Table SI. Mechanism of action of ursolic acid in gynecological and breast cancers.

First author/s, year	Model used	Possible mechanisms	Targets	Doses	(Ref.)
Ovarian cancer					
Song *et al*, 2012	Cell: SKOV3, A2780	Induce cell apoptosis	GSK-3β ↓, β-catenin ↓, caspase-3 ↑, caspase-9 ↑, AEG-1 ↓, p-ERK ↑, c-Myc ↓, Bcl-xl ↑	50 μM, 60 μM	(23)
Lin *et al*, 2020	Cell: SKOV3, normal ovarian surface epithelial cells	Increase reactive oxygen species' production and induce cell apoptosis	p-PI3K ↓, p-Akt ↓, Bax ↑, Bcl-2 ↓	35 μM, 75 μM	(37)
Ganapathy-Kanniappan and Geschwind, 2013	Cell: HEY, SKOV3 Animal: BALB/c nude mice	Inhibits ovarian cancer cell proliferation and promotes tumor apoptosis	KLF5 ↓, p-PI3K ↓. p-Akt ↓, c-Myc ↓,C-Caspase-3 ↑, Bax ↑, Bcl-2 ↓, CDK2 ↓, PFKP ↓, HK2 ↓, ALDOA ↓, GLUT1 ↓, LDHA ↓	80 μM, 40 μM	(38)
Xu *et al*, 2024	Animal: BALB/c mice	Mitigates cisplatin-induced ototoxic damage	TRPV1 ↓, Pro-Caspase 3 ↑, Cleaved-Caspase 3 ↓, calpain 2 ↓, 4-HNE ↓	80 mg/kg/day	(39)
Liu *et al*, 2025	Cell: SKOV3, A2780	Enhances the therapeutic efficacy of doxorubicin	MDR1 ↓, HuR ↓	10 μM	(40)
Talach *et al*, 2016	Cell: HEY, SKOV3, A2780	Enhances the sensitivity of ovarian CSCs to cisplatin	HIF-1α ↓, ABCG2 ↓, p-PI3k ↓, p-Akt ↓, CD44 ↓, CD133 ↓, Nanog ↓, OCT-4 ↓	28.223 μg/ml, 35.414 μg/ml, 30.031 μg/ml	(41)
Di *et al*, 2020	Cell: SKOV3	Suppresses stemness, EMT, and metastatic potential of ovarian cancer CSCs	Twist ↓, Slug, Snail ↓, Fibronectin ↓, CK19 ↓, Vimentin ↓, N-cadherin ↓, E-cadherin ↓	75 mg/l	(42)
Cervical cancer					
Li *et al*, 2021	Cell: HeLa	Induce cell apoptosis	Fas ↑, caspase-3/5/7/8 ↑, caspase-8 ↓, CDK5 ↑, TANK ↑, Calpain11 ↑, SAP18 ↓, CDC2L5 ↑, Testin ↑	15 μM	(43)
Batlle and Clevers, 2017	Cell: C33A, SiHa, CaSki, HeLa	Induces apoptosis and inhibits cell proliferation	Fas ↑, caspase-8 ↓, caspase-3 ↓, PARP ↓, p53 ↓, Rb ↓, E6/E7 ↑	15 μM	(44)

Saw *et al*, 2024	Cell: TC-1, HeLa Animal: C57BL/6J mice	Induces tumor cell death through the autophagic pathway	Caspase-3 ↓, Caspase-9 ↓, Bcl-2 ↓, Bax ↑, PARP ↓, LC3 I ↑, LC3 II ↑, Atg5 ↑, BECN1 ↓	30 μM, 50 mg/kg	(45)
Wang *et al*, 2016	Cell: HeLa	Induces tumor cell apoptosis through endoplasmic reticulum stress	cleaved caspase-3/Caspase-3 ↑, cleaved PARP /PARP ↑, CHOP ↑, GRP78 ↑	20 μM	(46)
Zhang *et al*, 2015	Cell: HeLa, SiHa, C-33A, ME-180	Enhances chemosensitivity and induces apoptosis	Caspase-3, Bcl-2 ↓, Bax ↑, cleaved PARP /PARP ↑, p21 ↑, cyclin D1 ↓, cyclin E ↓	8 μM	(47)
Endometrial cancer					
Yim *et al*, 2006	Cell: SNG-2, HEC108	Regulation of the Cell Cycle	cyclin D1 ↓, pERK1/2 ↓, FBXW8 ↓, Cullin1 ↓	50 μM	(25)
Yim *et al*, 2023	Cell: SNG-2, HEC108	Inhibit tumor cell proliferation and induce cell apoptosis	Caspase-3 ↑, PARP ↑, Bax ↑, Bcl-2 ↓, Apaf-1 ↓	75 μM	(48)
Leng *et al*, 2013	Cell: SNG-2	Inhibit tumor cell proliferation and induce mitochondria-dependent apoptosis	Caspase-3 ↑, Caspase-9 ↑, cytochrome c ↓, cleaved PARP /PARP ↑, Bax ↑, Bcl-2 ↓, Apaf-1 ↓	50 μM	(49)
Guo *et al*, 2019	Cell: SNG-2, HEC108	Inhibit tumor cell proliferation and induce cell apoptosis	PI3K ↓, Akt ↓, P44/42 ↓	50 μM	(50)
Breast cancer					
Li *et al*, 2010	Cell: MDA-MB-231	Inhibit the proliferation of tumor cells	Nrf-2 ↓, Keap1 ↑, SOD1 ↓, NQO1 ↓, EGFR ↓	20 μM	(51)
Achiwa *et al*, 2013	Animal: C57BL/6 mice	Inhibit tumor cell proliferation and induce apoptosis	Akt ↓, mTOR ↑, S6 ↑, MAPK p44/42 ↓, Cyclin D1 ↓	50 μM	(52)
Achiwa *et al*, 2005	Cell: MCF-7	Promote tumor cell apoptosis and inhibit tumor cell proliferation	FoxM1 ↓, CyclinD1 ↓, CDK4 ↓	30 μM	(53)
Achiwa *et al*, 2007	Cell: MCF-7, ATCC	Activate the mitochondrial pathway to induce intrinsic apoptosis	caspase-3 ↑, caspase-7 ↑, PARP ↓, Bcl-2 ↓	53 μM	(54)
Achiwa *et al*, 2005	Cell: MCF-7, MDA-MB-231	Regulate EMT and inhibit the growth and proliferation of breast cancer cells	Snail ↓, Slug ↓	20 μg/ml	(55)
Zhang *et al*, 2020	Cell: HCC1937	Enhance sensitivity to rhTRAIL and induce apoptosis	caspase 8 ↑, caspase 3 ↑, PARP ↓, DR4 ↑, DR5 ↑, c-FLIPL ↓	50 μM	(24)

De Angel *et al*, 2010	Cell: MCF7	Inhibit tumor cell proliferation	PLK1 ↓ , IKK ↓ , NF-κB ↓ , BRAF ↓ , ERK ↓ , IKKβ ↓ , p56 ↓	20 μM	(56)
Wang *et al*, 2012	Cell: MCF-7	Inhibit tumor cell proliferation	p38 ↑ , p53 ↑ , p21 ↑ , CDK4 ↓ , cyclin D ↓ , CDK2 ↓ , cyclin E ↓ , ERK ↓ , p-PI3K ↓ , p-Akt ↓ , FoxO3a ↑	20 μM	(57)
Kassi *et al*, 2009	Cell: MCF-7, MDA-MB-231	Induce endoplasmic reticulum stress and autophagy	LC3-I ↓ , LC3-II ↑ , BECN1 ↑ , ATG5 ↑ , MCL1 ↑ , MAPK1/3 ↑ , PARP1 ↑ , Akt ↓ , EIF4EBP1 ↑	20 μM	(58)
Mallepogu et al, 2023	Cell: MCF7, MDA-MB-231, MCF-12A	Synergize with oridonin to induce cytotoxic autophagy	PARP ↓ , mTOR ↓ , LC3-I ↓ , LC3-II ↑ , ATG-5 ↓ , ATG-7 ↓	10 μM	(59)
Manouchehri and Kalafatis, 2018	Cell: MCF-10, MDA-MB-231	Impact metabolic processes such as glycolysis, the TCA cycle, and lipid synthesis	NA	20 μM	(60)
Guo *et al*, 2020	Cell: MCF-7, MDA-MB-231, 4T1, HBL-100	Inhibit glycolysis and mitochondrial function in breast cancer cells, inducing mitochondria-dependent apoptosis	Bcl-2 ↓ , Bax ↑ , PARP ↑ , SP1 ↑ , CAV1 ↑ , PGC-1α ↓ , Nrf-1 ↓ , LDH-A ↓ , c-Myc ↓ ,	30 μM	(61)
Kim *et al*, 2021	Cell: MCF-7, MDA-MB-231, SK-BR-3	Induce autophagy and apoptosis in tumor cells through glycolysis	P53 ↑ , p21 ↑ , p27 ↑ , GLUT1 ↑ , HK2 ↑ , PKM2 ↓ , Akt ↓ , pAkt ↓ , AMPK ↑	20 μM	(62)
Zhao *et al*, 2013	Cell: MCF-7	Enhance lysosomal membrane permeability and cell death in breast cancer cells	NA	8 μM	(63)
Gupta *et al*, 2024	Cell: MCF7, MDA-MB-231, T47D	Suppress the proliferation, migration, and stemness characteristics of breast cancer stem cells	miRNA-499a-5 ↓ , caspase 3/7 ↑ , Bax ↑ , Bcl-2 ↓ , GSK-3β ↑	50 μM	(64)
Lewinska *et al*, 2017	Cell: MCF7, MDA-MB-231	Inhibit cancer stem cell characteristics as well as cell migration and invasion	AGO2 ↓ , Slug ↓ , Vimentin ↓ , FAK ↓ , c-Myc, PTEN ↑ , Akt ↓ , mTOR ↓ , CD133 ↓	30 μM	(65)
Fogde *et al*, 2022	Cell: MDA-MB-231, BT-549 Animal: BALB/c female mice	Induce ferroptosis in triple-negative breast cancer stem cells and inhibit their stemness and proliferation	KEAP1 ↑ , NRF2 ↓ , OCT4 ↓ , SOX2 ↓ , c-Myc ↓ , TFR1 ↓ , CD44 ↓ , CD24 ↑	20μM, 20 mg/kg	(66)

Guerra *et al*, 2020	Cell: MDA-MB-231	Inhibit the migration and invasion of tumor cells	MMP-2 ↓ , u-PA ↓ , TIMP-2 ↑ , PAI-1 ↑ , Akt ↓ , mTOR ↓ , JNK ↓	10μM	(67)
Wang *et al*, 2021	Cell: T47D, MCF-7, MDA-MB-231	Promote tumor cell apoptosis and inhibit tumor cell proliferation	IKKα ↓ , IκBα ↓ , p-NF-κB ↓ , IL-1β and IL-18 ↓ , PI3K ↓ , Akt ↓ , GSK3β ↑ and cyclin-D1 ↓	160 μg/ml	(68)
Mandal *et al*, 2021	Cell: MDA-MB-231, MDA-MB-468 Animal: BALB/c female nude mice	Inhibit tumor cell proliferation, migration, and invasion	MMP-2 ↓ , MMP-9 ↓ , caspase-3 ↑ , caspase-9 ↑ , Bcl-2 ↓ , PLK1 ↓ , CCNB1 ↓ , p53 ↑	25 μM, 100 mg/kg	(69)
Liao *et al*, 2022	Cell: MDA-MB-231, MDA-MB-436	Enhance sensitivity to chemotherapy drugs	ZEB1-AS1 ↓ , miR-186-5p ↓ , ABCC1 ↓	18 μg/ml, 22 μg/ml	(70)
Yang *et al*, 2024	Cell: MDA-MB-231, MCF-7	Enhance sensitivity to Epirubicin	Beclin-1 ↑ , LC3-II/LC3-I ↑ , Atg5 ↑ , Atg7 ↑ , PI3K ↓ , Akt ↓	20 μM	(71)
Yeh *et al*, 2010	Cell: MCF7	Enhance sensitivity to the chemotherapy drug DOX	NA	4 μM	(72)
Luo *et al*, 2017	Cell: MCF-7	Synergize with DOX to inhibit the invasion and migration of breast cancer cells	ODC ↓ , ERK1/2 ↓ , VEGF ↓ , MMP-9 ↓	2 μM	(73)
Zhang *et al*, 2021	Cell: MDA-MB-231, MCF-7 Animal: BALB/c female nude mice	Synergize with DOX to inhibit the proliferation and migration of drug-resistant breast cancer cells	Bcl-2 ↓ , Caspase3 ↓ , CDK4 ↓ , cyclin D1 ↓ , f Glut1 ↓ , AMPK ↑ , mTOR ↓ , PGC-1α ↓ , cytochrome C ↓	20 μM, 20 mg/kg	(74)
Lu *et al*, 2022	Cell: MDA-MB-231 Animal: female athymic nude mice	Reverse resistance to paclitaxel	miR-149-5p ↑ , Bax ↑ , Bcl-2 ↓ , My D88 ↓ , PI3K ↓ , Akt ↓	20 μM, 10 mg/kg	(75)

Table SII. Comparison of ursolic acid signaling pathways in different cancer types.

Signaling pathways / Targets	Ovarian cancer	Cervical cancer	Breast cancer	Endometrial cancer
PI3K/AKT	PI3K/AKT ↓ (inhibits glycolysis & survival)	PI3K/AKT ↓ (chemo-sensitization)	PI3K/AKT/mTOR ↓ (induces apoptosis, autophagy)	PI3K/AKT signaling ↓
NF-κB	NF-κB ↓ (enhances chemosensitivity)	NF-κB ↓ (sensitivity to paclitaxel ↑, CDDP)	NF-κB ↓ (reduces invasion, drug resistance)	N/A
MAPK/ERK	ROS-mediated MAPK activation ↑	N/A	RAF/ERK pathway ↓	N/A
JAK/STAT3	JAK2/STAT3 signaling ↓	N/A	STAT3 signaling ↓ (FZU3010, derivatives)	JAK2/STAT3 pathway ↓
Wnt/β-catenin	β-catenin ↓ (via GSK-3β activation)	N/A	Wnt/β-catenin ↓ via miR-499a-5p/sFRP4	N/A
p53 / Cell cycle regulators	p21, p27 ↑; G2/M arrest	CHOP ↑, GRP78 (ER stress-mediated apoptosis)	p53 ↑, p21; Cyclin D1/CDK4 ↓	Cell cycle arrest
Mitochondrial apoptosis (Bax/Bcl-2, Caspase cascade)	Bax/Bcl-2 ratio ↑; Caspase-3 ↑	Fas/caspase apoptosis ↑	Bax/Bcl-2 ratio ↑; Caspase-3 ↑	Caspase-3 ↑, apoptosis
Autophagy-related (AMPK, mTOR, Beclin-1, Atg5)	Autophagy ↑ (sensitizes to CDDP)	Atg5-dependent autophagy ↑ (cell death)	Autophagy ↑ / ↓ (context-dependent)	N/A
Stemness markers (CD133, ALDH1, EMT factors)	CSC stemness ↓ (CD133, ALDH1, HIF-1α/ABCG2)	N/A	BCSC stemness ↓ (miR-9, miR-221, KEAP1/NRF2, ferroptosis)	N/A
ROS generation / Oxidative stress	ROS production ↑	ROS via ER stress ↑	ROS ↑, mitochondrial apoptosis	ROS accumulation ↑
HPV oncogenes (E6/E7)	N/A	E6/E7 expression ↓	N/A	N/A
Fas/FasL pathway	Fas/FasL apoptosis ↑ (with CDDP)	Fas/FasL-caspase-8-BID axis ↑	TRAIL-mediated apoptosis ↑ (DR4/5 ↑, c-FLIPL ↓)	N/A

ROS, reactive oxygen species.