Anti-Cancer Effects of Pristimerin and the Mechanisms: A Critical Review

Jia-jun Li1†, Yan-yan Yan2,3†, Hong-mei Sun4†, Yun Liu1, Chao-yue Su1, Hu-biao Chen3* and Jian-ye Zhang1*

1 Guangdong Provincial Key Laboratory of Molecular Target & Clinical Pharmacology, School of Pharmaceutical Sciences and the Fifth Affiliated Hospital, Guangzhou Medical University, Guangzhou, China, 2 Institute of Respiratory and Occupational Diseases, Collaborative Innovation Center for Cancer, Medical College, Shanxi Datong University, Datong, China, 3 School of Chinese Medicine, Hong Kong Baptist University, Hong Kong, China, 4 Infinitus (China) Company Ltd., Jiangmen, China

As a quinonemethide triterpenoid extracted from species of the Celastraceae and Hippocrateaceae, pristimerin has been shown potent anti-cancer effects. Specifically, it was found that pristimerin can affect many tumor-related processes, such as apoptosis, autophagy, migration and invasion, vasculogenesis, and drug resistance. Various molecular targets or signaling pathways are also involved, such as cyclins, reactive oxygen species (ROS), microRNA, nuclear factor kappa B (NF-κB), mitogen-activated protein kinase (MAPK), and PI3K/AKT/mammalian target of rapamycin (mTOR) pathways. In this review, we will focus on the research about pristimerin-induced anti-cancer activities to achieve a deeper understanding of the targets and mechanisms, which offer evidences suggesting that pristimerin can be a potent anti-cancer drug.

Keywords: pristimerin, anti-cancer, mechanism, molecular target, pharmaceutical effect, apoptosis, autophagy

INTRODUCTION

In recent years, natural compound has received more and more attention for use in treating human diseases and conditions, due to their long history of use and various pharmacological therapeutic effects (Tao et al., 2015; Zhang et al., 2015; Peng et al., 2016; Zhang et al., 2016; Lin et al., 2017), especially their relative safety (fewer and less severe side effects) than chemical drugs. Naturally occurring triterpenoid can be used as anti-cancer, anti-inflammatory, anti-malarial, and insecticidal agent (Deeb et al., 2012; Larsen et al., 2012; Kim et al., 2013; Deeb et al., 2014a). It has been proven that some natural or synthetic triterpenoids have promising clinical potential, exhibiting both therapeutic and chemopreventive activities for cancer (Salminen et al., 2008; Alessia et al., 2009; Ke et al., 2016). Pristimerin (20α-3-hydroxy-2-oxo-24-nor-friedelan-1-10,3,5,7-tetraen-carboxyclic acid-29-methylester, molecular formula: C30H40O4) (Figure 1), a methyl ester of celastrol, is a quinonemethide triterpenoid which has been extracted from a variety of species of the Celastraceae and Hippocrateaceae families, such as Hippocratea excels (Mena-Rejon et al., 2007), Maytenus heterophylla (Murayama et al., 2007), and Celastrus aculeatus Merr. (Tang et al., 2014). Pristimerin was first isolated in 1951 from Pristimerae indica and P. grahami and was first identified in 1954 to confirm its molecular structure (Kulkarni and Shah, 1954). Pristimerin has displayed different pharmacological effects, such as anti-cancer, anti-oxidant, anti-inflammatory, anti-bacterial, anti-malarial, and insecticidal activities (Figueiredo...
Pristimerin possesses strong anti-proliferative activities with involvement of mitochondrial dysfunction, activation of both extrinsic and intrinsic caspases, and cleavage of poly ADP-ribose polymerase (PARP). It has been reported that pristimerin can induce caspase-dependent apoptosis in human glioma cancer cells (Yan et al., 2013), pancreatic cancer cells (Deeb et al., 2014b), and hepatoma cancer cells (Gao et al., 2014). Pristimerin-induced inhibition of Bcl-2 (as well as Bcl-2 mRNA) is sufficient to promote mitochondrial permeability transition and release of cytochrome c mediated by Bax and Bak without the inhibition of Bcl-xl in pancreatic cancer cells (Deeb et al., 2014b). On the other hand, caspase inhibitor failed to antagonize the effects of pristimerin, indicating that the lethal effect of pristimerin may not be caspase-dependent in human glioma U251 and U87 cells (Zhao et al., 2016).

The apoptotic effect of pristimerin is related to Bcl-2, and it mediates down-regulation of Bcl-2 through reactive oxygen species (ROS)-dependent ubiquitin-proteasomal degradation pathway in human prostate cancer LNCaP and PC-3 cells (Liu et al., 2013). ROS-induced apoptosis by pritimerin was also reported in hepatocellular carcinoma HepG2 cells, involving EGFR and Akt proteins (Guo et al., 2013). In colorectal carcinoma cells,
the associated induction of JNK activation and MMP loss was observed (Yousef et al., 2016b), similar with the results in cervical cancer cells (Byun et al., 2009).

In human colon cancer cells, pristimerin caused cell cycle arrest and apoptosis through cyclin-CDK, mitochondrial dysfunction, and caspase-dependent mechanisms. Besides, the inhibition of DNA synthesis in HL-60 was also associated with pristimerin-induced apoptosis (Costa et al., 2008).

Pristimerin-induced apoptosis could be mediated by microRNA (miRNA). miRNAs exert a post-transcriptional gene silencing effect through binding to target mRNA and endonucleolytic cleavage of the mRNA by protein argonaute-2 (AGO2) (Kobayashi and Tomari, 2016). It was reported that pristimerin induced apoptosis through inhibiting AGO2 and PTPN1 expression via miR-542-5p in glioma cancer cells U373 (Li et al., 2019). Synergization with cisplatin, pristimerin led to apoptosis via inhibiting the miR-23a, regulating PTEN/Akt signaling-related PTEN and the phosphorylation of Akt and GSK3β in lung carcinoma NCI-H446 and A549 cells (Zhang et al., 2019).

**Autophagy Induction**

As another programmed necrosis, autophagy is a homeostatic cellular self-destructive process. Autophagy triggered by various cellular stress plays vital role in cell death, providing novel target for developing anti-cancer drug (Mizushima et al., 2008; Ravanant et al., 2017). LC3-II promotes the expansion and maturation of autophagy, which is considered as signal of autophagy activation. Pristimerin-induced autophagy was reported in human breast cancer MDA-MB-231 (Cevatemre et al., 2018; Lee et al., 2018) and MCF-7 cells (Cevatemre et al., 2018). As evidenced by the increase of p62 and LC3-II with an unfolded protein response (UPR), pristimerin induced an incompletely autophagy through Wnt signaling. Although endoplasmic reticulum (ER) stress is also a trigger of autophagy (Smith and

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**TABLE 1** The cytotoxicity dosage of pristimerin in different cancer cell lines.

| Cancer type       | Time | Toxic dosage (IC$_{50}$ value or inhibition rate) | References       |
|-------------------|------|-------------------------------------------------|-----------------|
| Prostate cancer   | 72 h | 1.25 μM caused 55% LNCaP cell death             | (Liu et al., 2013) |
|                   |      | 1.25 μM caused 47% PC-3 cell death              |                  |
| Breast cancer     | 24 h | 2.40 μM IC$_{50}$ against SKBR3                 | (Lee et al., 2013) |
| Colorectal cancer | 72 h | 1.11 μM IC$_{50}$ against HCT-116               | (Yousef et al., 2018) |
|                   | 48 h | 1.22 μM IC$_{50}$ against HCT-116               | (Yousef et al., 2016a) |
|                   |      | 1.04 μM IC$_{50}$ against SW-620                 |                  |
|                   |      | 0.84 μM IC$_{50}$ against COLO-205               |                  |
| Hepatocellular carcinoma | 72 h | 1.44 μM IC$_{50}$ against HepG2                 | (Guo et al., 2013) |
|                   |      | 1.70 μM IC$_{50}$ against HepG2                 | (Wei et al., 2014) |
|                   |      | 0.68 μM IC$_{50}$ against Huh7                  |                  |
|                   |      | 0.85 μM IC$_{50}$ against Hep3B                  | (Zhao et al., 2016) |
| Pancreatic cancer | 24 h | 0.66 μM, 0.97 μM, 0.13 μM, IC$_{50}$ against BxPC-3, PANC-1, and AsPC-1, respectively | (Wang et al., 2012) |
|                   | 48 h | 0.28 μM, 0.34 μM, and 0.38 μM IC$_{50}$ against BxPC-3, PANC-1, and AsPC-1, respectively |                  |
|                   | 72 h | 0.19 μM, 0.26 μM and 0.30 μM IC$_{50}$ against BxPC-3, PANC-1, and AsPC-1, respectively |                  |
| Glioma            | 6 h  | 4.5 μM IC$_{50}$ against U251                   |                  |
|                   |      | 5.0 μM IC$_{50}$ against U87                    |                  |
| Leukemia          | 72 h | 0.61 μM IC$_{50}$ against HL-60                 | (Costa et al., 2008) |
|                   |      | 1.49 μM IC$_{50}$ against K562                  |                  |
|                   | 72 h | 199 nM IC$_{50}$ against KBM5                   | (Lu et al., 2010) |
|                   |      | 135 nM IC$_{50}$ against KBM5-T315i            |                  |
|                   |      | 450 nM IC$_{50}$ against K562                   |                  |
| Ovarian carcinoma | 72 h | 1.25 μM caused 44% OVCAR-5 cell death            | (Gao et al., 2014) |
|                   |      | 1.25 μM caused 28% MDAH-2774 cell death         | (Yousef et al., 2016a) |
|                   |      | 2.5 μM caused 36% SK-OV-3 cell death            | (Yousef et al., 2016a) |
|                   |      | 2.5 μM caused 27% OVCAR-3 cell death            | (Yousef et al., 2016a) |
| Osteosarcoma      | 24 h | 0.80 μM IC$_{50}$ against MNNG                 | (Mori et al., 2017) |
|                   | 48 h | 0.54 μM IC$_{50}$ against 143B                 |                  |
|                   |      | 0.39 μM IC$_{50}$ against 143B                 |                  |
|                   | 72 h | 0.32 μM IC$_{50}$ against 143B                 |                  |
|                   |      | 0.29 μM IC$_{50}$ against 143B                 |                  |
| Oral cancer       | 72 h | 0.54 μM IC$_{50}$ against KB                    | (Yan et al., 2017) |
|                   |      | 0.52 μM IC$_{50}$ against KBv200               | (Wu et al., 2019) |
|                   |      | 0.70 μM IC$_{50}$ against CAL-27               |                  |
|                   |      | 0.73 μM IC$_{50}$ against SCC-25               |                  |
| ESCC              | 72 h | 1.98 μM IC$_{50}$ against EC9708               | (Tu et al., 2018) |
|                   |      | 1.76 μM IC$_{50}$ against EC109                |                  |
|                   |      | 1.13 μM IC$_{50}$ against KYSE30                |                  |

ESCC, esophageal squamous cell carcinoma.
Wilkinson, 2017), it was not concluded whether the observed ER stress by pristimerin induced autophagy (Cevatemre et al., 2018). Additionally, a combination treatment of pristimerin and paclitaxel strengthened the extracellular signal-related kinase (ERK)-dependent autophagic cell death, with increase of p62 degradation and beclin1 expression (Lee et al., 2018).

On the contrary, pristimerin suppressed autophagy, downregulating LC3BII and beclin1 to sensitize the apoptosis caused by cisplatin in lung carcinoma A549 and NCI-H446 cells (Zhang et al., 2019).

Inhibition of Metastasis, Migration, Invasion, Angiogenesis, and Cancer Stem Cell

The cancer metastases include a series of process, such as the completion of a complex succession of cell-biological event, cancer cell invasion, migration, and forming metastatic colonization in clinic (Valastyan and Weinberg, 2011). Pristimerin was reported to inhibit migration and invasion via targeting G protein signaling 4 (RGS4) in breast cancer MDA-MB-231 cells (Mu et al., 2012a) and HER2 in human breast carcinoma SKBR3 cells (Lee et al., 2013). Furthermore, mammalian target of rapamycin (mTOR) may be associated with its upstream Akt in pristimerin-induced inhibition of migration and invasion in colorectal cancer HCT-116 cells (Yousef et al., 2016b). Pristimerin suppressed the invasion of human prostate cancer PC-3 through inhibition of epithelial-to-mesenchymal transition (EMT), which was confirmed by the EMT-related markers (Chaffer et al., 2016), including N-cadherin, fibronectin, vimentin and ZEB1 (Zuo et al., 2015). MMP2 and MMP9, which are important proteins regulating invasion and metastasis, were decreased by pristimerin in esophageal cancer EC9706 and EC109 cells in a dose-dependent manner, resulting in inhibition of migration and invasion (Tu et al., 2018).

To supply nutrients and clear metabolic wastes, novel capillary blood vessels grow from pre-existing vasculature, which is called angiogenesis. However, aberrant angiogenesis plays a key role in cancer development (Valastyan and Weinberg, 2011). Thus, anti-angiogenic therapy is promising and under development (Li et al., 2018). Pristimerin was reported to in vivo inhibit the neovascularization of chicken chorioallantoic membrane (CAM) and vessel ex vivo sprout in rat aortic ring assay, through a vascular endothelial growth factor (VEGF)-dependent mechanism (Mu et al., 2012b). Also, the decreased-VEGF by pristimerin was reported through the inhibition of HIF-1α via the SPHK-1 signaling pathway in hypoxic prostate cancer PC-3 cells (Lee et al., 2016). In addition, pristimerin-induced cancer stem cell toxicity was observed in breast cancer stem cells (Cevatemre et al., 2018) and esophageal squamous cell carcinoma (ESCC) (Tu et al., 2018).

Reversal of Drug Resistance

Multi-drug resistance (MDR) is defined as the resistance of cancer cells not limited to a specific chemotherapeutic drug through different structures and mechanisms of action (Wu et al., 2014). ABCB1 (P-glycoprotein, Pgp) is recognized as putative drug transporter, which is encoded by the ABCB1 gene, one of (ATP)-binding cassette (ABC) transporter family (Dewanjee et al., 2017). Pristimerin may overcome ABCB1-mediated chemotherapeutic drug resistance through disturbing the stability of ABCB1 independent of its mRNA expression in human oral epidermoid carcinoma cells KBv200 (Yan et al., 2017). In addition, with inhibition of NF-xB and Bcr-Abl, pristimerin is effective in vitro and in vivo against imatinib-resistant chronic myelogenous leukemia cells (Lu et al., 2010). Additionally, Akt signaling was related to the reversal of MDR in multidrug-resistant MCF-7/ADR breast cancer cells (Xie et al., 2016).

Synergization With Chemotherapeutic Drugs

Drug combination for cancer treatment has been well established to strengthen the anti-tumor action in varied aspects (Ho and Cheung, 2014; Andre et al., 2018), including therapeutic drug combination with natural product (Efferth, 2017; Sanchez et al., 2019). Pristimerin was reported to synergize with paclitaxel in human breast cancer cells (Lee et al., 2018), with 5-fluorouracil (5-FU) in esophageal ESCC (Tu et al., 2018). In cervical cancer cells, combination with taxol could induce cell death through ROS-mediated mitochondrial dysfunction (Eum et al., 2011). In NCI-H446 and A549 lung carcinoma cells, combination with cisplatin could induce cell apoptosis through inhibiting the miRNA-23a and Akt/GSK3β signaling pathway (Zhang et al., 2019). In pancreatic cancer cells, pristimerin could potentiate the cytotoxic effect of gemcitabine with the possible mechanism being the inhibition of gemcitabine-induced NF-xB activation (Wang et al., 2012).

In Vivo Anti-Tumor Activities

Pristimerin was widely reported its in vivo anti-tumor activities, which is summarized in Table 2.

PRISTIMERIN IN TUMORS: TARGETS AND PATHWAYS

Proteasome

As another important mechanism of maintaining homeostasis, proteasome-mediated degradation is associated with essential cellular processes, regulating the vast majority of cellular proteins (Livneh et al., 2016). Consistent with triterpenoids being reported to target proteasome (Chinthalapalli et al., 2007; Tiedemann et al., 2009), pristimerin also showed a potent activity to inhibit proteasome activity in prostate cancer cells (Yang et al., 2010; Liu et al., 2013; Liu et al., 2014), breast cancer cells (Mu et al., 2012a), cervical carcinoma cells (Eum et al., 2011), and myeloma cells (Tiedemann et al., 2009).

The β subunits of proteasome contain active protease sites with different peptidase activities, including caspase-like or peptidyl-glutamyl peptide-hydrolyzing-like (β1), trypsin-like post basic (β2), and chymotrypsin-like (β5) activities (Mayor et al., 2016).
Pristimerin was associated with the N-terminal threonine of the β5 subunit through its conjugated ketone carbon Cα, exerting a chymotrypsin-like activity (Yang et al., 2010), which is also associated with RGS4 (Mu et al., 2012a).

Pristimerin can inhibit Bcl-2, finally induced mitochondrial cell death via an ROS-dependent ubiquitin-proteasomal degradation pathway (Liu et al., 2013). Pristimerin combination with taxol caused mitochondrial apoptosis due to ROS generation and direct proteasome inhibition (Eum et al., 2011). In addition, pristimerin-induced inhibition of proteosome and IKK phosphorylation of IkB together led to UPR and suppression of NF-kB activity and cyclin D2 expression in myeloma cells H929 and U266 (Tiedemann et al., 2013).

**Telomerase**

Telomere is a ribonucleoprotein complex located in the end of chromosomes, maintaining telomere length homeostasis to keep chromosomal stability (Wang and Feigon, 2017). Due to the differences in telomere homeostasis between cancer and normal cells, targeting telomerase may be a promising approach to find effective and safe anti-cancer treatments (Armstrong and Tomita, 2017).

Pristimerin can inhibit telomerase activity in human prostate cancer LNCaP and PC-3 cells (Liu et al., 2015). The mechanism is related to inhibition of human telomerase reverse transcriptase (hTERT) and its mRNA expression, which codes the catalytic subunit of the telomerase. At the same time, knocking-down of hTERT strengthened the effects of pristimerin. Furthermore, hTERT regulatory proteins c-Myc, Sp1, p-STAT3, and p-Akt were inhibited in a dose-dependent manner (Liu et al., 2015).

**MAPK Pathway**

The generic MAPK signaling pathway is co-regulated by four different cascades including extracellular signal-related kinases (ERK1/2), Jun amino-terminal kinases (JNK1/2/3), p38-MAPK,
PI3K/AKT/mTOR Pathway
The phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR pathway cascade containing PI3K, AKT, and mTOR is the most frequently altered pathway in human for cancer development, such as cell cycle, cell survival, metabolism, motility, angiogenesis, chemoresistance, and genomic instability (Mabuchi et al., 2015). Pristimerin showed a potent apoptosis-inducing anti-proliferative activity in human osteosarcoma cells (Mori et al., 2017) by PI3K/AKT/mTOR pathway. The pristimerin-induced ROS-dependent mitochondrial cell apoptosis was also associated with the inhibition of EGFR and Akt in human glioma cells (Yan et al., 2013). It was confirmed that PI3K/AKT/mTOR pathway-activated activities were accompanied by the downstream Foxo-3a, cyclin D1 and Bcl-XL (Akt), p-S6K1, and p-4E-BP1 (mTOR) as well as p21, p27, and PKCe in human ovarian cancer cells (Deeb et al., 2014b; Gao et al., 2014; Park and Kim, 2018). Furthermore, downstream Bad and Bcl-XL pointed to drug resistance in MCF-7/ADR human breast cancer cells (Xie et al., 2016). In addition, pristimerin suppressed angiogenesis through VEGF-induced Akt, ERK1/2, mTOR, and ribosomal protein S6 kinase (Mu et al., 2012b).

NF-κB Pathway
NF-κB family transcription factors are crucial regulators of cell survival and inflammatory processes (Napetschnig and Wu, 2013). The inactive NF-κBPs are isolated from nucleus by inhibitor of NF-κB (IkB) proteins. When activated IKK (IkB kinase) makes a proteasomal degradation of IkB, the subsequent process will occur, including the release of NF-κB, translocation of NF-κB nuclear and activation of gene transcription. NF-κB can be activated by both intracellular and extracellular stimuli, including cytokines (TNF-α, IL-1β), bacterial, and viral products (LPS) (Xia et al., 2014).

NF-κB-regulated anti-apoptotic Bcl-2, Bcl-XL, c-IAP1, and surviving in human ovarian carcinoma cells (Gao et al., 2014), Cox-2 and VEGF in human pancreatic cancer cells (Deeb et al., 2014b). NF-κB pathway may link anti-tumor activity of pristimerin and its anti-inflammatory properties (Park and Kim, 2018). Pristimerin suppressed the translocation of NF-κB nuclear; however, there was no change of the total NF-κB protein in pancreatic cancer (Wang et al., 2012). In contrast, pristimerin inhibited both genetic expression and activation of NF-κB protein with suppression of p65 mRNA in human colorectal cancer cells (Yousef et al., 2018). TNFα-induced NF-κB activation was observed by the downstream MMP9, cyclin D1, and c-Myc in ESCC cells (Tu et al., 2018). When combined with pristimerin, the inactivation of Bcr-Abl by imatinib did not interfere with the TNFα-induced NF-κB activation, which implicated that NF-κB inactivation and Bcr-Abl inhibition may be parallel mechanisms of pristimerin-induced activity in human chronic myelogenous leukemia cells (Lu et al., 2010). G1 phase arrest was also associated with NF-κB pathway in human pancreatic cancer cells (Wang et al., 2012), as well as proteosome in human myeloma cells (Tiedemann et al., 2009). Moreover, pristimerin inhibited expression of miR-542-5p targeting PTPN1, which encodes protein tyrosine phosphatase 1B (PTP1B) related to NF-κB pathway (Li et al., 2019).

Wnt/β-Catenin Pathway
Wnt proteins are key mediators in a series of important cellular process. The abnormal activation of Wnt/β-catenin pathway can cause a wide range of diseases including cancers (Krishnamurthy and Kurzrock, 2018; Pedone and Marucci, 2019). Pristimerin was reported to suppress Wnt/β-catenin pathway through targeting and inhibiting the expression of LRP6 and its phosphorylation, which may contribute to autophagy in human breast cancer MCF-7 cells (Cevatemre et al., 2018).

CONCLUSIONS AND PERSPECTIVE
Plants, particularly medicinal herbs, have become increasingly popular due to their potent therapeutic effects. Pristimerin, a quininemethide triterpenoid compound isolated from species of the Celastraceae and Hippocrateaceae families, has displayed biological and pharmacological activities, particularly inhibiting cancer. This review summarizes the reported results on anti-cancer activities and related mechanisms of pristimerin.

Pristimerin has shown anti-cancer potency in vivo (Table 2) and in vitro (Table 3) via specific mechanisms (Figure 2). Like many other chemotherapy drugs, pristimerin exerts cytotoxicity largely related to apoptosis, while the mechanism of autophagy is merely reported. The cross-talk of apoptosis and autophagy mediated by pristimerin is still remained to be explored. So far, the mechanism study of pristimerin has little reported on lung cancer, epigenetic regulation, and combination with immunotherapy. Furthermore, pristimerin has been reported to have poor selective toxicity in some cancer cells or compared with its derivatives (Costa et al., 2008; Wei et al., 2014). Comprehensive evaluation of pristimerin toxicity is yet to be carried out (as well as clinical trials). In summary, pristimerin possesses potent anti-cancer effect and further study will bring about novel drug development based on pristimerin.
TABLE 3 | Anti-cancer mechanisms of pristimerin in different cell lines.

| Cancer type          | Cell lines              | Mechanisms                                                                 | References                     |
|----------------------|-------------------------|----------------------------------------------------------------------------|--------------------------------|
| Prostate cancer      | PC-3                    | Inhibited HIF-1α accumulation by inhibiting SPHK-1                        | (Huang et al., 2015)           |
|                      | LNCaP and PC-3          | Inhibited CD133 and CD44 protein expression, reduced VEGF                 |                                |
|                      |                         | Prevented survivin via the ubiquitin-proteasomal degradation pathway     | (Liu et al., 2013)             |
|                      |                         | Inhibited hTERT expression via the inhibition of SP1, c-Myc, STAT3, and B/Akt | (Liu et al., 2014)             |
|                      |                         | Suppressed proteasomal activity via increasing the levels of RGS4         | (Mu et al., 2012a)             |
|                      | LNCaP and PC-3          | Down-regulated Bcl-2 through an ROS-dependent ubiquitin-proteasomal degradation pathway | (Lee et al., 2013)             |
|                      |                         | Prevented survivin via the ubiquitin-proteasomal degradation pathway     | (Lee et al., 2013)             |
|                      |                         | Inhibited hTERT expression via the inhibition of SP1, c-Myc, STAT3, and B/Akt | (Liu et al., 2014)             |
|                      |                         | Suppressed the LC3-I levels of this protein via the ubiquitin-proteasomal degradation pathway | (Lee et al., 2015)             |
| Breast cancer        | SKBR3                   | Inhibited HER2, decreased fatty acid synthase                              | (Lee et al., 2018)             |
|                      | MDA-MB-231              | Suppressed the LC3-I levels of this protein via the ubiquitin-proteasomal degradation pathway | (Lee et al., 2015)             |
|                      |                        | Activated ROS, induced release of cytochrome c, and down-regulated EGFR protein | (Guo et al., 2013)             |
|                      |                        | Disrupted HSP90/CDC37 interaction, degraded and inhibited phosphorylation of protein kinases in the Raf/MEK/ERK and PI3K/AKT/mTOR signaling pathways | (Wei et al., 2014)             |
| Colorectal cancer    | HCT-116                 | Inhibited the AKT/FOXO3a pathway via decreasing cyclinD1 and Bcl-XL, increased the expression of p21 and p27 | (Park and Kim, 2018)           |
|                      | HCT-116                 | Inhibited activated NF-kB, TNFα, and activated LPS-induced NF-kB signaling pathway | (Yousef et al., 2018)         |
|                      | HCT-116, COLO-205, and SW-620 | Inhibited of phosphorylated EGFR and HER2 expression, caused inhibition of related downstream kinases. | (Yousef et al., 2016a)        |
| Hepatocellular cancer | HepG2                   | Generated ROS, induced release of cytochrome c, and down-regulated EGFR protein |                                |
| Pancreatic cancer    | BxPC-3, PAN-C-1, and AsPC-1 | Inhibited the translocation and DNA-binding activity of NF-κB             | (Wang et al., 2012)            |
|                      | MiaPaCa-2 and Panc-1    | Activated NF-κB via suppressing the transcription factors Sp1, c-Myc, and NF-κB | (Deeb et al., 2015)           |
| Gloma                | U87                     | Activated JNK through overproduction of ROS                               | (Zhao et al., 2016)            |
|                      | U373                    | Targeting AGO2 and PTEN1 expression via miR-542-5p                        | (Li et al., 2019)              |
| Myeloma              | H929 and U266           | Both inhibited IKK phosphorylation of iκB and proteosome, causing unfolded protein response and suppressing NF-κB activity and cyclin D expression | (Tiedemann et al., 2009)      |
|                     |                        | Activated ROS-dependent JNK, Bax, and PARP-1                             | (Eum et al., 2011)             |
| Cervical cancer      | HeLa                    | Interfered DNA synthesis                                                  | (Costa et al., 2009)           |
| Leukemia             | HIL-60                  | Depleted Bcr-Abl, activated TAK1/TNK and IκKStα in NF-κB signaling parallel but independent | (Lu et al., 2010)              |
| Ovarian carcinoma    | OVCAR-5, MDAH-2774,     | Inhibited prosurvival signaling proteins Akt, mTOR and NF-κB; inhibited NF-κB-regulated anti-apoptotic proteins Bcl-2, Bcl-XL, c-IAP1 and survivin | (Gao et al., 2014)             |
|                      | OVCAR-3, and SK-OV-3    | Decreased expression of Akt, mTOR, and NF-κB                              | (Mori et al., 2017)            |
| Osteosarcoma         | MNG and 143B            | Decreased expression of Akt, mTOR, and NF-κB                              | (Yan et al., 2017)             |
| Oral cancer          | KB200                   | Decreased P-gp through interrupt protein stability in MAPK and PI3K/Akt pathways | (Wu et al., 2019)              |
| ESCC                 | EC9706, EC109, and KYSE30 | Inhibited NF-κB pathway, synergistic effect with 5-FU                     | (Tu et al., 2018)              |

ESCC, esophageal squamous cell carcinoma; ROS, reactive oxygen species.

FIGURE 2 | Brief summary of anti-cancer mechanisms and activities of pristimerin.
DATA AVAILABILITY

All datasets analyzed for this study are included in the manuscript and the supplementary files.

AUTHOR CONTRIBUTIONS

JZ and HC conceived this review; JL and YY wrote the article. HS, YL, and CS revised the article.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.