)	References
cisplatin	inter- and intra-strand DNA cross-linker	rat C6, human U-138 MG (10–25 μ M), human U-118 MG (1.875–60 μ M ACT001)	human U-118 MG in female nude BALB/c mice (200 mg ACT001/kg 6x each 7th day)	[115,128]
DHEA (dehydroepiandrosterone)	NF- κ B signaling pathway inhibitor	murine AtT-20 (1–10 μ M)	male BALB/c nude mice (200 μ g/mouse daily)	[112]
doxorubicin	topoisomerase II inhibitor	rat C6, human U-138 MG (10–25 μ M)	–	[115]
temozolomide	DNA alkylator	human LN-18, human T98G (10 μ M)	human T98G in SCID mice (2.5–10 mg/kg daily)	[124]
Gastric Cancers				
cisplatin	inter- and intra-strand DNA cross-linker	human MKN-28, human MKN-45, human MKN-74/5-15 μ M, human SGC-7901 (5–10 μ M)	–	[27,34]
paclitaxel	microtubules stabilizer	human MKN-28, human MKN-45, human MKN-74 (3–9 μ M)	human MKN-45 in female BALBc nu/nu mice (0.25–4 mg/kg daily)	[34]
Other Cancers				
ganciclovir Burkitt's lymphoma	DNA polymerases inhibitor	human Raji (4–6 μ M)	–	[28]
bicalutamide prostate cancer	androgen receptor blocker	–	human CWR22Rv1 in nude athymic mice (40 mg/kg daily)	[32]
Docetaxel prostate cancer	microtubules stabilizer	human CWR22Rv1 (0.5–10 μ M)	human CWR22Rv1 in nude athymic mice (40 mg/kg daily)	[32]
geldanamycin ovarian carcinoma	Hsp90 inhibitor	human OVCAR-3, human SK-OV-3 (1–8 μ M)	–	[164]
OKA (okadaic acid) retinoblastoma	phosphoserine/threonine protein phosphatase 1 and 2a inhibitor	human Y79 (0.25–0.5 μ M)	–	[160]

4HT, 4-hydroxytamoxifen; AML, acute myeloid leukemia; ATO, arsenic trioxide; ATRA, all-trans retinoic acid; BALB/cByJ-Hfh11^{null}, nude mice, Daejeon, South Korea; CAC, colitis-associated colon cancers; COX, cyclooxygenase; DHEA, dehydroepiandrosterone; DTIC, dacarbazine; FLT3, FMS-like tyrosine kinase 3; Hsp90, heat shock protein 90; mTOR, mammalian target of rapamycin; NF- κ B, nuclear transcription factor-kappa B; NOD/SCID mice, nonobese diabetic/severe combined immunodeficient mice; NSCLC, non-small-cell lung cancer; OKA, okadaic acid; PI3K, phosphoinositide 3-kinases; SAHA, suberoylanilide hydroxamic acid; SCID, severe combined immunodeficiency; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand.

Table 2. Clinical evaluation of activity of PN and its derivatives.

	Phase	Purpose	Clinical Trial Registry
PN	I	pharmacokinetics and toxicity	none [18]
DMAPT	I	AML, ALL, and other blood-lymph tumors	none [unpublished] (United Kingdom)
ACT001	I/II	safety, tolerability, pharmacokinetics, recurrent glioblastoma	ACTRN12616000228482 (Australia & New Zealand) ChiCTR-OIC-17013604 (China)

In a phase I dose escalation trial, PN given daily as an oral Feverfew tablet was well tolerated without dose-limiting toxicity but did not provide detectable plasma concentrations [18]. ACT001 (dimethylamino-micheliolide (DMAMCL) fumarate salt) developed by Accendatech Co was certified by Food and Drug Administration (FDA) and European Medicines Agency (EMA) as an orphan drug for the treatment of gliomas, and it is used in the clinical trials in Australia [201] and China. Besides new derivatives of PN with better bioavailability, alternative delivering systems are in the focus of current research. Encapsulation into the micelles, drug-loaded nano-vectors or nanographene delivery [16,203–206] might allow to exploit the full spectrum of the anticancer activities of PN and may be crucial for the development of new combination therapies.

Finally, it is worth mentioning that a potent anti-inflammatory activity of PN also contributes to the scientific interest in this compound [2,207,208]. Most recently, PN has been suggested for clinical evaluation as a part of anti-cytokine storm therapy in patients with pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [209].

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Abbreviations

5-FU	5-fluorouracil
ABCB5	ATP-binding cassette sub-family B member-5
AML	acute myeloid leukemia
ATM	ataxia telangiectasia mutated serine/threonine kinase
ATRA	all-trans retinoic acid
BL	Burkitt lymphoma
CAC	colitis-associated colon cancer
CC	cholangiocarcinoma
COX	cyclooxygenase
CRC	colorectal cancer
DHEA	dehydroepiandrosterone
DMAPT	dimethylamino-parthenolide
DNMT1	DNA methyltransferase 1
Dox	doxorubicin
DR	death receptor
DTIC	dacarbazine
EBV	Epstein-Barr virus
ER	estrogen receptor
FLT3	FMS-like tyrosine kinase 3
GBM	glioblastoma multiforme
GSH	glutathione in reduced state

HCC	hepatocellular carcinoma
HDAC1	histone deacetylase 1
HDACIs	histone deacetylase inhibitors
HSP	heat-shock proteins
IκB	inhibitor-of-κB
IKK	IκB complex kinase
JNK	c-Jun N-terminal kinase
MDM2	mouse double minute 2 homolog
MGMT	O6-methylguanine-DNA methyltransferase
MITF	microphthalmia-associated transcription factor
MMP9	matrix metalloproteinase 9
Mn-SOD	manganese superoxide dismutase
NF-κB	nuclear transcription factor-kappa B
NSAID	nonsteroidal anti-inflammatory drugs
NSCLC	non-small-cell lung cancer
PARP	poly (ADP-ribose) polymerase
PN	parthenolide
ROS	reactive oxygen species
SAHA	suberoylanilide hydroxamic acid, vorinostat
SP	side-population of cells
TNF-α	tumor necrosis factor α
TRAIL	tumor necrosis factor-related apoptosis-inducing ligand
TRAMP	transgenic adenocarcinoma of the mouse prostate
VEGF	vascular endothelial growth factor

References

- Bork, P.M.; Schmitz, M.L.; Kuhnt, M.; Escher, C.; Heinrich, M. Sesquiterpene lactone containing Mexican Indian medical plants and pure sesquiterpene lactones as potent inhibitors of transcription factor NF-κB. *FEBS Lett.* **1997**, *402*, 85–90. [[CrossRef](#)]
- Juliana, C.; Fernandes-Alnemri, T.; Wu, J.; Datta, P.; Solorzano, L.; Yu, J.W.; Meng, R.; Quong, A.A.; Latz, E.; Scott, C.P.; et al. Anti-inflammatory compounds parthenolide and Bay 11-7082 are direct inhibitors of the inflammasome. *J. Biol. Chem.* **2010**, *285*, 9792–9802. [[CrossRef](#)] [[PubMed](#)]
- Shah, V.O.; Ferguson, J.E.; Hunsaker, L.A.; Deck, L.M.; Vander Jagt, D.L. Natural products inhibit LPS-induced activation of pro-inflammatory cytokines in peripheral blood mononuclear cells. *Nat. Prod. Res.* **2010**, *24*, 1177–1188. [[CrossRef](#)] [[PubMed](#)]
- Di Cesare Mannelli, L.; Tenci, B.; Zanardelli, M.; Maidecchi, A.; Lugli, A.; Mattoli, L.; Ghelardini, C. Widespread pain reliever profile of a flower extract of *Tanacetum parthenium*. *Phytomedicine* **2015**, *22*, 752–758. [[CrossRef](#)]
- Ghantous, A.; Gali-Muhtasib, H.; Vuorela, H.; Saliba, N.A.; Darwiche, N. What made sesquiterpene lactones reach cancer clinical trials? *Drug Discov. Today* **2007**, *15*, 668–678. [[CrossRef](#)]
- Carlisi, D.; D'Anneo, A.; Angileri, L.; Lauricella, M.; Emanuele, S.; Santulli, A.; Vento, R.; Tesoriere, G. Parthenolide sensitizes hepatocellular carcinoma cells to TRAIL by inducing the expression of death receptors through inhibition of STAT3 activation. *J. Cell. Physiol.* **2011**, *226*, 1632–1641. [[CrossRef](#)]
- Wen, J.; You, K.R.; Lee, S.Y.; Song, C.H.; Kim, D.G. Oxidative stress-mediated apoptosis. The anticancer effect of the sesquiterpene lactone parthenolide. *J. Biol. Chem.* **2002**, *277*, 38954–38964. [[CrossRef](#)]
- Zunino, S.J.; Ducore, J.M.; Storms, D.H. Parthenolide induces significant apoptosis and production of reactive oxygen species in high-risk pre-B leukemia cells. *Cancer Lett.* **2007**, *254*, 119–127. [[CrossRef](#)]
- Duechler, M.; Stanczyk, M.; Czyz, M.; Stepnik, M. Potentiation of arsenic trioxide cytotoxicity by Parthenolide and buthionine sulfoximine in murine and human leukemic cells. *Cancer Chemother. Pharmacol.* **2008**, *61*, 727–737. [[CrossRef](#)]
- Suvannasankha, A.; Crean, C.D.; Shanmugam, R.; Farag, S.S.; Abonour, R.; Boswell, H.S.; Nakshatri, H. Antimyeloma effects of a sesquiterpene lactone parthenolide. *Clin. Cancer Res.* **2008**, *14*, 1814–1822. [[CrossRef](#)]

11. Dai, Y.; Guzman, M.L.; Chen, S.; Wang, L.; Yeung, S.K.; Pei, X.Y.; Dent, P.; Jordan, C.T.; Grant, S. The NF (Nuclear factor)- κ B inhibitor parthenolide interacts with histone deacetylase inhibitors to induce MKK7/JNK1-dependent apoptosis in human acute myeloid leukaemia cells. *Br. J. Haematol.* **2010**, *151*, 70–83. [[CrossRef](#)]
12. Czyz, M.; Lesiak-Mieczkowska, K.; Koprowska, K.; Szulawska-Mroczek, A.; Wozniak, M. Cell context-dependent activities of parthenolide in primary and metastatic melanoma cells. *Br. J. Pharmacol.* **2010**, *160*, 1144–1157. [[CrossRef](#)] [[PubMed](#)]
13. Lesiak, K.; Koprowska, K.; Zalesna, I.; Nejc, D.; D uchler, M.; Czyz, M. Parthenolide, a sesquiterpene lactone from the medical herb feverfew, shows anticancer activity against human melanoma cells in vitro. *Melanoma Res.* **2010**, *20*, 21–34. [[CrossRef](#)] [[PubMed](#)]
14. Czyz, M.; Koprowska, K.; Sztiller-Sikorska, M. Parthenolide reduces the frequency of ABCB5-positive cells and clonogenic capacity of melanoma cells from anchorage independent melanospheres. *Cancer Biol. Ther.* **2013**, *14*, 135–145. [[CrossRef](#)]
15. Ren, Y.; Yu, J.; Kinghorn, A.D. Development of Anticancer Agents from Plant-Derived Sesquiterpene Lactones. *Curr. Med. Chem.* **2016**, *23*, 2397–2420. [[CrossRef](#)]
16. Baranello, M.P.; Bauer, L.; Jordan, C.T.; Benoit, D.S.W. Micelle Delivery of Parthenolide to Acute Myeloid Leukemia Cells. *Cell. Mol. Bioeng.* **2015**, *8*, 455–470. [[CrossRef](#)]
17. Carlisi, D.; Buttitta, G.; Di Fiore, R.; Scerri, C.; Drago-Ferrante, R.; Vento, R.; Tesoriere, G. Parthenolide and DMAPT exert cytotoxic effects on breast cancer stem-like cells by inducing oxidative stress, mitochondrial dysfunction and necrosis. *Cell Death Dis.* **2016**, *7*, e2194. [[CrossRef](#)]
18. Curry, E.A., III; Murry, D.J.; Yoder, C.; Fife, K.; Armstrong, V.; Nakshatri, H.; O’Connell, M.; Sweeney, C.J. Phase I dose escalation trial of feverfew with standardized doses of parthenolide in patients with cancer. *Invest. New Drugs* **2004**, *22*, 299–305. [[CrossRef](#)] [[PubMed](#)]
19. D’Anneo, A.; Carlisi, D.; Lauricella, M.; Puleio, R.; Martinez, R.; Di Bella, S.; Di Marco, P.; Emanuele, S.; Di Fiore, R.; Guercio, A.; et al. Parthenolide generates reactive oxygen species and autophagy in MDA-MB231 cells. A soluble parthenolide analogue inhibits tumour growth and metastasis in a xenograft model of breast cancer. *Cell Death Dis.* **2013**, *4*, e891. [[CrossRef](#)] [[PubMed](#)]
20. Gopal, Y.N.; Arora, T.S.; Van Dyke, M.W. Parthenolide specifically depletes histone deacetylase 1 protein and induces cell death through ataxia telangiectasia mutated. *Chem. Biol.* **2007**, *14*, 813–823. [[CrossRef](#)]
21. Gopal, Y.N.; Chanchorn, E.; Van Dyke, M.W. Parthenolide promotes the ubiquitination of MDM2 and activates p53 cellular functions. *Mol. Cancer Ther.* **2009**, *8*, 552–562. [[CrossRef](#)]
22. Guzman, M.L.; Rossi, R.M.; Karnischky, L.; Li, X.; Peterson, D.R.; Howard, D.S.; Jordan, C.T. The sesquiterpene lactone parthenolide induces apoptosis of human acute myelogenous leukemia stem and progenitor cells. *Blood* **2005**, *105*, 4163–4169. [[CrossRef](#)] [[PubMed](#)]
23. Hartman, M.L.; Talar, B.; Sztiller-Sikorska, M.; Nejc, D.; Czyz, M. Parthenolide induces MITF-M downregulation and senescence in patient-derived MITF-M (high) melanoma cell populations. *Oncotarget* **2016**, *7*, 9026–9040. [[CrossRef](#)] [[PubMed](#)]
24. Kim, J.H.; Liu, L.; Lee, S.O.; Kim, Y.T.; You, K.R.; Kim, D.G. Susceptibility of cholangiocarcinoma cells to parthenolide-induced apoptosis. *Cancer Res.* **2005**, *65*, 6312–6320. [[CrossRef](#)] [[PubMed](#)]
25. Kim, S.L.; Liu, Y.C.; Park, Y.R.; Seo, S.Y.; Kim, S.H.; Kim, I.H.; Lee, S.O.; Lee, S.T.; Kim, D.G.; Kim, S.W. Parthenolide enhances sensitivity of colorectal cancer cells to TRAIL by inducing death receptor 5 and promotes TRAIL-induced apoptosis. *Int. J. Oncol.* **2015**, *46*, 1121–1130. [[CrossRef](#)]
26. Koprowska, K.; Hartman, M.L.; Sztiller-Sikorska, M.; Czyz, M.E. Parthenolide enhances dacarbazine activity against melanoma cells. *Anticancer Drugs* **2013**, *24*, 835–845. [[CrossRef](#)]
27. Li, H.; Lu, H.; Lv, M.; Wang, Q.; Sun, Y. Parthenolide facilitates apoptosis and reverses drug-resistance of human gastric carcinoma cells by inhibiting the STAT3 signaling pathway. *Oncol. Lett.* **2018**, *15*, 3572–3579. [[CrossRef](#)]
28. Li, Y.; Zhang, Y.; Fu, M.; Yao, Q.; Zhuo, H.; Lu, Q.; Niu, X.; Zhang, P.; Pei, Y.; Zhang, K. Parthenolide induces apoptosis and lytic cytotoxicity in Epstein-Barr virus-positive Burkitt lymphoma. *Mol. Med. Rep.* **2012**, *6*, 477–482. [[CrossRef](#)]
29. Liu, M.; Xiao, C.; Sun, M.; Tan, M.; Hu, L.; Yu, Q. Parthenolide Inhibits STAT3 Signaling by Covalently Targeting Janus Kinases. *Molecules* **2018**, *23*, E1478. [[CrossRef](#)]

30. Mendonca, M.S.; Chin-Sinex, H.; Gomez-Millan, J.; Datzman, N.; Hardacre, M.; Comerford, K.; Nakshatri, H.; Nye, M.; Benjamin, L.; Mehta, S.; et al. PN sensitizes cells to X-ray-induced cell killing through inhibition of NF-kappaB and split-dose repair. *Radiat. Res.* **2007**, *168*, 689–697. [[CrossRef](#)]
31. Morel, K.L.; Ormsby, R.J.; Bezak, E.; Sweeney, C.J.; Sykes, P.J. Parthenolide Selectively Sensitizes Prostate Tumor Tissue to Radiotherapy while Protecting Healthy Tissues In Vivo. *Radiat. Res.* **2017**, *187*, 501–512. [[CrossRef](#)] [[PubMed](#)]
32. Shanmugam, R.; Jayaprakasan, V.; Gokmen-Polar, Y.; Kelich, S.; Miller, K.D.; Yip-Schneider, M.; Cheng, L.; Bhat-Nakshatri, P.; Sledge, G.W., Jr.; Nakshatri, H.; et al. Restoring chemotherapy and hormone therapy sensitivity by parthenolide in a xenograft hormone refractory prostate cancer model. *Prostate* **2006**, *66*, 1498–1511. [[CrossRef](#)] [[PubMed](#)]
33. Sobota, R.; Szwed, M.; Kasza, A.; Bugno, M.; Kordula, T. Parthenolide inhibits activation of signal transducers and activators of transcription (STATs) induced by cytokines of the IL-6 family. *Biochem. Biophys. Res. Commun.* **2000**, *267*, 329–333. [[CrossRef](#)] [[PubMed](#)]
34. Sohma, I.; Fujiwara, Y.; Sugita, Y.; Yoshioka, A.; Shirakawa, M.; Moon, J.H.; Takiguchi, S.; Miyata, H.; Yamasaki, M.; Mori, M.; et al. Parthenolide, an NF-κB inhibitor, suppresses tumor growth and enhances response to chemotherapy in gastric cancer. *Cancer Genomics Proteomics* **2011**, *8*, 39–47.
35. Sun, Y.; St Clair, D.K.; Xu, Y.; Crooks, P.A.; St Clair, W.H. A NADPH oxidase-dependent redox signaling pathway mediates the selective radiosensitization effect of parthenolide in prostate cancer cells. *Cancer Res.* **2010**, *70*, 2880–2890. [[CrossRef](#)]
36. Wozniak, M.; Szulawska-Mroczek, A.; Hartman, M.L.; Nejc, D.; Czyz, M. Parthenolide complements the cell death-inducing activity of doxorubicin in melanoma cells. *Anticancer Res.* **2013**, *33*, 3205–3212.
37. Yang, C.; Yang, Q.O.; Kong, Q.J.; Yuan, W.; Ou Yang, Y.P. Parthenolide Induces Reactive Oxygen Species-Mediated Autophagic Cell Death in Human Osteosarcoma Cells. *Cell. Physiol. Biochem.* **2016**, *40*, 146–154. [[CrossRef](#)]
38. Zhang, S.; Ong, C.N.; Shen, H.M. Critical roles of intracellular thiols and calcium in parthenolide-induced apoptosis in human colorectal cancer cells. *Cancer Lett.* **2004**, *208*, 143–153. [[CrossRef](#)]
39. Hassane, D.C.; Sen, S.; Minhajuddin, M.; Rossi, R.M.; Corbett, C.A.; Balys, M.; Wei, L.; Crooks, P.A.; Guzman, M.L.; Jordan, C.T. Chemical genomic screening reveals synergism between parthenolide and inhibitors of the PI-3 kinase and mTOR pathways. *Blood* **2010**, *116*, 5983–5990. [[CrossRef](#)]
40. Diamanti, P.; Cox, C.V.; Moppett, J.P.; Blair, A. Parthenolide eliminates leukemia-initiating cell populations and improves survival in xenografts of childhood acute lymphoblastic leukemia. *Blood* **2013**, *121*, 1384–1393. [[CrossRef](#)]
41. Spagnuolo, P.A.; Hurren, R.; Gronda, M.; MacLean, N.; Datti, A.; Basheer, A.; Lin, F.H.; Wang, X.; Wrana, J.; Schimmer, A.D. Inhibition of intracellular dipeptidyl peptidases 8 and 9 enhances parthenolide's anti-leukemic activity. *Leukemia* **2013**, *27*, 1236–1244. [[CrossRef](#)] [[PubMed](#)]
42. Siveen, K.S.; Uddin, S.; Mohammad, R.M. Targeting acute myeloid leukemia stem cell signaling by natural products. *Mol. Cancer* **2017**, *16*, 13. [[CrossRef](#)] [[PubMed](#)]
43. Guzman, M.L.; Rossi, R.M.; Neelakantan, S.; Li, X.; Corbett, C.A.; Hassane, D.C.; Becker, M.W.; Bennett, J.M.; Sullivan, E.; Lachowicz, J.L.; et al. An orally bioavailable parthenolide analog selectively eradicates acute myelogenous leukemia stem and progenitor cells. *Blood* **2007**, *110*, 4427–4435. [[CrossRef](#)] [[PubMed](#)]
44. Kawasaki, B.T.; Hurt, E.M.; Kalathur, M.; Duhagon, M.A.; Milner, J.A.; Kim, Y.S.; Farrar, W.L. Effects of the sesquiterpene lactone parthenolide on prostate tumor initiating cells: An integrated molecular profiling approach. *Prostate* **2009**, *69*, 827–837. [[CrossRef](#)]
45. Zhou, J.; Zhang, H.; Gu, P.; Bai, J.; Margolick, J.B.; Zhang, Y. NF-kappaB pathway inhibitors preferentially inhibit breast cancer stem-like cells. *Breast Cancer Res. Treat.* **2008**, *111*, 419–427. [[CrossRef](#)]
46. Flores-Lopez, G.; Moreno-Lorenzana, D.; Ayala-Sanchez, M.; Aviles-Vazquez, S.; Torres-Martinez, H.; Crooks, P.A.; Guzman, M.L.; Mayani, H.; Chávez-González, A. Parthenolide and DMAPT induce cell death in primitive CML cells through reactive oxygen species. *J. Cell Mol. Med.* **2018**, *22*, 4899–4912. [[CrossRef](#)]
47. Neelakantan, S.; Nasim, S.; Guzman, M.L.; Jordan, C.T.; Crooks, P.A. Aminoparthenolides as novel anti-leukemic agents: Discovery of the NF-kappaB inhibitor, DMAPT (LC-1). *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4346–4349. [[CrossRef](#)]

48. Song, J.M.; Qian, X.; Upadhyayya, P.; Hong, K.H.; Kassie, F. Dimethylaminoparthenolide, a water soluble parthenolide, suppresses lung tumorigenesis through down-regulating the STAT3 signaling pathway. *Curr. Cancer Drug Targets* **2014**, *14*, 59–69. [[CrossRef](#)]
49. Nakshatri, H.; Appaiah, H.N.; Anjanappa, M.; Gilley, D.; Tanaka, H.; Badve, S.; Crooks, P.A.; Mathews, W.; Sweeney, C.; Bhat-Nakshatri, P. NF-kappa B-dependent and -independent epigenetic modulation using the novel anti-cancer agent DMAPT. *Cell Death Dis.* **2015**, *6*, e1608. [[CrossRef](#)]
50. Penthala, N.R.; Janganati, V.; Alpe, T.L.; Apana, S.M.; Berridge, M.S.; Crooks, P.A.; Borrelli, M.J. N-[11CH3] Dimethylaminoparthenolide (DMAPT) uptake into orthotopic 9LSF glioblastoma tumors in the rat. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 5883–5886. [[CrossRef](#)]
51. Kwok, B.H.; Koh, B.; Ndubuisi, M.I.; Elofsson, M.; Crews, C.M. The anti-inflammatory natural product parthenolide from the medicinal herb Feverfew directly binds to and inhibits I kappa B kinase. *Chem. Biol.* **2001**, *8*, 759–766. [[CrossRef](#)]
52. Nagel, D.; Vincendeau, M.; Eitelhuber, A.C.; Krappmann, D. Mechanisms and consequences of constitutive NF-κB activation in B-cell lymphoid malignancies. *Oncogene* **2014**, *33*, 5655–5665. [[CrossRef](#)] [[PubMed](#)]
53. de Oliveira, K.A.; Kaergel, E.; Heinig, M.; Fontaine, J.F.; Patone, G.; Muro, E.M.; Mathas, S.; Hummel, M.; Andrade-Navarro, M.A.; Hübner, N.; et al. A roadmap of constitutive NF-κB activity in Hodgkin lymphoma: Dominant roles of p50 and p52 revealed by genome-wide analyses. *Genome Med.* **2016**, *8*, 28. [[CrossRef](#)]
54. Thu, Y.M.; Su, Y.; Yang, J.; Splittgerber, R.; Na, S.; Boyd, A.; Mosse, C.; Simons, C.; Richmond, A. NF-κB inducing kinase (NIK) modulates melanoma tumorigenesis by regulating expression of pro-survival factors through the β-catenin pathway. *Oncogene* **2012**, *31*, 2580–2592. [[CrossRef](#)] [[PubMed](#)]
55. Tilborgs, S.; Corthouts, J.; Verhoeven, Y.; Arias, D.; Rolfo, C.; Trinh, X.B.; van Dam, P.A. The role of Nuclear Factor-kappa B signaling in human cervical cancer. *Crit. Rev. Oncol. Hematol.* **2017**, *120*, 141–150. [[CrossRef](#)] [[PubMed](#)]
56. Baldwin, A.S. Control of oncogenesis and cancer therapy resistance by the transcription factor NF-κB. *J. Clin. Investig.* **2001**, *107*, 241–246. [[CrossRef](#)]
57. Wang, Z.; Zhao, X.; Wang, W.; Liu, Y.; Li, Y.; Gao, J.; Wang, C.; Zhou, M.; Liu, R.; Xu, G.; et al. ZBTB7 evokes 5-fluorouracil resistance in colorectal cancer through the NF-κB signaling pathway. *Int. J. Oncol.* **2018**, *53*, 2102–2110. [[CrossRef](#)]
58. Tian, M.; Tian, D.; Qiao, X.; Li, J.; Zhang, L. Modulation of Myb-induced NF-κB -STAT3 signaling and resulting cisplatin resistance in ovarian cancer by dietary factors. *J. Cell. Physiol.* **2019**, *234*, 21126–21134. [[CrossRef](#)]
59. García-Piñeres, A.J.; Lindenmeyer, M.T.; Merfort, I. Role of cysteine residues of p65/NF-kappaB on the inhibition by the sesquiterpene lactone parthenolide and N-ethyl maleimide, and on its transactivating potential. *Life Sci.* **2004**, *75*, 841–856. [[CrossRef](#)]
60. Zhang, S.; Lin, Z.N.; Yang, C.F.; Shi, X.; Ong, C.N.; Shen, H.M. Suppressed NF-kappaB and sustained JNK activation contribute to the sensitization effect of parthenolide to TNF-alpha-induced apoptosis in human cancer cells. *Carcinogenesis* **2004**, *25*, 2191–2199. [[CrossRef](#)]
61. Nakshatri, H.; Rice, S.E.; Bhat-Nakshatri, P. Antitumor agent parthenolide reverses resistance of breast cancer cells to tumor necrosis factor-related apoptosis-inducing ligand through sustained activation of c-Jun N-terminal kinase. *Oncogene* **2004**, *23*, 7330–7344. [[CrossRef](#)] [[PubMed](#)]
62. Schnyder, B.; Schnyder-Candrian, S.; Panski, A.; Bömmel, H.; Heim, M.; Duschl, A.; Moser, R. Phytochemical inhibition of interleukin-4-activated Stat6 and expression of VCAM-1. *Biochem. Biophys. Res. Commun.* **2002**, *292*, 841–847. [[CrossRef](#)] [[PubMed](#)]
63. Li, X.; Kong, L.; Yang, Q.; Duan, A.; Ju, X.; Cai, B.; Chen, L.; An, T.; Li, Y. Parthenolide inhibits ubiquitin-specific peptidase 7 (USP7), Wnt signaling, and colorectal cancer cell growth. *J. Biol. Chem.* **2020**, *295*, 3576–3589. [[CrossRef](#)] [[PubMed](#)]
64. Wang, W.; Adachi, M.; Kawamura, R.; Sakamoto, H.; Hayashi, T.; Ishida, T.; Imai, K.; Shinomura, Y. Parthenolide-induced apoptosis in multiple myeloma cells involves reactive oxygen species generation and cell sensitivity depends on catalase activity. *Apoptosis* **2006**, *11*, 2225–2235. [[CrossRef](#)]
65. Fonrose, X.; Ausseil, F.; Soleilhac, E.; Masson, V.; David, B.; Pouny, I.; Cintrat, J.C.; Rousseau, B.; Barette, C.; Massiot, G.; et al. Parthenolide inhibits tubulin carboxypeptidase activity. *Cancer Res.* **2007**, *67*, 3371–3378. [[CrossRef](#)]

66. Freund, R.R.A.; Gobrecht, P.; Rao, Z.; Gerstmeier, J.; Schlosser, R.; Görls, H.; Werz, O.; Fischer, D.; Arndt, H.D. Stereoselective total synthesis of parthenolides indicates target selectivity for tubulin carboxypeptidase activity. *Chem. Sci.* **2019**, *10*, 7358–7364. [[CrossRef](#)]
67. Liu, Z.; Liu, S.; Xie, Z.; Pavlovicz, R.E.; Wu, J.; Chen, P.; Aimiwu, J.; Pang, J.; Bhasin, D.; Neviani, P.; et al. Modulation of DNA methylation by a sesquiterpene lactone parthenolide. *J. Pharmacol. Exp. Ther.* **2009**, *329*, 505–514. [[CrossRef](#)]
68. Umemura, K.; Itoh, T.; Hamada, N.; Fujita, Y.; Akao, Y.; Nozawa, Y.; Matsuura, N.; Iinuma, M.; Ito, M. Preconditioning by sesquiterpene lactone enhances H₂O₂-induced Nrf2/ARE activation. *Biochem. Biophys. Res. Commun.* **2008**, *368*, 948–954. [[CrossRef](#)]
69. Hartman, M.L.; Rozanski, M.; Osrodek, M.; Zalesna, I.; Czyz, M. Vemurafenib and trametinib reduce expression of CTGF and IL-8 in V600EBRAF melanoma cells. *Lab. Invest.* **2017**, *97*, 217–227. [[CrossRef](#)]
70. Braig, S.; Wallner, S.; Junglas, B.; Fuchshofer, R.; Bosserhoff, A.K. CTGF is overexpressed in malignant melanoma and promotes cell invasion and migration. *Br. J. Cancer.* **2011**, *105*, 231–238. [[CrossRef](#)]
71. Rowinsky, E.K. The development and clinical utility of the taxane class of antimicrotubule chemotherapy agents. *Annu. Rev. Med.* **1997**, *48*, 353–374. [[CrossRef](#)] [[PubMed](#)]
72. Joerger, M. Treatment regimens of classical and newer taxanes. *Cancer Chemother. Pharmacol.* **2016**, *77*, 221–233. [[CrossRef](#)] [[PubMed](#)]
73. Ojima, I.; Lichtenthal, B.; Lee, S.; Wang, C.; Wang, X. Taxane anticancer agents: A patent perspective. *Expert Opin. Ther. Pat.* **2016**, *26*, 1–20. [[CrossRef](#)] [[PubMed](#)]
74. Mekhail, T.M.; Markman, M. Paclitaxel in cancer therapy. *Expert Opin. Pharmacother.* **2002**, *3*, 755–766. [[PubMed](#)]
75. Jordan, M.A.; Wilson, L. Microtubules as a target for anticancer drugs. *Nat. Rev. Cancer* **2004**, *4*, 253–265. [[CrossRef](#)]
76. Patel, N.M.; Nozaki, S.; Shortle, N.H.; Bhat-Nakshatri, P.; Newton, T.R.; Rice, S.; Gelfanov, V.; Boswell, S.H.; Goulet, R.J., Jr.; Sledge, G.W., Jr.; et al. Paclitaxel sensitivity of breast cancer cells with constitutively active NF- κ B is enhanced by IkappaBalpha super-repressor and parthenolide. *Oncogene* **2000**, *19*, 4159–4169. [[CrossRef](#)]
77. Riedel, R.F.; Porrello, A.; Pontzer, E.; Chenette, E.J.; Hsu, D.S.; Balakumaran, B.; Potti, A.; Nevins, J.; Febbo, P.G. A genomic approach to identify molecular pathways associated with chemotherapy resistance. *Mol. Cancer Ther.* **2008**, *7*, 3141–3149. [[CrossRef](#)]
78. O'Neill, A.J.; Prencipe, M.; Dowling, C.; Fan, Y.; Mulrane, L.; Gallagher, W.M.; O'Connor, D.; O'Connor, R.; Devery, A.; Corcoran, C.; et al. Characterisation and manipulation of docetaxel resistant prostate cancer cell lines. *Mol. Cancer* **2011**, *10*, 126. [[CrossRef](#)]
79. Gao, Z.W.; Zhang, D.L.; Guo, C.B. Paclitaxel efficacy is increased by parthenolide via nuclear factor- κ B pathways in in vitro and in vivo human non-small cell lung cancer models. *Curr. Cancer Drug Targets* **2010**, *10*, 705–715. [[CrossRef](#)]
80. Jin, X.; Qiu, L.; Zhang, D.; Zhang, M.; Wang, Z.; Guo, Z.; Deng, C.; Guo, C. Chemosensitization in non-small cell lung cancer cells by IKK inhibitor occurs via NF- κ B and mitochondrial cytochrome c cascade. *J. Cell. Mol. Med.* **2009**, *13*, 4596–4607. [[CrossRef](#)]
81. Zhang, D.; Qiu, L.; Jin, X.; Guo, Z.; Guo, C. Nuclear factor- κ B inhibition by parthenolide potentiates the efficacy of Taxol in non-small cell lung cancer in vitro and in vivo. *Mol. Cancer Res.* **2009**, *7*, 1139–1149. [[CrossRef](#)] [[PubMed](#)]
82. Gill, K.K.; Kaddoumi, A.; Nazzal, S. Mixed micelles of PEG(2000)-DSPE and vitamin-E TPGS for concurrent delivery of paclitaxel and parthenolide: Enhanced chemosensitization and antitumor efficacy against non-small cell lung cancer (NSCLC) cell lines. *Eur. J. Pharm. Sci.* **2012**, *46*, 64–71. [[CrossRef](#)] [[PubMed](#)]
83. Sweeney, C.J.; Mehrotra, S.; Sadaria, M.R.; Kumar, S.; Shortle, N.H.; Roman, Y.; Sheridan, C.; Campbell, R.A.; Murry, D.J.; Badve, S.; et al. The sesquiterpene lactone parthenolide in combination with docetaxel reduces metastasis and improves survival in a xenograft model of breast cancer. *Mol. Cancer Ther.* **2005**, *4*, 1004–1012. [[CrossRef](#)] [[PubMed](#)]
84. Parrondo, R.; de las Pozas, A.; Reiner, T.; Rai, P.; Perez-Stable, C. NF- κ B activation enhances cell death by antimetabolic drugs in human prostate cancer cells. *Mol. Cancer* **2010**, *9*, 182. [[CrossRef](#)]
85. Xu, Y.C.; Wang, H.X.; Tang, L.; Ma, Y.; Zhang, F.C. A systematic review of vinorelbine for the treatment of breast cancer. *Breast, J.* **2013**, *19*, 180–188. [[CrossRef](#)]

86. Faller, B.A.; Pandit, T.N. Safety and efficacy of vinorelbine in the treatment of non-small cell lung cancer. *Clin. Med. Insights Oncol.* **2011**, *5*, 131–144. [[CrossRef](#)]
87. Liu, Y.; Lu, W.L.; Guo, J.; Du, J.; Li, T.; Wu, J.W.; Wang, G.L.; Wang, J.C.; Zhang, X.; Zhang, Q. A potential target associated with both cancer and cancer stem cells: A combination therapy for eradication of breast cancer using vinorelbine stealthy liposomes plus parthenolide stealthy liposomes. *J. Control. Release* **2008**, *129*, 18–25. [[CrossRef](#)]
88. Gonzalez, F.; Ashkenazi, A. New insights into apoptosis signaling by Apo2L/TRAIL. *Oncogene* **2010**, *29*, 4752–4765. [[CrossRef](#)]
89. Mert, U.; Sanlioglu, A.D. Intracellular localization of DR5 and related regulatory pathways as a mechanism of resistance to TRAIL in cancer. *Cell. Mol. Life Sci.* **2017**, *74*, 245–255. [[CrossRef](#)]
90. Trivedi, R.; Mishra, D.P. Trailing TRAIL Resistance: Novel Targets for TRAIL Sensitization in Cancer Cells. *Front. Oncol.* **2015**, *5*, 69. [[CrossRef](#)]
91. Trang, K.T.; Kim, S.L.; Park, S.B.; Seo, S.Y.; Choi, C.H.; Park, J.K.; Moon, J.C.; Lee, S.T.; Kim, S.W. Parthenolide Sensitizes Human Colorectal Cancer Cells to Tumor Necrosis Factor-related Apoptosis-inducing Ligand through Mitochondrial and Caspase Dependent Pathway. *Intest. Res.* **2014**, *12*, 34–41. [[CrossRef](#)]
92. Tang, S.C.; Chen, Y.C. Novel therapeutic targets for pancreatic cancer. *World J. Gastroenterol.* **2014**, *20*, 10825–10844. [[CrossRef](#)] [[PubMed](#)]
93. Pang, L.Y.; Hurst, E.A.; Argyle, D.J. Cyclooxygenase-2: A Role in Cancer Stem Cell Survival and Repopulation of Cancer Cells during Therapy. *Stem Cells Int.* **2016**, *2016*, 2048731. [[CrossRef](#)] [[PubMed](#)]
94. Yip-Schneider, M.T.; Nakshatri, H.; Sweeney, C.J.; Marshall, M.S.; Wiebke, E.A.; Schmidt, C.M. Parthenolide and sulindac cooperate to mediate growth suppression and inhibit the nuclear factor-kappa B pathway in pancreatic carcinoma cells. *Mol. Cancer Ther.* **2005**, *4*, 587–594. [[CrossRef](#)]
95. Yip-Schneider, M.T.; Wu, H.; Ralstin, M.; Yiannoutsos, C.; Crooks, P.A.; Neelakantan, S.; Noble, S.; Nakshatri, H.; Sweeney, C.J.; Schmidt, C.M. Suppression of pancreatic tumor growth by combination chemotherapy with sulindac and LC-1 is associated with cyclin D1 inhibition in vivo. *Mol. Cancer Ther.* **2007**, *6*, 1736–1744. [[CrossRef](#)] [[PubMed](#)]
96. Yip-Schneider, M.T.; Wu, H.; Hruban, R.H.; Lowy, A.M.; Crooks, P.A.; Schmidt, C.M. Efficacy of dimethylaminoparthenolide and sulindac in combination with gemcitabine in a genetically engineered mouse model of pancreatic cancer. *Pancreas* **2013**, *42*, 160–167. [[CrossRef](#)] [[PubMed](#)]
97. Yip-Schneider, M.T.; Wu, H.; Njoku, V.; Ralstin, M.; Holcomb, B.; Crooks, P.A.; Neelakantan, S.; Sweeney, C.J.; Schmidt, C.M. Effect of celecoxib and the novel anti-cancer agent, dimethylamino-parthenolide, in a developmental model of pancreatic cancer. *Pancreas* **2008**, *37*, e45–e53. [[CrossRef](#)]
98. Ralstin, M.C.; Gage, E.A.; Yip-Schneider, M.T.; Klein, P.J.; Wiebke, E.A.; Schmidt, C.M. Parthenolide cooperates with NS398 to inhibit growth of human hepatocellular carcinoma cells through effects on apoptosis and G0-G1 cell cycle arrest. *Mol. Cancer Res.* **2006**, *4*, 387–400. [[CrossRef](#)]
99. Baker, D.E. Safety of balsalazide therapy in the treatment of inflammatory bowel disease. *Rev. Gastroenterol. Disord.* **2005**, *5*, 135–141.
100. Kim, H.Y.; Kim, S.L.; Park, Y.R.; Liu, Y.C.; Seo, S.Y.; Kim, S.H.; Kim, I.H.; Lee, S.O.; Lee, S.T.; Kim, S.W. Balsalazide Potentiates Parthenolide-Mediated Inhibition of Nuclear Factor- κ B Signaling in HCT116 Human Colorectal Cancer Cells. *Intest. Res.* **2015**, *13*, 233–241. [[CrossRef](#)]
101. Kim, S.L.; Kim, S.H.; Park, Y.R.; Liu, Y.C.; Kim, E.M.; Jeong, H.J.; Kim, Y.N.; Seo, S.Y.; Kim, I.H.; Lee, S.O.; et al. Combined Parthenolide and Balsalazide Have Enhanced Antitumor Efficacy Through Blockade of NF- κ B Activation. *Mol. Cancer Res.* **2017**, *15*, 141–151. [[CrossRef](#)] [[PubMed](#)]
102. Clarke, R.; Liu, M.C.; Bouker, K.B.; Gu, Z.; Lee, R.Y.; Zhu, Y.; Skaar, T.C.; Gomez, B.; O'Brien, K.; Wang, Y.; et al. Antiestrogen resistance in breast cancer and the role of estrogen receptor signaling. *Oncogene* **2003**, *22*, 7316–7339. [[CrossRef](#)] [[PubMed](#)]
103. Zhou, Y.; Eppenberger-Castori, S.; Marx, C.; Yau, C.; Scott, G.K.; Eppenberger, U.; Benz, C.C. Activation of nuclear factor-kappaB (NFkappaB) identifies a high-risk subset of hormone-dependent breast cancers. *Int. J. Biochem. Cell Biol.* **2005**, *37*, 1130–1144. [[CrossRef](#)] [[PubMed](#)]
104. de Graffenried, L.A.; Chandrasekar, B.; Friedrichs, W.E.; Donzis, E.; Silva, J.; Hidalgo, M.; Freeman, J.W.; Weiss, G.R. NF-kappa B inhibition markedly enhances sensitivity of resistant breast cancer tumor cells to tamoxifen. *Ann. Oncol.* **2004**, *15*, 885–890. [[CrossRef](#)] [[PubMed](#)]

105. Zhou, Y.; Yau, C.; Gray, J.W.; Chew, K.; Dairkee, S.H.; Moore, D.H.; Eppenberger, U.; Eppenberger-Castori, S.; Benz, C.C. Enhanced NF kappa B and AP-1 transcriptional activity associated with antiestrogen resistant breast cancer. *BMC Cancer* **2007**, *7*, 59. [[CrossRef](#)] [[PubMed](#)]
106. Nehra, R.; Riggins, R.B.; Shajahan, A.N.; Zwart, A.; Crawford, A.C.; Clarke, R. BCL2 and CASP8 regulation by NF-kappaB differentially affect mitochondrial function and cell fate in antiestrogen-sensitive and resistant breast cancer cells. *FASEB J.* **2010**, *24*, 2040–2055. [[CrossRef](#)]
107. Nobert, G.S.; Kraak, M.M.; Crawford, S. Estrogen dependent growth inhibitory effects of tamoxifen but not genistein in solid tumors derived from estrogen receptor positive (ER+) MCF7: Single agent and novel combined treatment approaches. *Bull. Cancer* **2006**, *93*, E59–E66.
108. Nathan, M.R.; Schmid, P. A Review of Fulvestrant in Breast Cancer. *Oncol. Ther.* **2017**, *5*, 17–29. [[CrossRef](#)]
109. Gu, Z.; Lee, R.Y.; Skaar, T.C.; Bouker, K.B.; Welch, J.N.; Lu, J.; Liu, A.; Zhu, Y.; Davis, N.; Leonessa, F.; et al. Association of interferon regulatory factor-1, nucleophosmin, nuclear factor-kappaB, and cyclic AMP response element binding with acquired resistance to Faslodex (ICI 182,780). *Cancer Res.* **2002**, *62*, 3428–3437.
110. Riggins, R.B.; Zwart, A.; Nehra, R.; Clarke, R. The nuclear factor kappa B inhibitor parthenolide restores ICI 182,780 (Faslodex; fulvestrant)-induced apoptosis in antiestrogen-resistant breast cancer cells. *Mol. Cancer Ther.* **2005**, *4*, 33–41.
111. Aragno, M.; Mastrocola, R.; Brignardello, E.; Catalano, M.; Robino, G.; Manti, R.; Parola, M.; Danni, O.; Boccuzzi, G. Dehydroepiandrosterone modulates nuclear factor-kappaB activation in hippocampus of diabetic rats. *Endocrinology* **2002**, *143*, 3250–3258. [[CrossRef](#)]
112. Taguchi, T.; Takao, T.; Iwasaki, Y.; Nishiyama, M.; Asaba, K.; Hashimoto, K. Suppressive effects of dehydroepiandrosterone and the nuclear factor-kappaB inhibitor parthenolide on corticotroph tumor cell growth and function in vitro and in vivo. *J. Endocrinol.* **2006**, *188*, 321–331. [[CrossRef](#)]
113. Frank, N.Y.; Margaryan, A.; Huang, Y.; Schatton, T.; Waaga-Gasser, A.M.; Gasser, M.; Sayegh, M.H.; Sadee, W.; Frank, M.H. ABCB5-mediated doxorubicin transport and chemoresistance in human malignant melanoma. *Cancer Res.* **2005**, *65*, 4320–4333. [[CrossRef](#)] [[PubMed](#)]
114. Smylie, M.G.; Wong, R.; Mihalciu, C.; Lee, C.; Pouliot, J.F. A phase II, open label, monotherapy study of liposomal doxorubicin in patients with metastatic malignant melanoma. *Invest. New Drugs* **2007**, *25*, 155–159. [[CrossRef](#)]
115. Zanotto-Filho, A.; Braganhol, E.; Schröder, R.; de Souza, L.H.; Dalmolin, R.J.; Pasquali, M.A.; Gelain, D.P.; Battastini, A.M.; Moreira, J.C. NFκB inhibitors induce cell death in glioblastomas. *Biochem. Pharmacol.* **2011**, *81*, 412–424. [[CrossRef](#)] [[PubMed](#)]
116. Bellarosa, D.; Binaschi, M.; Maggi, C.A.; Goso, C. Sabarubicin- (MEN 10755) and paclitaxel show different kinetics in nuclear factor-kappaB (NF-kB) activation: Effect of parthenolide on their cytotoxicity. *Anticancer Res.* **2005**, *25*, 2119–2128.
117. Carlisi, D.; De Blasio, A.; Drago-Ferrante, R.; Di Fiore, R.; Buttitta, G.; Morreale, M.; Scerri, C.; Vento, R.; Tesoriere, G. Parthenolide prevents resistance of MDA-MB231 cells to doxorubicin and mitoxantrone: The role of Nrf2. *Cell Death Discov.* **2017**, *3*, 17078. [[CrossRef](#)] [[PubMed](#)]
118. Mishra, H.; Mishra, P.K.; Ekielski, A.; Jaggi, M.; Iqbal, Z.; Talegaonkar, S. Melanoma treatment: From conventional to nanotechnology. *J. Cancer Res. Clin. Oncol.* **2018**, *144*, 2283–2302. [[CrossRef](#)] [[PubMed](#)]
119. Stupp, R.; Hegi, M.E.; Mason, W.P.; van den Bent, M.J.; Taphoorn, M.J.; Janzer, R.C.; Ludwin, S.K.; Allgeier, A.; Fisher, B.; Belanger, K.; et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol.* **2009**, *10*, 459–466. [[CrossRef](#)]
120. Mason, W.P. Emerging drugs for malignant glioma. *Expert Opin. Emerg. Drugs* **2008**, *13*, 81–94. [[CrossRef](#)] [[PubMed](#)]
121. Hegi, M.E.; Diserens, A.C.; Godard, S.; Dietrich, P.Y.; Regli, L.; Ostermann, S.; Otten, P.; Van Melle, G.; de Tribolet, N.; Stupp, R. Clinical trial substantiates the predictive value of O-6-methylguanine-DNA methyltransferase promoter methylation in glioblastoma patients treated with temozolomide. *Clin. Cancer Res.* **2004**, *10*, 1871–1874. [[CrossRef](#)] [[PubMed](#)]
122. Bredel, M.; Bredel, C.; Juric, D.; Duran, G.E.; Yu, R.X.; Harsh, G.R.; Vogel, H.; Recht, L.D.; Scheck, A.C.; Sikic, B.I. Tumor necrosis factor-alpha-induced protein 3 as a putative regulator of nuclear factor-kappaB-mediated resistance to O6-alkylating agents in human glioblastomas. *J. Clin. Oncol.* **2006**, *24*, 274–287. [[CrossRef](#)] [[PubMed](#)]

123. Lavon, I.; Fuchs, D.; Zrihan, D.; Efroni, G.; Zelikovitch, B.; Fellig, Y.; Siegal, T. Novel mechanism whereby nuclear factor kappaB mediates DNA damage repair through regulation of O(6)-methylguanine-DNA-methyltransferase. *Cancer Res.* **2007**, *67*, 8952–8959. [[CrossRef](#)] [[PubMed](#)]
124. Yu, Z.; Chen, Y.; Wang, S.; Li, P.; Zhou, G.; Yuan, Y. Inhibition of NF- κ B results in anti-glioma activity and reduces temozolomide-induced chemoresistance by down-regulating MGMT gene expression. *Cancer Lett.* **2018**, *428*, 77–89. [[CrossRef](#)] [[PubMed](#)]
125. Dasari, S.; Tchounwou, P.B. Cisplatin in cancer therapy: Molecular mechanisms of action. *Eur. J. Pharmacol.* **2014**, *740*, 364–378. [[CrossRef](#)]
126. Ghosh, S. Cisplatin: The first metal based anticancer drug. *Bioorg. Chem.* **2019**, *88*, 102925. [[CrossRef](#)]
127. Fang, L.J.; Shao, X.T.; Wang, S.; Lu, G.H.; Xu, T.; Zhou, J.Y. Sesquiterpene lactone parthenolide markedly enhances sensitivity of human A549 cells to low-dose oxaliplatin via inhibition of NF-kappaB activation and induction of apoptosis. *Planta Med.* **2010**, *76*, 258–264. [[CrossRef](#)]
128. Xi, X.; Liu, N.; Wang, Q.; Chu, Y.; Yin, Z.; Ding, Y.; Lu, Y. ACT001, a novel PAI-1 inhibitor, exerts synergistic effects in combination with cisplatin by inhibiting PI3K/AKT pathway in glioma. *Cell Death Dis.* **2019**, *10*, 757. [[CrossRef](#)]
129. Yuan, J.; Llamas Luceño, N.; Sander, B.; Golas, M.M. Synergistic anti-cancer effects of epigenetic drugs on medulloblastoma cells. *Cell. Oncol. Dordr* **2017**, *40*, 263–279. [[CrossRef](#)]
130. Izumi, K.M.; Kieff, E.D. The Epstein-Barr virus oncogene product latent membrane protein 1 engages the tumor necrosis factor receptor-associated death domain protein to mediate B lymphocyte growth transformation and activate NF-kappaB. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 12592–12597. [[CrossRef](#)]
131. Longley, D.B.; Harkin, D.P.; Johnston, P.G. 5-fluorouracil: Mechanisms of action and clinical strategies. *Nat. Rev. Cancer* **2003**, *3*, 330–338. [[CrossRef](#)] [[PubMed](#)]
132. Kim, S.L.; Kim, S.H.; Trang, K.T.; Kim, I.H.; Lee, S.O.; Lee, S.T.; Kim, D.G.; Kang, S.B.; Kim, S.W. Synergistic antitumor effect of 5-fluorouracil in combination with parthenolide in human colorectal cancer. *Cancer Lett.* **2013**, *335*, 479–486. [[CrossRef](#)] [[PubMed](#)]
133. Liu, D.; Liu, Y.; Liu, M.; Ran, L.; Li, Y. Reversing resistance of multidrug-resistant hepatic carcinoma cells with parthenolide. *Future Oncol.* **2013**, *9*, 595–604. [[CrossRef](#)] [[PubMed](#)]
134. Ding, Y.; Li, S.; Ge, W.; Liu, Z.; Zhang, X.; Wang, M.; Chen, T.; Chen, Y.; Zhang, Q. Design and synthesis of parthenolide and 5-fluorouracil conjugates as potential anticancer agents against drug resistant hepatocellular carcinoma. *Eur. J. Med. Chem.* **2019**, *183*, 111706. [[CrossRef](#)]
135. Gesto, D.S.; Cerqueira, N.M.; Fernandes, P.A.; Ramos, M.J. Gemcitabine: A critical nucleoside for cancer therapy. *Curr. Med. Chem.* **2012**, *19*, 1076–1087. [[CrossRef](#)]
136. Holcomb, B.K.; Yip-Schneider, M.T.; Waters, J.A.; Beane, J.D.; Crooks, P.A.; Schmidt, C.M. Dimethylamino parthenolide enhances the inhibitory effects of gemcitabine in human pancreatic cancer cells. *J. Gastrointest. Surg.* **2012**, *16*, 1333–1340. [[CrossRef](#)]
137. Marks, P.A.; Jiang, X. Histone deacetylase inhibitors in programmed cell death and cancer therapy. *Cell Cycle* **2005**, *4*, 549–551. [[CrossRef](#)]
138. Ruefli, A.A.; Ausserlechner, M.J.; Bernhard, D.; Sutton, V.R.; Tainton, K.M.; Kofler, R.; Smyth, M.J.; Johnstone, R.W. The histone deacetylase inhibitor and chemotherapeutic agent suberoylanilide hydroxamic acid (SAHA) induces a cell-death pathway characterized by cleavage of Bid and production of reactive oxygen species. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 10833–10838. [[CrossRef](#)]
139. Rosato, R.R.; Grant, S. Histone deacetylase inhibitors in clinical development. *Expert Opin. Investig. Drugs* **2004**, *13*, 21–38. [[CrossRef](#)]
140. Mayo, M.W.; Denlinger, C.E.; Broad, R.M.; Yeung, F.; Reilly, E.T.; Shi, Y.; Jones, D.R. Ineffectiveness of histone deacetylase inhibitors to induce apoptosis involves the transcriptional activation of NF-kappa B through the Akt pathway. *J. Biol. Chem.* **2003**, *278*, 18980–18989. [[CrossRef](#)]
141. Rundall, B.K.; Denlinger, C.E.; Jones, D.R. Combined histone deacetylase and NF-kappaB inhibition sensitizes non-small cell lung cancer to cell death. *Surgery* **2004**, *136*, 416–425. [[CrossRef](#)] [[PubMed](#)]
142. Yeow, W.S.; Ziauddin, M.F.; Maxhimer, J.B.; Shamimi-Noori, S.; Baras, A.; Chua, A.; Schrupp, D.S.; Nguyen, D.M. Potentiation of the anticancer effect of valproic acid, an antiepileptic agent with histone deacetylase inhibitory activity, by the kinase inhibitor Staurosporine or its clinically relevant analogue UCN-01. *Br. J. Cancer* **2006**, *94*, 1436–1445. [[CrossRef](#)] [[PubMed](#)]

143. Blaheta, R.A.; Cinatl, J., Jr. Anti-tumor mechanisms of valproate: A novel role for an old drug. *Med. Res. Rev.* **2002**, *22*, 492–511. [[CrossRef](#)] [[PubMed](#)]
144. Carlisi, D.; Lauricella, M.; D'Anneo, A.; Buttitta, G.; Emanuele, S.; di Fiore, R.; Martinez, R.; Rolfo, C.; Vento, R.; Tesoriere, G. The synergistic effect of SAHA and parthenolide in MDA-MB231 breast cancer cells. *J. Cell. Physiol.* **2015**, *230*, 1276–1289. [[CrossRef](#)]
145. Ge, W.; Liu, Z.; Sun, Y.; Wang, T.; Guo, H.; Chen, X.; Li, S.; Wang, M.; Chen, Y.; Ding, Y.; et al. Design and synthesis of parthenolide-SAHA hybrids for intervention of drug-resistant acute myeloid leukemia. *Bioorg. Chem.* **2019**, *87*, 699–713. [[CrossRef](#)]
146. Chen, L.F.; Fischle, W.; Verdin, E.; Greene, W.C. Duration of nuclear NF-kappaB action regulated by reversible acetylation. *Science* **2001**, *293*, 1653–1657. [[CrossRef](#)]
147. Law, A.Y.; Lai, K.P.; Lui, W.C.; Wan, H.T.; Wong, C.K. Histone deacetylase inhibitor-induced cellular apoptosis involves stanniocalcin-1 activation. *Exp. Cell Res.* **2008**, *314*, 2975–2984. [[CrossRef](#)]
148. Pei, S.; Minhajuddin, M.; D'Alessandro, A.; Nemkov, T.; Stevens, B.M.; Adane, B.; Khan, N.; Hagen, F.K.; Yadav, V.K.; De, S.; et al. Rational Design of a Parthenolide-based Drug Regimen That Selectively Eradicates Acute Myelogenous Leukemia Stem Cells. *J. Biol. Chem.* **2016**, *291*, 21984–22000. [[CrossRef](#)]
149. Sen, S.; Hassane, D.C.; Corbett, C.; Becker, M.W.; Jordan, C.T.; Guzman, M.L. Novel mTOR inhibitory activity of ciclopirox enhances parthenolide antileukemia activity. *Exp. Hematol.* **2013**, *41*, 799–807.e4. [[CrossRef](#)]
150. Cicconi, L.; Fenaux, P.; Kantarjian, H.; Tallman, M.; Sanz, M.A.; Lo-Coco, F. Molecular remission as a therapeutic objective in acute promyelocytic leukemia. *Leukemia* **2018**, *32*, 1671–1678. [[CrossRef](#)]
151. Duprez, E.; Wagner, K.; Koch, H.; Tenen, D.G. C/EBPbeta: A major PML-RARA-responsive gene in retinoic acid-induced differentiation of APL cells. *EMBO J.* **2003**, *22*, 5806–5816. [[CrossRef](#)]
152. Kim, S.H.; Danilenko, M.; Kim, T.S. Differential enhancement of leukaemia cell differentiation without elevation of intracellular calcium by plant-derived sesquiterpene lactone compounds. *Br. J. Pharmacol.* **2008**, *155*, 814–825. [[CrossRef](#)] [[PubMed](#)]
153. Song, J.H.; Kim, S.H.; Cho, K.M.; Hwang, S.Y.; Kim, H.J.; Kim, T.S. Analysis of gene profiles involved in the enhancement of all-trans retinoic acid-induced HL-60 cell differentiation by sesquiterpene lactones identifies asparagine synthetase as a novel target for differentiation-inducing therapy. *Int. J. Oncol.* **2014**, *44*, 970–976. [[CrossRef](#)] [[PubMed](#)]
154. Park, J.H.; Liu, L.; Kim, I.H.; Kim, J.H.; You, K.R.; Kim, D.G. Identification of the genes involved in enhanced fenretinide-induced apoptosis by parthenolide in human hepatoma cells. *Cancer Res.* **2005**, *65*, 2804–2814. [[CrossRef](#)] [[PubMed](#)]
155. Mathieu, C.; Degrande, E. Vildagliptin: A new oral treatment for type 2 diabetes mellitus. *Vasc. Health Risk Manag.* **2008**, *4*, 1349–1360. [[CrossRef](#)]
156. Hoonjan, M.; Jadhav, V.; Bhatt, P. Arsenic trioxide: Insights into its evolution to an anticancer agent. *J. Biol. Inorg. Chem.* **2018**, *23*, 313–329. [[CrossRef](#)]
157. Kouhpaikar, H.; Sadeghian, M.H.; Rafatpanah, H.; Kazemi, M.; Iranshahi, M.; Delbari, Z.; Khodadadi, F.; Ayatollahi, H.; Rassouli, F.B. Synergy between parthenolide and arsenic trioxide in adult T-cell leukemia/lymphoma cells in vitro. *Iran. J. Basic Med. Sci.* **2020**, *23*, 616–622.
158. Wang, W.; Adachi, M.; Zhang, R.; Zhou, J.; Zhu, D. A novel combination therapy with arsenic trioxide and parthenolide against pancreatic cancer cells. *Pancreas* **2009**, *38*, e114–e123. [[CrossRef](#)]
159. Fu, L.L.; Zhao, X.Y.; Ji, L.D.; Xu, J. Okadaic acid (OA): Toxicity, detection and detoxification. *Toxicol* **2019**, *160*, 1–7. [[CrossRef](#)]
160. Di Fiore, R.; Drago-Ferrante, R.; D'Anneo, A.; Augello, G.; Carlisi, D.; De Blasio, A.; Giuliano, M.; Tesoriere, G.; Vento, R. In human retinoblastoma Y79 cells okadaic acid-parthenolide co-treatment induces synergistic apoptotic effects, with PTEN as a key player. *Cancer Biol. Ther.* **2013**, *14*, 922–931. [[CrossRef](#)]
161. Antar, A.I.; Otrrock, Z.K.; Jabbour, E.; Mohty, M.; Bazarbachi, A. FLT3 inhibitors in acute myeloid leukemia: Ten frequently asked questions. *Leukemia* **2020**, *34*, 682–696. [[CrossRef](#)] [[PubMed](#)]
162. Wang, C.; Lu, J.; Wang, Y.; Bai, S.; Wang, Y.; Wang, L.; Sheng, G. Combined effects of FLT3 and NF-κB selective inhibitors on acute myeloid leukemia in vivo. *J. Biochem. Mol. Toxicol.* **2012**, *26*, 35–43. [[CrossRef](#)] [[PubMed](#)]
163. Whitesell, L.; Lindquist, S.L. HSP90 and the chaperoning of cancer. *Nat. Rev. Cancer* **2005**, *5*, 761–772. [[CrossRef](#)] [[PubMed](#)]

164. Lee, C.S.; Kim, Y.J.; Lee, S.A.; Myung, S.C.; Kim, W. Combined effect of Hsp90 inhibitor geldanamycin and parthenolide via reactive oxygen species-mediated apoptotic process on epithelial ovarian cancer cells. *Basic Clin. Pharmacol. Toxicol.* **2012**, *111*, 173–181. [[CrossRef](#)]
165. Yun, B.R.; Lee, M.J.; Kim, J.H.; Kim, I.H.; Yu, G.R.; Kim, D.G. Enhancement of parthenolide-induced apoptosis by a PKC-alpha inhibition through heme oxygenase-1 blockage in cholangiocarcinoma cells. *Exp. Mol. Med.* **2010**, *42*, 787–797. [[CrossRef](#)]
166. Sobell, H.M. Actinomycin and DNA transcription. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 5328–5331. [[CrossRef](#)]
167. Hill, C.R.; Cole, M.; Errington, J.; Malik, G.; Boddy, A.V.; Veal, G.J. Characterisation of the clinical pharmacokinetics of actinomycin D and the influence of ABCB1 pharmacogenetic variation on actinomycin D disposition in children with cancer. *Clin. Pharmacokinet.* **2014**, *53*, 741–751. [[CrossRef](#)]
168. Lamture, G.; Crooks, P.A.; Borrelli, M.J. Actinomycin-D and dimethylamino-parthenolide synergism in treating human pancreatic cancer cells. *Drug Dev. Res.* **2018**, *79*, 287–294. [[CrossRef](#)]
169. de Thé, H. Differentiation therapy revisited. *Nat. Rev. Cancer* **2018**, *18*, 117–127. [[CrossRef](#)]
170. Kang, S.N.; Kim, S.H.; Chung, S.W.; Lee, M.H.; Kim, H.J.; Kim, T.S. Enhancement of 1 alpha,25-dihydroxyvitamin D(3)-induced differentiation of human leukaemia HL-60 cells into monocytes by parthenolide via inhibition of NF-kappa B activity. *Br. J. Pharmacol.* **2002**, *135*, 1235–1244. [[CrossRef](#)]
171. Cory, A.H.; Cory, J.G. Lactacystin, a proteasome inhibitor, potentiates the apoptotic effect of parthenolide, an inhibitor of NFkappaB activation, on drug-resistant mouse leukemia L1210 cells. *Anticancer Res.* **2002**, *22*, 3805–3809. [[PubMed](#)]
172. Wu, C.; Chen, F.; Rushing, J.W.; Wang, X.; Kim, H.J.; Huang, G.; Haley-Zitlin, V.; He, G. Antiproliferative activities of parthenolide and golden feverfew extract against three human cancer cell lines. *J. Med. Food* **2006**, *9*, 55–61. [[CrossRef](#)] [[PubMed](#)]
173. Barker, H.E.; Paget, J.T.; Khan, A.A.; Harrington, K.J. The tumour microenvironment after radiotherapy: Mechanisms of resistance and recurrence. *Nat. Rev. Cancer* **2015**, *15*, 409–425. [[CrossRef](#)] [[PubMed](#)]
174. Veuger, S.J.; Hunter, J.E.; Durkacz, B.W. Ionizing radiation-induced NF-kappaB activation requires PARP-1 function to confer radioresistance. *Oncogene* **2009**, *28*, 832–842. [[CrossRef](#)] [[PubMed](#)]
175. Meng, A.; Yu, T.; Chen, G.; Brown, S.A.; Wang, Y.; Thompson, J.S.; Zhou, D. Cellular origin of ionizing radiation-induced NF-kappaB activation in vivo and role of NFkappaB in ionizing radiation-induced lymphocyte apoptosis. *Int. J. Radiat. Biol.* **2003**, *79*, 849–861. [[CrossRef](#)]
176. Watson, C.; Miller, D.A.; Chin-Sinex, H.; Losch, A.; Hughes, W.; Sweeney, C.; Mendonca, M.S. Suppression of NF-kappaB activity by parthenolide induces X-ray sensitivity through inhibition of split-dose repair in TP53 null prostate cancer cells. *Radiat. Res.* **2009**, *171*, 389–396. [[CrossRef](#)]
177. Sun, Y.; St Clair, D.K.; Fang, F.; Warren, G.W.; Rangnekar, V.M.; Crooks, P.A.; St Clair, W.H. The radiosensitization effect of parthenolide in prostate cancer cells is mediated by nuclear factor-kappaB inhibition and enhanced by the presence of PTEN. *Mol. Cancer Ther.* **2007**, *6*, 2477–2486. [[CrossRef](#)]
178. Deraska, P.V.; O’Leary, C.; Reavis, H.D.; Labe, S.; Dinh, T.K.; Lazaro, J.B.; Sweeney, C.; D’Andrea, A.D.; Kozono, D. NF-κB inhibition by dimethylaminoparthenolide radiosensitizes non-small-cell lung carcinoma by blocking DNA double-strand break repair. *Cell Death Discov.* **2018**, *4*, 10. [[CrossRef](#)]
179. Estabrook, N.C.; Chin-Sinex, H.; Borgmann, A.J.; Dhaemers, R.M.; Shapiro, R.H.; Gilley, D.; Huda, N.; Crooks, P.; Sweeney, C.; Mendonca, M.S. Inhibition of NF-κB and DNA double-strand break repair by DMAPT sensitizes non-small-cell lung cancers to X-rays. *Free Radic. Biol. Med.* **2011**, *51*, 2249–2258. [[CrossRef](#)]
180. Mendonca, M.S.; Turchan, W.T.; Alpuche, M.E.; Watson, C.N.; Estabrook, N.C.; Chin-Sinex, H.; Shapiro, J.B.; Imasuen-Williams, I.E.; Rangel, G.; Gilley, D.P.; et al. DMAPT inhibits NF-κB activity and increases sensitivity of prostate cancer cells to X-rays in vitro and in tumor xenografts in vivo. *Free Radic. Biol. Med.* **2017**, *112*, 318–326. [[CrossRef](#)]
181. Meazza, C.; Scanagatta, P. Metastatic osteosarcoma: A challenging multidisciplinary treatment. *Expert Rev. Anticancer Ther.* **2016**, *16*, 543–556. [[CrossRef](#)] [[PubMed](#)]
182. Zuch, D.; Giang, A.H.; Shapovalov, Y.; Schwarz, E.; Rosier, R.; O’Keefe, R.; Eliseev, R.A. Targeting radioresistant osteosarcoma cells with PN. *J. Cell Biochem.* **2012**, *113*, 1282–1291. [[CrossRef](#)] [[PubMed](#)]
183. Sugiyasu, K.; Nanno, K.; Tamai, N.; Hashimoto, N.; Kishida, Y.; Yoshikawa, H.; Myoui, A. Radio-sensitization of the murine osteosarcoma cell line LM8 with parthenolide, a natural inhibitor of NF-κB. *Oncol. Lett.* **2011**, *2*, 407–412. [[CrossRef](#)] [[PubMed](#)]

184. Mahmood, J.; Shukla, H.D.; Soman, S.; Samanta, S.; Singh, P.; Kamlapurkar, S.; Saeed, A.; Amin, N.P.; Vujaskovic, Z. Immunotherapy, Radiotherapy, and Hyperthermia: A Combined Therapeutic Approach in Pancreatic Cancer Treatment. *Cancers (Basel)* **2018**, *10*, E469. [CrossRef]
185. Poland, J.; Schadendorf, D.; Lage, H.; Schnölzer, M.; Celis, J.E.; Sinha, P. Study of therapy resistance in cancer cells with functional proteome analysis. *Clin. Chem. Lab. Med.* **2002**, *40*, 221–234. [CrossRef]
186. Habash, R.W.Y. Therapeutic hyperthermia. *Handb. Clin. Neurol.* **2018**, *157*, 853–868.
187. Hayashi, S.; Hatashita, M.; Hayashi, A.; Matsumoto, H.; Shioura, H.; Kitai, R. Thermosensitization by PN in human lung adenocarcinoma A549 cells and p53- and hsp72-independent apoptosis induction via the nuclear factor-kappaB signal pathway. *Int. J. Mol. Med.* **2008**, *21*, 585–592.
188. Hayashi, S.; Sakurai, H.; Hayashi, A.; Tanaka, Y.; Hatashita, M.; Shioura, H. Inhibition of NF-kappaB by combination therapy with PN and hyperthermia and kinetics of apoptosis induction and cell cycle arrest in human lung adenocarcinoma cells. *Int. J. Mol. Med.* **2010**, *25*, 81–87.
189. Hayashi, S.; Koshiba, K.; Hatashita, M.; Sato, T.; Jujo, Y.; Suzuki, R.; Tanaka, Y.; Shioura, H. Thermosensitization and induction of apoptosis or cell-cycle arrest via the MAPK cascade by PN, an NF- κ B inhibitor, in human prostate cancer androgen-independent cell lines. *Int. J. Mol. Med.* **2011**, *28*, 1033–1042.
190. Kruk, P.J. Beneficial effect of additional treatment with widely available anticancer agents in advanced small lung cell carcinoma: A case report. *Mol. Clin. Oncol.* **2018**, *9*, 647–650. [CrossRef] [PubMed]
191. Jin, P.; Madiheh, S.; Augsburger, L.L. The solution and solid state stability and excipient compatibility of parthenolide in feverfew. *AAPS PharmSciTech.* **2007**, *8*, E105. [CrossRef] [PubMed]
192. Nasim, S.; Crooks, P.A. Antileukemic activity of aminoparthenolide analogs. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3870–3873. [CrossRef] [PubMed]
193. Long, J.; Ding, Y.H.; Wang, P.P.; Zhang, Q.; Chen, Y. Protection-group-free semisyntheses of parthenolide and its cyclopropyl analogue. *J. Org. Chem.* **2013**, *78*, 10512–10518. [CrossRef]
194. Long, J.; Zhang, S.F.; Wang, P.P.; Zhang, X.M.; Yang, Z.J.; Zhang, Q.; Chen, Y. Total syntheses of parthenolide and its analogues with macrocyclic stereocontrol. *J. Med. Chem.* **2014**, *57*, 7098–7112. [CrossRef] [PubMed]
195. Yang, Z.; Kuang, B.; Kang, N.; Ding, Y.; Ge, W.; Lian, L.; Gao, Y.; Wei, Y.; Chen, Y.; Zhang, Q. Synthesis and anti-acute myeloid leukemia activity of C-14 modified parthenolide derivatives. *Eur. J. Med. Chem.* **2017**, *127*, 296–304. [CrossRef] [PubMed]
196. Yang, Z.J.; Ge, W.Z.; Li, Q.Y.; Lu, Y.; Gong, J.M.; Kuang, B.J.; Xi, X.; Wu, H.; Zhang, Q.; Chen, Y. Syntheses and Biological Evaluation of Costunolide, Parthenolide, and Their Fluorinated Analogues. *J. Med. Chem.* **2015**, *58*, 7007–7020. [PubMed]
197. Zhang, Q.; Lu, Y.; Ding, Y.; Zhai, J.; Ji, Q.; Ma, W.; Yang, M.; Fan, H.; Long, J.; Tong, Z.; et al. Guaianolide sesquiterpene lactones, a source to discover agents that selectively inhibit acute myelogenous leukemia stem and progenitor cells. *J. Med. Chem.* **2012**, *55*, 8757–8769. [CrossRef]
198. Ding, Y.; Yang, Z.; Ge, W.; Kuang, B.; Xu, J.; Yang, J.; Chen, Y.; Zhang, Q. Synthesis and biological evaluation of dithiocarbamate esters of parthenolide as potential anti-acute myelogenous leukaemia agents. *J. Enzyme Inhib. Med. Chem.* **2018**, *33*, 1376–1391. [CrossRef]
199. Jia, X.; Liu, Q.; Wang, S.; Zeng, B.; Du, G.; Zhang, C.; Li, Y. Synthesis, cytotoxicity, and in vivo antitumor activity study of parthenolide semicarbazones and thiosemicarbazones. *Bioorg. Med. Chem.* **2020**, *28*, 115557. [CrossRef]
200. Taleghani, A.; Nasser, M.A.; Iranshahi, M. Synthesis of dual-action parthenolide prodrugs as potent anticancer agents. *Bioorg Chem.* **2017**, *71*, 128–134. [CrossRef]
201. Lickliter, J. A Phase 1 Dose-Escalation Study to Evaluate the Safety, Tolerability and Pharmacokinetics of ACT001 in Patients with Advanced Solid Tumors. Available online: <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12616000228482p>.
202. Tong, L.; Li, J.; Li, Q.; Wang, X.; Medikonda, R.; Zhao, T.; Li, T.; Ma, H.; Yi, L.; Liu, P.; et al. ACT001 reduces the expression of PD-L1 by inhibiting the phosphorylation of STAT3 in glioblastoma. *Theranostics* **2020**, *10*, 5943–5956. [CrossRef] [PubMed]
203. Ridolfo, R.; Ede, B.C.; Diamanti, P.; White, P.B.; Perriman, A.W.; van Hest, J.C.M.; Blair, A.; Williams, D.S. Biodegradable, Drug-Loaded Nanovectors via Direct Hydration as a New Platform for Cancer Therapeutics. *Small* **2018**, *14*, e1703774. [CrossRef] [PubMed]

204. Karmakar, A.; Xu, Y.; Mustafa, T.; Kannarpady, G.; Bratton, S.M.; Radominska-Pandya, A.; Crooks, P.A.; Biris, A.S. Nanodelivery of Parthenolide Using Functionalized Nanographene Enhances its Anticancer Activity. *RSC Adv.* **2015**, *5*, 2411–2420. [[CrossRef](#)] [[PubMed](#)]
205. Darwish, N.H.E.; Sudha, T.; Godugu, K.; Bharali, D.J.; Elbaz, O.; El-Ghaffar, H.A.A.; Azmy, E.; Anber, N.; Mousa, S.A. Novel Targeted Nano-Parthenolide Molecule against NF- κ B in Acute Myeloid Leukemia. *Molecules* **2019**, *24*, 2103. [[CrossRef](#)] [[PubMed](#)]
206. Gao, W.; Li, L.; Zhang, X.; Luo, L.; He, Y.; Cong, C.; Gao, D. Nanomagnetic liposome-encapsulated parthenolide and indocyanine green for targeting and chemo-photothermal antitumor therapy. *Nanomedicine (Lond.)* **2020**, *15*, 871–890. [[CrossRef](#)]
207. Mathema, V.B.; Koh, Y.S.; Thakuri, B.C.; Sillanpa, M. Parthenolide, a sesquiterpene lactone, expresses multiple anti-cancer and anti-inflammatory activities. *Inflammation* **2012**, *35*, 560–565. [[CrossRef](#)]
208. Zhang, M.; Liu, R.T.; Zhang, P.; Zhang, N.; Yang, C.L.; Yue, L.T.; Li, X.L.; Liu, Y.; Li, H.; Du, J.; et al. Parthenolide inhibits the initiation of experimental autoimmune neuritis. *J. Neuroimmunol.* **2017**, *15*, 154–161. [[CrossRef](#)]
209. Bahrami, M.; Kamalinejad, M.; Latifi, S.A.; Seif, F.; Dadmehr, M. Cytokine storm in COVID-19 and parthenolide: Preclinical evidence. *Phytother. Res.* **2020**, *10*, 1002. [[CrossRef](#)]



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