

Ursolic acid: A natural pentacyclic triterpenoid with clinical promise in gynecological and breast cancers (Review)

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Abstract. Gynecological and breast cancers pose significant challenges to women's health worldwide. Despite notable advancements in diagnosis and treatment, they remain leading causes of cancer-related mortality. Ursolic acid (UA), a naturally occurring pentacyclic triterpenoid widely found in plants, has garnered considerable attention due to its diverse pharmacological activities. It has been demonstrated that UA exhibits a range of biological effects, including antitumor, anti-inflammatory, and antioxidant properties, with particularly promising therapeutic potential in breast and gynecological cancers. UA exerts its anticancer effects by modulating multiple signaling pathways, such as PI3K/AKT, NF- κ B, and Wnt/ β -catenin, thereby effectively inhibiting tumor cell proliferation, inducing apoptosis, reversing chemoresistance, and suppressing cancer stem cell characteristics. When combined with chemotherapeutic agents such as cisplatin and doxorubicin, UA not only enhances antitumor efficacy but also mitigates the adverse effects associated with chemotherapy. The present review summarizes the recent research progress and underlying mechanisms of UA in the treatment of gynecological and breast cancers, aiming to provide valuable insights for researchers and clinicians in the field.

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1. Introduction

Gynecological malignancies represent a major threat to women's health. According to data from the International Agency for Research on Cancer in 2020, there are ~1.33 million new cases and 540,000 deaths related to gynecological cancers worldwide each year (1,2). Cervical, endometrial and ovarian cancers are the three most common malignancies of the female reproductive system and, together with breast cancer, constitute a substantial global health burden for women, accounting for nearly one-third of all cancer-related incidence and mortality among female patients (3). Despite significant progress in screening, diagnosis and treatment, these malignancies remain leading causes of female cancer-related deaths due to their biological heterogeneity, late-stage diagnosis and therapeutic resistance (4,5). Breast cancer is the most prevalent malignancy in women. Molecular subtyping-such as estrogen/progesterone receptor (ER/PR)-positive, HER2-enriched, and triple-negative breast cancer (TNBC)-has led to breakthroughs in targeted therapies, including CDK4/6 inhibitors and anti-HER2 agents (6). However, the management of metastatic disease and the emergence of drug resistance continue to pose major challenges. Among gynecological cancers, ovarian cancer has the highest mortality rate due to its asymptomatic nature and frequent diagnosis at an advanced stage (7). Recent advances, such as PARP inhibitors for BRCA-mutated tumors and immunotherapy, have redefined treatment strategies, yet the high recurrence rate underscores the urgent need for novel biomarkers (8). Endometrial cancer has traditionally been associated with obesity and metabolic disorders, and molecular subtypes identified through The Cancer Genome Atlas-including POLE-ultra-mutated and microsatellite instability-high types-have provided a basis for risk stratification and immunotherapy application (9). While cervical cancer is largely preventable through HPV vaccination and early screening, it remains prevalent in low-resource regions. Emerging therapies, such as PD-1/PD-L1 inhibitors and therapeutic vaccines, offer new hope for patients with advanced disease (10).

Currently, surgical resection, radiotherapy, chemotherapy, targeted therapy and immunotherapy are employed in the treatment of gynecological malignancies. However, the incidence and mortality rates of these cancers continue to rise annually (11,12). Despite advances in modern medicine, therapeutic efficacy remains limited, and challenges such as drug resistance

and adverse side effects persist (13). Increasing attention has therefore been directed toward bioactive compounds from traditional Chinese medicine as complementary or alternative therapeutic strategies in breast and gynecological cancers (14). Natural products such as curcumin, quercetin and tanshinone have demonstrated anti-proliferative, pro-apoptotic, anti-metastatic and chemo-sensitizing activities via regulation of multiple signaling pathways, including PI3K/AKT, NF- κ B and Wnt/ β -catenin (15-17). Among them, ursolic acid (UA), a pentacyclic triterpenoid widely distributed in vegetables, fruits and medicinal herbs (18), has attracted increasing interest due to its potent anticancer properties and relatively low toxicity. UA exerts broad antitumor effects by modulating diverse cellular processes, including proliferation, apoptosis, metastasis and chemoresistance, while sparing normal cells (19,20). Furthermore, UA exhibits neuroprotective effects such as analgesic, anxiolytic, antidepressant and memory-enhancing properties, underscoring its vast pharmacological potential and clinical applicability (21,22). Recent studies suggest that UA holds significant therapeutic potential in gynecological and breast cancers, particularly through regulation of key oncogenic pathways and enhancement of conventional treatment efficacy (23-25). The present review summarizes current progress on the anticancer mechanisms of UA in these malignancies, with emphasis on molecular targets, the development of UA derivatives, and novel formulations aimed at improving its bioavailability and clinical applicability.

2. Structural properties, natural origins and extraction methods of UA

UA, with the molecular formula $C_{30}H_{48}O_3$, is a pentacyclic triterpenoid compound (26). It exists either in its free acid form or as the aglycone component of triterpenoid saponins, and is widely distributed in natural plants such as *Plantago asiatica*, *Cornus officinalis*, *Crataegus pinnatifida*, *Hedyotis diffusa*, *Prunella vulgaris*, rosemary, loquat and apples (27). UA is a structurally complex molecule featuring 10 chiral centers, making it challenging to synthesize via conventional chemical methods. At present, extraction from natural plant sources remains the primary approach for obtaining UA.

Pure UA appears as white crystals that are soluble in methanol, ethanol and butanol, sparingly soluble in ether and chloroform, and insoluble in water and petroleum ether (28). Traditional extraction techniques-such as Soxhlet extraction, pulverization extraction and reflux extraction-often suffer from limitations including low purity and extended processing time (29). With technological advancements, novel extraction methods such as ultrasonic-assisted extraction, supercritical fluid extraction and semi-bionic extraction have gained attention (30). Among these, the semi-bionic approach, which simulates gastrointestinal digestion and absorption based on biopharmaceutics theory, has shown improved efficiency in isolating target compounds. Studies have demonstrated that parameters such as the solvent-to-material ratio, ethanol concentration, ultrasonic duration and power significantly influence the yield of UA during ultrasonic-assisted extraction (21,31,32). Due to its strong lipophilicity, UA is optimally extracted using low-polarity solvents such as ethanol (33). Furthermore, with continued research, the pharmacological

potential of UA derivatives has been increasingly recognized. Structural modifications at the C-3 and C-28 positions have been found to enhance its bioactivity (19,34). Some derivatives exhibit notable antitumor, antifungal and antioxidant properties, providing a theoretical foundation and experimental support for novel drug development (35,36).

3. Anticancer mechanisms of UA in gynecological and breast cancers

UA, a natural pentacyclic triterpenoid compound, has demonstrated broad-spectrum anticancer potential in various gynecological malignancies, including ovarian, endometrial and cervical cancers, as well as in breast cancer. Its multifaceted mechanisms of action include induction of apoptosis, inhibition of cell proliferation and metastasis, regulation of metabolic reprogramming, suppression of cancer stem cell (CSC) properties, and enhancement of chemosensitivity (Table SI).

UA and ovarian cancer

Induction of tumor cell apoptosis. UA can effectively inhibit the proliferation of tumor cells by inducing apoptosis and causing cell cycle arrest. Song *et al* (23) systematically elucidated the pro-apoptotic mechanisms of UA and found that it induces a classical apoptotic process in SKOV3 ovarian cancer cells, activates the caspase cascade, suppresses the expression of oncogenic proteins such as c-Myc, and enhances its antitumor effects by activating the GSK-3 β / β -catenin signaling pathway. Subsequently, Lin and Ye (37) further confirmed the inhibitory effects of UA on ovarian cancer cells, demonstrating that it suppresses cell proliferation in a dose-dependent manner with high selectivity. The underlying mechanisms include the induction of apoptosis, G2/M phase cell cycle arrest, elevation of intracellular reactive oxygen species (ROS) levels, modulation of the Bax/Bcl-2 ratio, and inhibition of the PI3K/AKT signaling pathway.

Regulation of metabolic reprogramming. Beyond apoptosis, UA also disrupts ovarian cancer metabolism. Glycolysis serves as a critical energy metabolism pathway in ovarian cancer cells, and its dysregulation is closely associated with tumor progression and chemoresistance (38). RNA sequencing and a series of *in vitro* and *in vivo* experiments have demonstrated that UA significantly inhibits ovarian cancer cell proliferation, induces apoptosis, and reduces glycolytic activity (39). Mechanistically, UA binds to and inhibits the transcription factor KLF5, thereby blocking the transcriptional activation of the downstream PI3K/AKT signaling pathway. This dual inhibition of glycolysis and cancer cell survival highlights the therapeutic potential of UA in targeting metabolic vulnerabilities in ovarian cancer.

Enhancing efficacy and reducing toxicity via chemotherapy combination. In addition to direct tumor inhibition, UA also plays an important role in improving chemotherapy outcomes. Cisplatin (CDDP) is widely used in the treatment of various cancers; however, its ototoxicity often leads to irreversible hearing loss (40,41). A study by Di *et al* (42) demonstrated that UA significantly alleviates CDDP-induced ototoxic damage and preserves auditory function by inhibiting the TRPV1/Ca²⁺/calpain-oxidative stress signaling pathway.

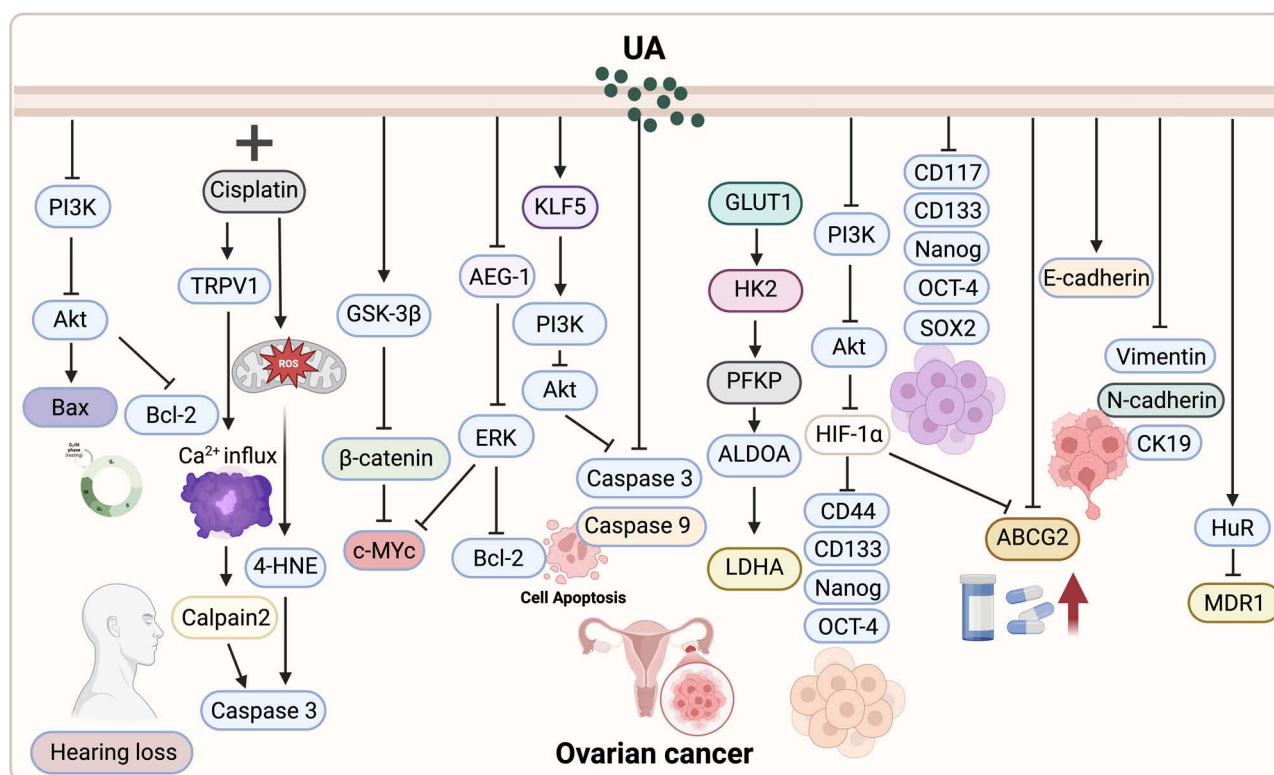


Figure 1. UA exerts multifaceted antitumor effects against ovarian cancer. It induces apoptosis and cell cycle arrest by activating the caspase cascade, modulating the Bax/Bcl-2 ratio, and inhibiting the PI3K/AKT and GSK-3 β / β -catenin pathways. UA also suppresses glycolysis and metabolic reprogramming by targeting KLF5 and downstream PI3K/AKT signaling. When combined with chemotherapeutic agents such as cisplatin and doxorubicin, UA enhances efficacy while reducing toxicity and reversing drug resistance through regulation of HuR/MDR1 expression. Additionally, UA targets ovarian cancer stem cells, inhibiting their self-renewal, migration and stemness via suppression of the PI3K/AKT and HIF-1 α /ABCG2 pathways, and downregulation of CD133, ALDH1, N-cadherin and vimentin. These mechanisms collectively highlight UA's therapeutic potential in overcoming chemoresistance and improving ovarian cancer treatment outcomes. UA, ursolic acid.

Notably, UA also enhances the antitumor efficacy of CDDP against ovarian cancer cells, exerting synergistic and protective effects without compromising its anticancer potency. Beyond CDDP, ovarian cancer is also prone to developing resistance to chemotherapeutic agents such as doxorubicin, which remains a major cause of treatment failure. Li *et al* (43) established a doxorubicin-resistant SKOV3-Adr cell model and found that UA markedly increased the sensitivity of these cells to doxorubicin. Furthermore, UA synergistically enhanced the efficacy of doxorubicin in both parental SKOV3 and A2780 cells. Mechanistically, although HuR mRNA expression levels were comparable between SKOV3 and SKOV3-Adr cells, HuR protein was predominantly accumulated in the cytoplasm of resistant cells, where it stabilized MDR1 mRNA and promoted drug resistance. UA facilitated the translocation of HuR from the cytoplasm to the nucleus, thereby reducing MDR1 mRNA stability and downregulating its expression, ultimately restoring sensitivity to doxorubicin. The present study highlights a novel mechanism by which UA reverses chemoresistance in ovarian cancer through post-transcriptional regulation of mRNA stability, underscoring its potential as an adjuvant to conventional chemotherapy.

Inhibition of CSC traits and drug-resistant phenotype. In ovarian cancer, CSCs are recognized as key contributors to tumor recurrence, metastasis and chemoresistance (44,45). Emerging evidence suggests that UA can enhance the sensitivity

of ovarian cancer CSCs to CDDP, significantly reversing the stemness and drug-resistant phenotypes typically induced by the hypoxic tumor microenvironment (TME). This effect is closely associated with inhibition of the PI3K/Akt signaling pathway and downregulation of the HIF-1 α /ABCG2 axis, with further therapeutic enhancement observed when combined with HIF-1 α inhibitors (46). Moreover, UA suppresses the self-renewal and migratory capacities of ovarian CSCs by downregulating stem cell markers such as CD133 and ALDH1, as well as epithelial-mesenchymal transition (EMT)-related factors including N-cadherin and vimentin. These changes contribute to a marked improvement in the efficacy of chemotherapeutic agents (47). Collectively, these findings highlight the promising potential of UA in targeting CSC-associated stemness maintenance and overcoming chemoresistance in ovarian cancer (Fig. 1).

UA and cervical cancer

Antiviral and pro-apoptotic effects. UA exhibits multiple biological effects in cervical cancer cells, with particularly notable advantages in antiviral activity and apoptosis induction. Using proteomic techniques including 2DE/MALDI-TOF-MS and SELDI-TOF-MS, Yim *et al* (25) analyzed HeLa cells treated with UA and identified significant alterations in the expression of 25 proteins, most of which were associated with apoptotic processes. Additionally, eight

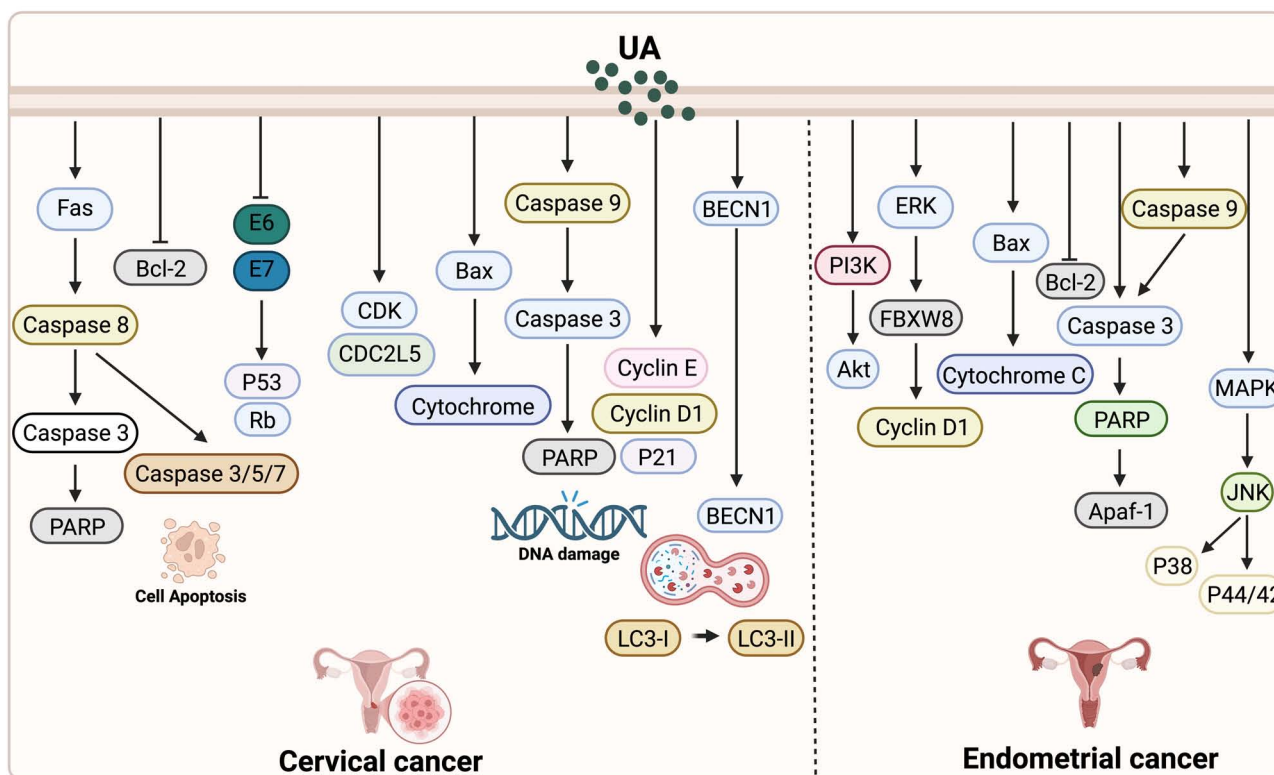


Figure 2. Antitumor mechanisms of UA in cervical and endometrial cancers. In cervical cancer, UA induces apoptosis via Fas/caspase signaling, downregulates HPV E6/E7, promotes autophagy through Atg5, triggers ER stress-mediated apoptosis, and enhances cisplatin/paclitaxel sensitivity by inhibiting NF- κ B. In endometrial cancer, UA suppresses Cyclin D1 via MAPK and SCF complex inhibition, induces mitochondrial apoptosis through caspase activation and Bcl-2/Bax modulation, and inhibits PI3K-Akt and MAPK pathways to block proliferation and promote cell death. UA, ursolic acid.

distinct peptide peaks were observed. In a subsequent study, Yim *et al* (48) further demonstrated that UA exerts potent antiproliferative and pro-apoptotic effects specifically in HPV-positive cervical cancer cells, along with measurable antiviral activity. Mechanistically, UA was shown to activate the Fas/caspase-mediated apoptotic pathway and suppress the expression of HPV oncogenes E6 and E7.

Autophagy-mediated cell death. Beyond apoptosis, UA also induces autophagy as an alternative form of tumor cell death. Leng *et al* (49) reported that in mouse cervical cancer TC-1 cells, UA predominantly induces Atg5-dependent autophagy rather than classical apoptosis to exert its anticancer effects. Inhibition of autophagy or knockdown of Atg5 significantly increased cell viability, suggesting that UA promotes tumor cell death primarily through autophagic pathways. These findings provide new insights into autophagy as a complementary mechanism to apoptosis in UA-mediated cancer therapy. Notably, however, in other tumor types such as breast cancer, UA-induced autophagy may not uniformly lead to cell death but instead exert context-dependent, and occasionally cytoprotective, effects.

Endoplasmic reticulum (ER) stress-related apoptotic mechanism. Another important mechanism by which UA induces cervical cancer cell death involves the activation of the ER stress pathway. Guo *et al* (50) treated HeLa cells with UA and/or the ER stress inhibitor 4-phenylbutyric acid (4-PBA), and found that UA inhibited cell viability and induced apoptosis in a time- and dose-dependent manner. Mechanistically, UA significantly upregulated the expression of key ER stress

markers such as GRP78 and CHOP, while the addition of 4-PBA partially reversed its pro-apoptotic effects.

Chemotherapy synergistic effect. In addition to its direct anticancer actions, UA enhances the efficacy of conventional chemotherapy in cervical cancer. Li *et al* (51) reported that UA increases the sensitivity of cervical cancer cells to commonly used chemotherapeutic agents such as paclitaxel and CDDP by inhibiting the NF- κ B signaling pathway. Combination treatment activates the Fas/FasL-caspase-8-BID axis and enhances the mitochondrial apoptotic pathway, selectively promoting apoptosis in tumor cells without exerting toxicity on normal cells. Furthermore, co-treatment with UA and CDDP significantly downregulates the expression of NF- κ B p65 and Bcl-2, while upregulating the levels of Bax, cleaved caspase-3 and PARP cleavage products, thereby markedly increasing the rate of apoptosis (Fig. 2).

UA and endometrial cancer. UA has demonstrated multiple antitumor mechanisms in endometrial cancer research (Fig. 2). Achiwa *et al* (52) found that UA downregulates Cyclin D1 expression and interferes with cell cycle regulation by inhibiting the MAPK-Cyclin D1 signaling pathway and the RING-type E3 ligase SCF complex, thereby preventing the ubiquitin-dependent degradation of Cyclin D1. Additionally, UA has been identified to exert its effects via the CD36 membrane receptor, suggesting a potentially important role in protein homeostasis and membrane receptor signaling regulation (53). In terms of apoptosis' induction, UA inhibits the proliferation of endometrial cancer cells in a dose- and

time-dependent manner. It triggers mitochondrial-mediated apoptosis by activating caspases-3, -8, and -9, promoting PARP cleavage, inducing DNA fragmentation, and facilitating cytochrome c release. This is accompanied by downregulation of the anti-apoptotic protein Bcl-2 and upregulation of the pro-apoptotic protein Bax (54). Moreover, UA significantly suppresses the PI3K-Akt and MAPK signaling pathways (including JNK, p38 and ERK1/2), reducing the phosphorylation levels of key proteins and thereby further enhancing its antiproliferative and pro-apoptotic effects-particularly notable in SNG-II cells (55). Taken together, UA exerts synergistic effects through multiple signaling pathways to regulate the cell cycle, inhibit proliferation, and induce apoptosis, highlighting its therapeutic potential in endometrial cancer.

UA and breast cancer

Inhibition of cell proliferation and induction of apoptosis.

One of the most extensively studied effects of UA in breast cancer is its ability to suppress tumor cell proliferation and trigger apoptosis. Zhang *et al* (24) found that UA suppresses the proliferation of MDA-MB-231 breast cancer cells by modulating the Keap1/Nrf2 and EGFR/Nrf2 pathways. It also upregulates Nrf2 and its downstream target genes such as NQO1 and SOD1 via post-translational regulation. De Angel *et al* (56) demonstrated that UA inhibits tumor growth in breast cancer mouse models, potentially through modulation of the Akt/mTOR pathway, induction of apoptosis, and disruption of the cell cycle. Wang *et al* (57) reported that UA suppresses MCF-7 cell proliferation by downregulating the transcription factor FoxM1 and inhibiting the Cyclin D1/CDK4 signaling pathway. Additionally, Kassi *et al* (58) observed that UA induces intrinsic apoptosis via activation of the mitochondrial pathway and may interact with the glucocorticoid receptor (GR), suggesting a regulatory effect on GR function. Mallepogu *et al* (59) found that UA induces cell cycle arrest and apoptosis, and inhibits EMT by downregulating EMT-related genes such as Snail and Slug. Manouchehri and Kalafatis (60) revealed that UA sensitizes triple-negative breast cancer cells to rhTRAIL-induced apoptosis by upregulating death receptors DR4/5 and downregulating the anti-apoptotic molecule c-FLIPL. Guo *et al* (61) showed that UA significantly inhibits the proliferation of MCF-7 cells by suppressing both the RAF/ERK and IKK/NF- κ B signaling pathways. Furthermore, Kim (62) reported that UA induces cell cycle arrest in breast cancer stem-like cells by increasing the expression of p53 and p21 and decreasing the expression of cyclins D and E, as well as CDK4 and CDK2. This is accompanied by inhibition of the ERK and PI3K/AKT signaling pathways, contributing to the anti-proliferative effects.

Induction of autophagy and improvement of metabolism.

UA exhibits significant potential in inducing autophagy and modulating cellular metabolism in breast cancer cells, but its effects appear to be context-dependent. Regarding autophagy, Zhao *et al* (63) reported that UA upregulates MCL1 via the MAPK1/3 signaling pathway, which partially counteracts UA-induced apoptosis, indicating a cytoprotective role of autophagy. By contrast, Gupta *et al* (64) demonstrated that UA, in combination with oleanolic acid, synergistically induces cytotoxic autophagy, thereby enhancing its antitumor efficacy.

Lewinska *et al* (65) further showed that UA promotes oxidative stress and DNA damage by inhibiting the AKT pathway and activating the AMPK pathway, ultimately triggering both autophagy and apoptosis, while Fogde *et al* (66) found that UA induces apoptosis by disrupting lysosomal function and indirectly suppressing autophagy. Collectively, these findings suggest that UA-induced autophagy in breast cancer may function as a 'double-edged sword', either supporting tumor cell survival or promoting cell death depending on the cellular and signaling context.

In addition to its role in autophagy, UA also exhibits pronounced metabolic regulatory effects. Guerra *et al* (67) revealed that UA influences key metabolic processes, including glycolysis the tricarboxylic acid cycle and lipid biosynthesis, in both breast cancer cells and normal mammary epithelial cells, suggesting a broader cellular detoxification response. Similarly, Wang *et al* (68) demonstrated that UA activates the SP1/Caveolin-1 pathway to suppress glycolysis and impair mitochondrial function, leading to mitochondria-dependent apoptosis. These findings highlight that UA not only reprograms cancer cell metabolism but also couples metabolic stress with cell death pathways. Taken together, UA enhances its antitumor activity in breast cancer through the dual regulation of autophagy and metabolic reprogramming.

Importantly, the context-dependent nature of UA-induced autophagy also carries therapeutic implications. When autophagy functions as a pro-death mechanism, UA may synergize with apoptosis to maximize anticancer efficacy. Conversely, when autophagy plays a pro-survival role, it could undermine UA's therapeutic effects, suggesting that combination with autophagy inhibitors (for example, chloroquine or 3-methyladenine) may enhance treatment outcomes. This dualistic role underscores the necessity of identifying tumor-specific contexts and potential biomarkers to predict autophagy responses. Future studies should therefore not only clarify the upstream and downstream signaling pathways of UA-mediated autophagy but also evaluate combined therapeutic strategies that either exploit or counteract autophagy, thereby optimizing the clinical benefit of UA-based interventions.

Targeting breast CSCs. CSCs play a crucial role in therapy resistance and disease relapse. Accumulating evidence suggests that UA effectively targets breast CSCs (BCSCs). Mandal *et al* (69) found that UA downregulates the oncogenic microRNA miR-499a-5p and upregulates the Wnt inhibitor sFRP4, thereby inhibiting the Wnt/ β -catenin signaling pathway and attenuating the proliferation, migration and stem-like traits of BCSCs. Similarly, Liao *et al* (70) demonstrated that UA suppresses the expression of Argonaute 2, leading to reduced levels of miR-9 and miR-221, which in turn decreases the expression of stemness markers and EMT-related proteins. This results in the inhibition of CSC characteristics, as well as diminished migratory and invasive capacities. Moreover, Yang *et al* (71) reported that UA stabilizes KEAP1 and inhibits NRF2 pathway activation, inducing ferroptosis in triple-negative BCSCs. This effectively impairs their stemness and proliferative abilities and has been validated *in vivo* using animal models. Collectively, these findings highlight the potential of UA in targeting BCSCs, offering novel insights into its application as an anticancer therapeutic agent.

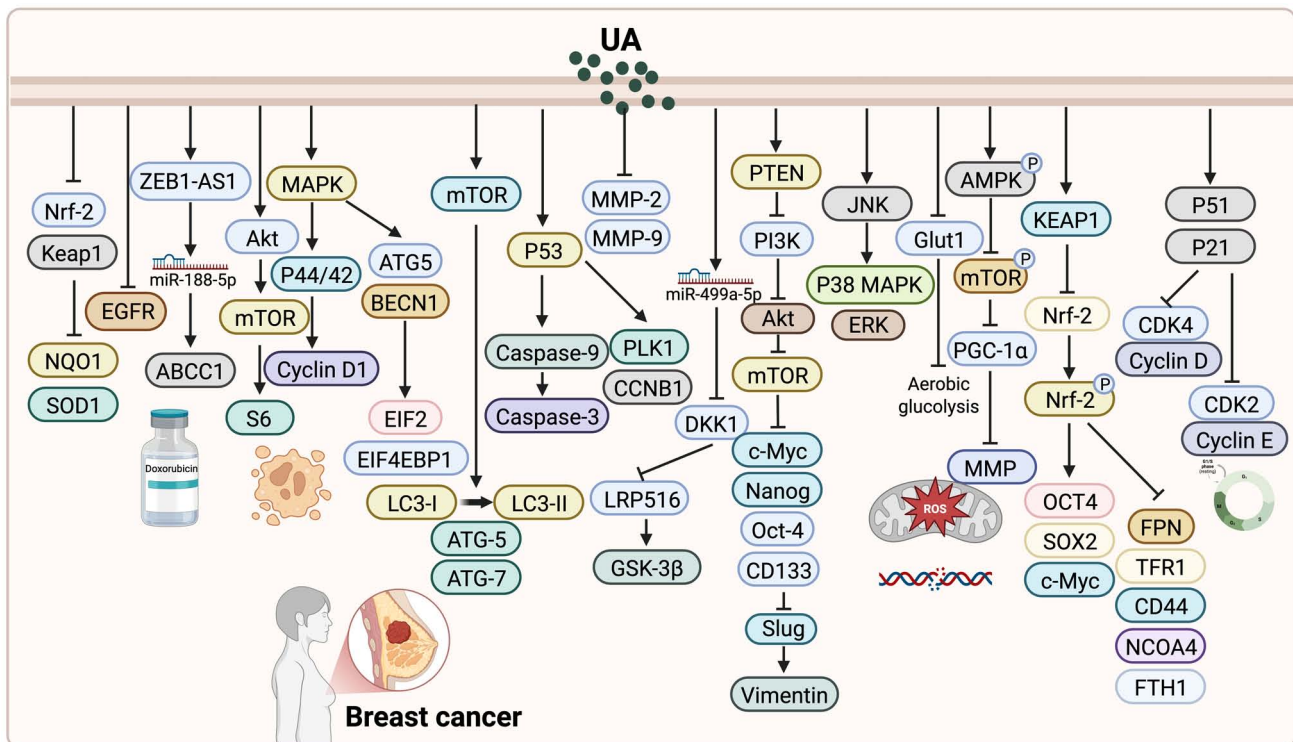


Figure 3. Antitumor mechanisms of UA in breast cancer. UA inhibits proliferation and induces apoptosis in breast cancer cells via pathways such as Keap1/Nrf2, Akt/mTOR, FoxM1 and mitochondrial caspase signaling. It induces autophagy and metabolic disruption through modulation of MAPK, SP1/CAV1, AMPK and AKT pathways, and regulates glycolysis and mitochondrial function. UA also targets breast cancer stem cells by suppressing Wnt/ β -catenin, AGO2/miR-9/miR-221 and NRF2 signaling, impairing stemness and promoting ferroptosis. Additionally, UA inhibits invasion and metastasis by downregulating MMP-2, u-PA, and PI3K/Akt, while enhancing autophagy, apoptosis, and anti-inflammatory responses. UA, ursolic acid.

Interfering with metastasis and invasion. Metastasis is the leading cause of breast cancer mortality, and UA has been shown to effectively inhibit this process. Yeh *et al* (72) reported that UA, at non-cytotoxic concentrations, markedly suppresses the migration and invasion of TNBC cells. This effect is mediated by the downregulation of MMP-2 and u-PA expression, along with the upregulation of endogenous inhibitors, thereby disrupting metastatic signaling pathways. Luo *et al* (73) further confirmed that UA inhibits the PI3K/Akt signaling pathway, activates GSK and caspase-3, and downregulates Cyclin D1 and Bcl-2 expression. These molecular events collectively induce autophagy and apoptosis while suppressing NF- κ B signaling, contributing to both anti-inflammatory effects and reduced cellular invasiveness. Additionally, Zhang *et al* (74) demonstrated that UA inhibits TNBC cell proliferation, migration and invasion in a dose-dependent manner by inducing cell cycle arrest and apoptosis. Together, these studies highlight the potential of UA as a promising agent for targeting metastasis and invasion in breast cancer therapy.

Enhancing drug sensitivity and reversing drug resistance. Chemoresistance is a major obstacle in breast cancer treatment, and UA has shown significant promise in overcoming this challenge. Lu *et al* (75) found that UA reverses doxorubicin (DOX) resistance in TNBC by downregulating ZEB1-AS1, thereby releasing its sponging effect on miR-186-5p and ultimately suppressing ABCC1 expression. Similarly, Wang *et al* (76) reported that UA significantly increases the sensitivity of breast cancer cells to epirubicin, partly by modulating the PI3K/Akt/mTOR signaling pathway to enhance

chemotherapeutic efficacy. Zong *et al* (77) demonstrated that UA, when co-administered with DOX, markedly increases DOX accumulation in multidrug-resistant breast cancer cells and promotes its nuclear translocation, thereby enhancing its antitumor activity. Further studies by the same group revealed that UA also inhibits the Erk-VEGF/MMP-9 signaling pathway, thereby reducing cell invasion and migration while concurrently increasing intracellular DOX accumulation (78). Luo *et al* (79) showed that the combination of UA and DOX significantly suppresses the proliferation and migration of drug-resistant breast cancer cells. This effect is mediated through modulation of the AMPK/mTOR/PGC-1 α axis, resulting in elevated ROS production and inhibition of aerobic glycolysis, ultimately enhancing DOX efficacy. Additionally, UA has been shown to reverse paclitaxel resistance in breast cancer by upregulating miR-149-5p, inhibiting MyD88, and downregulating the Akt signaling pathway (80). Collectively, these findings provide robust theoretical and experimental support for the use of UA as an adjuvant agent in combination chemotherapy to overcome drug resistance (Fig. 3).

4. Advances in drug delivery strategies and derivatives of UA

In recent years, various drug delivery strategies and structural derivatives have been developed to address the clinical limitations of UA, including poor water solubility, low bioavailability and limited targeting capacity. In ovarian cancer, Wang *et al* (81) designed a reduction-responsive amphiphilic

prodrug, Pt(IV)-UA-PEG, which self-assembles into nanoparticles [Pt(IV)-UA NPs] with high drug-loading efficiency. These nanoparticles enable efficient drug release in the reductive and acidic TME, effectively overcoming cisplatin resistance and significantly suppressing the proliferation of resistant ovarian cancer cells. In breast cancer, Jin *et al* (82) reported folic acid-modified chitosan nanoparticles that enhance targeted uptake and mitochondrial localization, inducing apoptosis via the mitochondrial pathway. Similarly, Fu *et al* (83) fabricated UA nanofibers for topical therapy in advanced breast cancer with skin ulceration, achieving improved transdermal penetration, inhibition of STAT3 and ERK1/2 signaling, and caspase-3-mediated apoptosis. For TNBC, Sharma *et al* (84) developed enzyme-responsive HA-UA/PTX nanoparticles, which enhanced CD44-mediated cellular uptake, apoptosis, and tumor suppression *in vivo*. Additionally, Liu *et al* (85) combined UA with a Nectin-4-targeted oncolytic measles virus, demonstrating synergistic apoptosis induction and enhanced autophagic flux, while UA-loaded nanoparticles further reinforced antitumor effects across breast cancer cell lines. In cervical cancer, Wang *et al* (86) constructed UA-loaded gold/PLGA nanocomposites for intranasal delivery, which inhibited proliferation, invasion and migration, while activating p53 and caspase signaling to induce apoptosis *in vitro* and *in vivo*.

Beyond delivery systems, structural optimization of UA has yielded derivatives with improved anticancer activity and pharmacological properties. The derivative FZU3010 demonstrated stronger anticancer activity than UA, particularly in renal cancer and TNBC cells, where it induced G1-phase arrest and apoptosis by inhibiting STAT3 and upregulating p21/p27 (87,88). The same group also reported an Asp-UA co-drug that effectively inhibited breast cancer cell adhesion, migration and invasion, highlighting its potential against metastasis (89). Pattnaik *et al* (90) synthesized novel UA derivatives with selective activity against MDA-MB-231 cells, among which compound 17 showed superior efficacy compared with doxorubicin. UA232, another optimized derivative, inhibited breast and cervical cancer cell proliferation by inducing apoptosis, cell cycle arrest, ER stress and lysosomal dysfunction, and exhibited robust antitumor effects *in vivo* (91). Other derivatives, such as water-soluble UAOS-Na with improved pharmacokinetics (92) and UA312 with radioprotective effects in zebrafish models (93), further demonstrate the versatility of rational structural modifications. Substitutions at key positions (for example, C-3 or C-28) have also generated potent derivatives with selective activity against leukemia and glioma cells (94).

Collectively, nanoparticle-based strategies, including polymeric nanoparticles and gold/PLGA nanocomposites, have proven most effective in improving water solubility, tumor targeting and controlled release, thereby enhancing intra-tumoral accumulation and antitumor efficacy. Liposomal and nanofiber-based formulations provide additional advantages in topical delivery and tissue penetration, making them particularly promising for breast cancer with skin involvement. By contrast, structural derivatives such as FZU3010 and UA232 demonstrate superior pharmacological potency and a broader range of mechanisms, including apoptosis, ferroptosis and ER stress, although their pharmacokinetic advantages

remain less established compared with nanoparticle systems. Taken together, these complementary approaches indicate that while nanoparticles effectively overcome bioavailability limitations, rational structural modifications expand UA's mechanistic spectrum and therapeutic potential. Future translational studies could benefit from combining both strategies—for example, encapsulating potent derivatives into advanced nanocarriers—to maximize bioavailability, therapeutic efficacy and clinical applicability.

5. Challenges and future perspectives

UA has demonstrated broad-spectrum antitumor potential in gynecologic malignancies, including ovarian endometrial cervical and breast cancers. Its anticancer mechanisms are multifaceted, involving the induction of apoptosis, cell cycle arrest, regulation of metabolic reprogramming, inhibition of CSC properties and enhancement of chemotherapeutic efficacy (95). Studies have shown that UA induces apoptosis in ovarian cancer cells through the activation of caspase cascades, upregulation of the Bax/Bcl-2 ratio and inhibition of the PI3K/AKT signaling pathway, thereby effectively suppressing tumor cell proliferation. Notably, when used in combination with chemotherapeutic agents, UA not only enhances their antitumor effects but also alleviates associated toxicities, such as CDDP-induced ototoxicity. Moreover, UA has been reported to exert antitumor effects in ovarian cancer by inhibiting glycolysis and modulating the KLF5/PI3K/AKT signaling axis, offering a novel strategy to overcome chemoresistance. In endometrial and cervical cancers, UA also exhibits potent antiproliferative and pro-apoptotic activities. Particularly in cervical cancer, UA activates the Fas/caspase-mediated apoptotic pathway and suppresses HPV-related oncogene expression, demonstrating both antiviral and antitumor effects. Regarding its synergistic role in cervical cancer chemotherapy, UA has been found to enhance the efficacy of paclitaxel and CDDP by inhibiting the NF- κ B signaling pathway. Importantly, it exerts minimal toxicity on normal cells, highlighting its potential for clinical application as an adjuvant therapeutic agent (Table SII).

Although UA demonstrates promising antitumor activity *in vitro* and in animal models, its clinical application is significantly hindered by poor oral bioavailability and complex metabolic processing. As a Biopharmaceutics Classification System Class IV compound, UA suffers from low aqueous solubility and limited intestinal permeability, resulting in poor absorption and diminished therapeutic efficacy (96). Following oral administration, UA is primarily distributed to the lungs, spleen and liver, but undergoes extensive first-pass metabolism—mainly through cytochrome P450 enzymes CYP3A4 and CYP2C9 in the liver and intestines—thereby reducing its systemic exposure and bioactivity (90,92). To overcome these limitations, various advanced drug delivery systems—such as chitosan-modified nanoparticles, liposomes and co-amorphous formulations—have been developed to improve UA's solubility, bioavailability and tumor-targeting capacity (87-91). These strategies have shown encouraging results in preclinical models, including enhanced oral absorption and increased accumulation at tumor sites. Nonetheless, their clinical utility remains uncertain and requires further optimization and validation (97). In addition, the safety and

long-term toxicity profile of UA are not yet fully understood. Although current data suggest minimal toxicity toward normal cells in short-term studies, potential off-target effects, bioaccumulation and organ-specific toxicity following prolonged administration cannot be excluded. Most available evidence is limited to preclinical research, highlighting the urgent need for systematic and long-term toxicological evaluations to support future clinical development.

UA has shown promise as an adjuvant agent in gynecological cancers, where it can enhance the efficacy of conventional chemotherapeutic drugs such as CDDP and paclitaxel while reversing drug resistance. Its therapeutic potential in breast cancer, particularly TNBC, also merits further investigation. However, most current evidence derives from *in vitro* studies and small animal models, and robust clinical trial data are still lacking. Future research should therefore prioritize clinical evaluation of UA to clarify its pharmacodynamics, safety and potential synergistic effects with standard treatments. In addition, the development of UA derivatives and novel combinatory regimens with other anticancer agents, including immunotherapies, represents an important direction. Notably, UA's anti-inflammatory and immunomodulatory properties suggest that it may improve the tumor immune microenvironment and enhance responsiveness to immune checkpoint inhibitors such as PD-1/PD-L1 blockade, although this hypothesis requires validation in preclinical and clinical studies.

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Authors' contributions

TC drafted the manuscript and prepared the figures. SS conducted the literature search and data collection. ZZ revised and proofread the manuscript. XZ supervised the overall study design, guided the research direction, and was responsible for manuscript drafting and final approval of the submitted version. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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