

Advances in the chemo-preventive effects and mechanisms of ursolic acid against lung cancer (Review)

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Abstract. Ursolic acid (UA), a natural pentacyclic triterpenoid carboxylic acid, exhibits diverse biological activities and notable antitumor properties. Lung cancer (LC), a leading malignancy of the respiratory system, is predominantly classified into small cell LC and non-small cell LC. The increasing incidence and mortality rates of LC have spurred considerable interest in the chemo-preventive potential of UA. Accumulating evidence demonstrates that UA markedly inhibits LC cell proliferation and induces apoptosis. Mechanistically, UA induces cell cycle arrest at the G0/G1 phase, thereby suppressing LC cell invasion, migration and tumor growth. Furthermore, UA has shown synergistic effects when combined with other therapeutic agents, including mitotic kinase inhibitors and multifunctional nanomedicines, effectively overcoming drug resistance in LC cells. These multifaceted mechanisms collectively contribute to the chemo-preventive efficacy of UA against LC. Consequently, UA represents a promising candidate for LC prevention and therapy. The present review comprehensively summarizes the anticancer effects and molecular mechanisms of UA in LC, offering insights to guide future research and facilitate the development of innovative therapeutic strategies.

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1. Introduction

Lung cancer (LC) is among the most prevalent and lethal malignancies worldwide, ranking as the leading cause of cancer-related mortality (1). Early-stage LC is often asymptomatic and difficult to detect, resulting in delayed diagnosis. For patients diagnosed at advanced stages, the five-year survival rate remains dismally low at ~6% (2). Globally, ~1.6 million new LC cases are reported annually (3). In men, LC constitutes the primary cause of both cancer incidence and mortality, whereas among women, its incidence ranks second only to breast and colorectal cancers (4). LC poses a significant public health burden, with major risk factors including exogenous environmental exposures such as tobacco exposure, occupational and environmental carcinogens, and air pollution, as well as endogenous biological factors such as genetic predisposition, chronic lung disease, and hormonal and metabolic factors (5,6). Despite substantial advancements in diagnostic and therapeutic modalities in recent years, the overall prognosis of LC remains poor, particularly for patients with advanced disease (7,8).

Chemoprevention, defined as the use of natural or synthetic agents to prevent, inhibit, delay, or reverse carcinogenesis, has attracted considerable attention as a strategy to combat LC (9). Although various candidate chemo-preventive agents such as vitamin E, isotretinoin and aspirin have been evaluated, none have demonstrated definitive clinical efficacy (10). Natural bioactive compounds, characterized by diverse pharmacological activities and relatively low toxicity, have emerged as promising candidates in cancer prevention and treatment, thereby becoming a central focus of chemoprevention research (11). Ursolic acid (UA; PubChem Compound ID: 64945) is a pentacyclic triterpenoid compound (C₃₀H₄₈O₃) widely distributed in various plants, including calendula, lavender, oregano, Melaleuca, sage, apple, rosemary and pear. It has garnered significant scientific interest due to its diverse biological activities (12,13). Previous studies have revealed that UA possesses multifaceted biological activities, including anti-inflammatory (14), antioxidant (15), and

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anti-obesity effects (16). Additionally, UA exhibits therapeutic potential in a variety of conditions, including diabetes (17), liver diseases (18), cardiovascular diseases (19), gastrointestinal disorders (20) and neurodegenerative diseases (21). Of particular note is its remarkable anticancer potential (22). UA has been demonstrated to inhibit tumor cell proliferation, induce apoptosis, and suppress tumor invasion and metastasis across multiple cancer types, including breast (23), pancreatic (24), prostate (25), colorectal (26), cervical (27) and renal cancers (28).

In LC chemoprevention, UA exerts its effects through multiple molecular mechanisms. Although extensive preclinical evidence supports the potential role of UA in LC prevention, the precise molecular pathways remain to be fully elucidated. Moreover, challenges related to the bioavailability, safety, and clinical efficacy of UA must be addressed to facilitate its translational application. The present review aims to comprehensively summarize the chemo-preventive effects and molecular mechanisms of UA in LC, thereby providing new insights and a theoretical framework for its future application in LC prevention and therapy.

2. UA and its derivatives

UA is a pentacyclic triterpenoid compound that naturally occurs either as triterpene saponins or in its free acid form (29,30). It is also referred to as ursone, malol, prunol, or 3 β -3-hydroxy-urs-12-en-28-oic acid (31). UA has the molecular formula C₃₀H₄₈O₃, a molecular weight of 456.68 g/mol, and a melting point ranging from 283-285°C (12,32). Its chemical structure comprises five rings—four six-membered and one five-membered—along with multiple hydroxyl and carboxyl functional groups. This distinctive molecular framework confers a broad spectrum of biological activities, including anti-inflammatory, antioxidant, antimicrobial and anticancer effects (33-35). Numerous studies have demonstrated that UA exerts potent anticancer effects across various malignancies (36,37). Its mechanisms of action extend beyond conventional pathways such as apoptosis induction and proliferation inhibition, encompassing unique molecular targets and biological processes. Importantly, UA selectively targets cancer stem cells (CSCs), impairing their self-renewal capacity, which is critical for tumor initiation and recurrence (38). Moreover, UA exhibits context-dependent modulation of autophagy, a process highly relevant to cancer therapy. At low concentrations, UA activates the AMP-activated protein kinase/mammalian target of rapamycin pathway, inducing protective autophagy that facilitates the clearance of damaged cellular components and enhances chemoresistance. Conversely, at high concentrations, UA inhibits autophagy by blocking autophagosome-lysosome fusion, thereby promoting autophagic cell death and augmenting its anticancer efficacy. Beyond autophagy regulation, UA exerts precise anticancer effects by modulating glycolytic metabolism (39), inducing structural modifications (40), and remodeling the tumor microenvironment (41). These multifaceted actions underscore UA as a promising candidate for cancer therapy.

To improve the pharmacological activity and therapeutic potential of UA, various derivatives have been synthesized through chemical modifications targeting its hydroxyl,

carboxyl and cyclic backbone moieties. Most reported UA derivatives fall into two principal categories: modifications at C-3/C-28, C-11, C-17 and C-28 positions, and structural alterations involving C-2/C-3 and the A-ring (13,42). Representative examples include UA-piperazine-dithio-carbamate ruthenium (II) polypyridyl complexes, which induce antitumor activity via necrosis (43); corosolic acid (CA), a natural UA derivative that inhibits cancer cell proliferation through β -catenin down-regulation (44); UA232, which promotes apoptosis by inducing cell cycle arrest and endoplasmic reticulum (ER) stress (45); and compound 17, a UA-derived small molecule that triggers cancer cell death through macropinocytosis (46). Collectively, these findings suggest that UA derivatives exert anticancer effects through multi-target and multi-pathway mechanisms, enhancing the pharmacological potency and drug-like properties of UA. This not only reinforces its therapeutic efficacy but also offers novel insights for the development of innovative anticancer agents.

3. Chemo-preventive effects of UA on LC

Induction of autophagy and apoptosis in LC cells. Apoptosis plays a pivotal role in tumor development, progression and metastasis, yet cancer cells often evade apoptotic mechanisms to sustain survival (47). Induction of apoptosis facilitates the elimination of potentially harmful or precancerous cells, whereas inhibition of apoptotic pathways contributes to uncontrolled cell proliferation and malignant transformation (48). UA primarily induces apoptosis in LC cells through mitochondria-dependent (MD) pathways, ER stress pathways, and modulation of associated signaling cascades (Fig. 1).

Multiple studies have demonstrated that UA inhibits the proliferation of non-small cell LC (NSCLC) cells in a dose- and time-dependent manner while promoting apoptosis. UA activates caspase-3 and caspase-9, downregulates the anti-apoptotic protein Bcl-2, and upregulates the pro-apoptotic protein Bax, collectively inducing apoptotic cell death in LC cells (49). Matrix metalloproteinases (MMPs), a family of zinc-dependent endopeptidases, mediate extracellular matrix (ECM) remodeling, which is implicated in various pathological processes (50). Notably, upregulation of MMP gene expression has been associated with apoptosis induction in NSCLC cells. Lai *et al* (51) reported that treatment of H460 cells with UA for 24 h led to increased expression of MMP-1, -2, -3, -9, and -10, concomitant with activation of caspase-3, nuclear morphological changes, and DNA fragmentation, thereby promoting apoptosis. Additionally, Gou *et al* (45) demonstrated that the UA derivative UA232 induces apoptosis in A549 and H460 cells by causing G0/G1 phase cell cycle arrest and upregulating C/EBP-homologous protein, which triggers apoptosis via the ER stress pathway. Consistently, UA has been shown to exert anticancer effects in both A549 and H460 cells by inducing G0/G1 arrest and apoptosis, thereby suppressing tumor growth and progression (52).

Mitochondria are essential organelles involved in regulating cellular functions such as autophagy and apoptosis under stress conditions (53). Chen *et al* (54) observed that UA increases the expression of apoptosis-inducing factor and endonuclease G in NCI-H292 cells, promoting their release via the MD pathway and triggering apoptosis. To address UA's

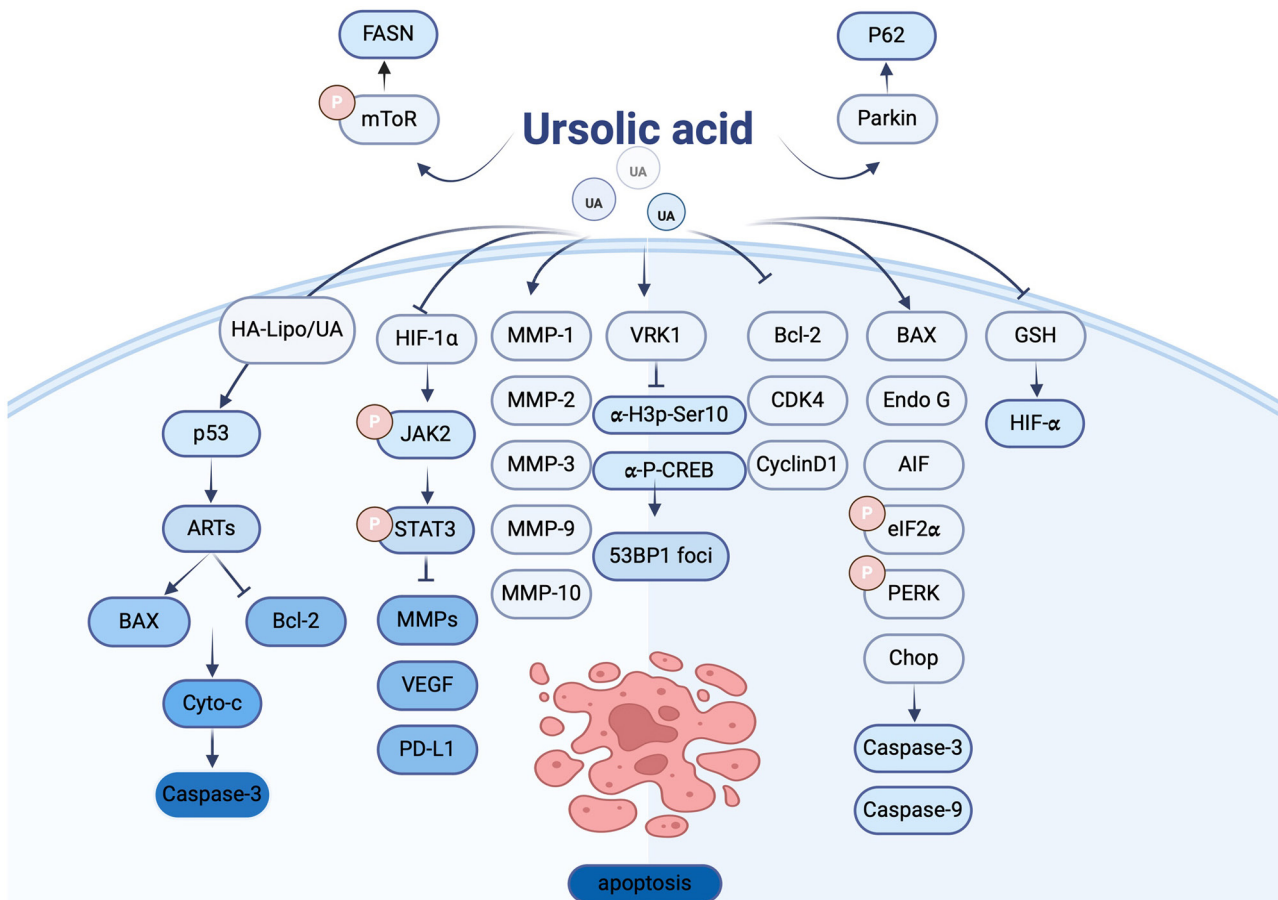


Figure 1. Molecular targets regulated by UA and their effects on cellular autophagy and apoptosis. UA, ursolic acid; HA-Lipo/UA, hyaluronic acid-liposome UA; GSH, glutathione; MMP, matrix metalloproteinase; ARTS, apoptosis-related protein in the TGF- β signaling pathway; HIF, hypoxia-inducible factor; PD-L1, programmed death-ligand 1; VRK1, vaccinia-related kinase 1; Chop, C/EBP-homologous protein. Figure created using Adobe Illustrator 2024 (v28.0), Adobe Inc.

limited solubility and lack of tumor specificity, Ma *et al* (55) developed a hyaluronic acid-liposome UA delivery system (HA-Lipo/UA). Their results showed that HA-Lipo/UA upregulated apoptosis-related protein in the TGF- β signaling pathway and p53 expression in A549 cells, activated caspase-3, and enhanced mitochondrial apoptosis, suggesting a promising strategy for targeted LC therapy.

Mitophagy, a selective autophagic process that degrades damaged mitochondria via lysosomal pathways, is another mechanism by which UA exerts anticancer effects. Castrejon-Jiménez *et al* (56) reported that UA induces mitophagy in A549 cells through a Parkin-independent mechanism, leading to p62 overexpression and subsequent apoptosis. Furthermore, Song *et al* (57) demonstrated that UA significantly enhances radiosensitivity in NSCLC cells, especially in radiation-resistant cells overexpressing hypoxia-inducible factor 1 alpha (HIF-1 α). By reducing the glutathione ratio and downregulating HIF-1 α in H1299/M-HIF-1 α cells, UA increases radiosensitivity and promotes radiation-induced cell death.

DNA damage repair (DDR) is critical for maintaining genomic stability (58). A strong correlation exists between DNA damage and the initiation of cell death pathways (59). When DNA repair mechanisms are compromised, apoptosis acts as a safeguard to eliminate damaged cells (60). Vaccinia-related

kinase 1 (VRK1), a mitotic kinase frequently overexpressed in lung adenocarcinoma, belongs to the nuclear serine-threonine chromatin kinase family (61). UA has been shown to bind the catalytic domain of VRK1, inhibiting its kinase activity. This interference impairs VRK1-mediated 53BP1 foci formation, thereby disrupting DDR and contributing to the therapeutic efficacy of UA against LC (62).

Inhibition of LC cell invasion and migration. Tumor metastasis is a major contributor to the high morbidity and mortality associated with cancer (63). Dysregulation of cancer cell migration critically influences the ability of tumor cells to detach from the primary site and invade surrounding tissues, thereby facilitating metastasis (63).

Proteases play a vital role in cancer progression not only by mediating ECM remodeling but also by regulating the bioavailability of growth factors, pro-angiogenic factors, and cytokines, which collectively promote tumor development through both direct and indirect mechanisms (64). However, the clinical application of UA is limited by its poor water solubility and insufficient tumor-targeting capability (65). To address these challenges, Xu *et al* (66) developed a novel multifunctional nanoparticle formulation [HA-modified UA and astragaloside IV (AS-IV)-loaded polydopamine nanoparticles (NPs; UA/(AS-IV)@PDA-HA)]. This delivery system significantly

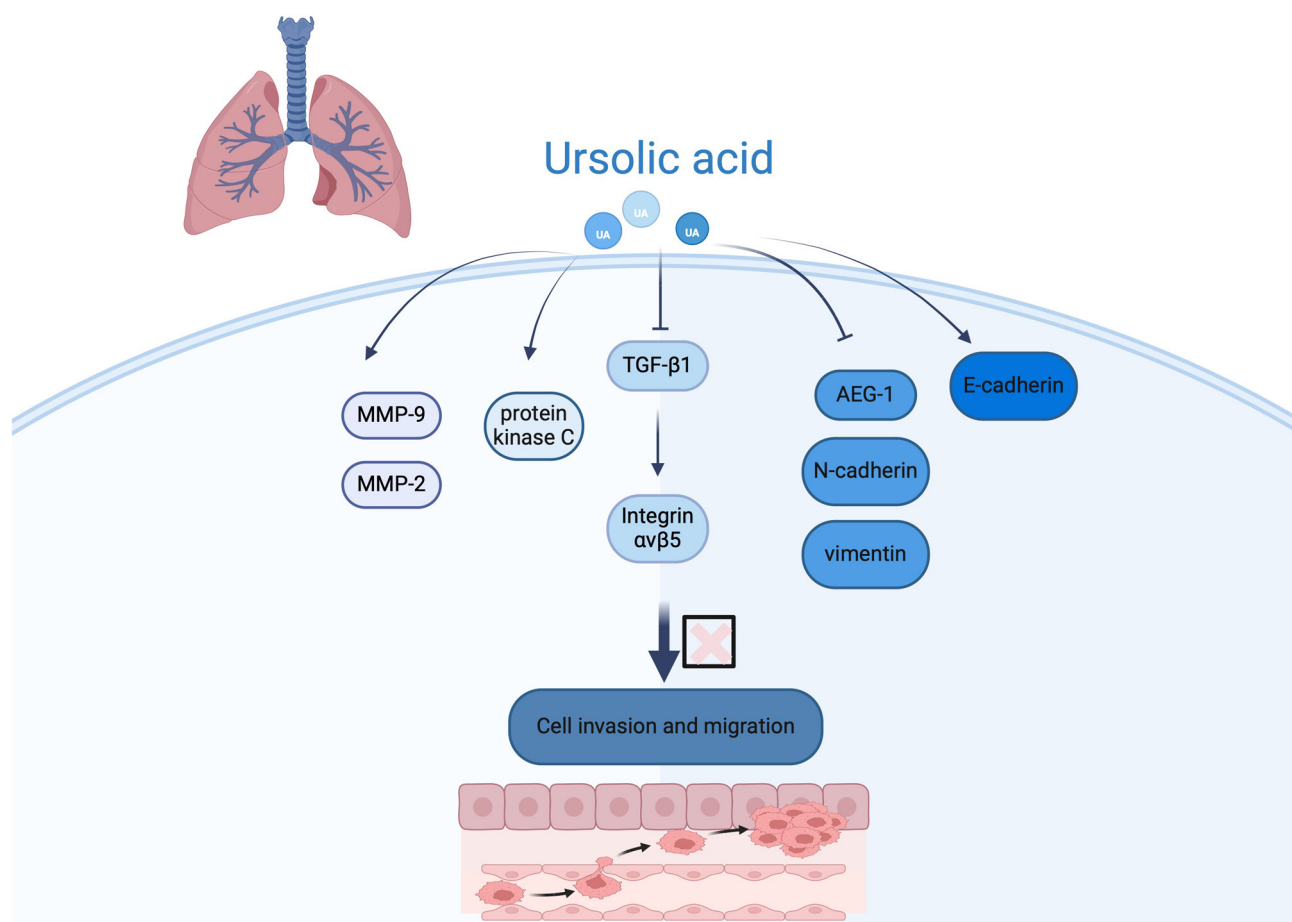


Figure 2. Molecular targets regulated by UA and their effects on cell invasion and migration. UA, ursolic acid; MMP, matrix metalloproteinase; AEG-1, astrocyte-elevated gene-1. Figure created using Adobe Illustrator 2024 (v28.0), Adobe Inc.

enhanced the cytotoxicity of UA and improved its anti-metastatic efficacy in NSCLC cells. Furthermore, UA has been shown to inhibit LC cell invasion in a concentration-dependent manner, with notable suppression of cell migration observed at concentrations between 4 and 16 $\mu\text{mol/l}$ (67).

Epithelial-mesenchymal transition (EMT) is a fundamental cellular program involved in embryonic development, tissue repair and stem cell plasticity, but it also contributes pathologically to fibrosis and cancer metastasis by enhancing cellular motility and invasiveness (68). Experimental studies demonstrated that UA reduces EMT induction in H1975 LC cells triggered by transforming growth factor- β 1, thereby inhibiting metastatic potential (69). Additionally, investigations in human NSCLC A549 cells revealed that UA suppresses EMT by inhibiting the nuclear factor Kappa-light-chain-enhancer of activated B Cells (NF- κ B) signaling pathway, downregulating astrocyte-elevated gene-1 (AEG-1), and modulating key EMT markers-upregulating epithelial marker E-cadherin while downregulating mesenchymal markers N-cadherin and vimentin. This mechanism effectively curtails tumor cell migration and invasion, underscoring the promise of UA as an anti-metastatic agent in LC treatment (Fig. 2) (70).

Inhibition of LC cell proliferation and growth. Cell proliferation is fundamental to the normal development and homeostasis of multicellular organisms. Dysregulated cell proliferation

is a hallmark of tumorigenesis and can also contribute to congenital malformations (71).

Cancer/Testis Antigen Family 45 Member A2 (CT45A2) is implicated as an oncogene in NSCLC and is associated with Epidermal Growth Factor Receptor (EGFR) T790 mutations. The antitumor effects of UA in NSCLC predominantly depend on CT45A2 expression in H1975 cells. UA inhibits CT45A2 transcription by targeting the β -catenin/transcription factor 4 (TCF4) signaling pathway. Specifically, UA negatively regulates the β -catenin/TCF4/CT45A2 axis, thereby suppressing the proliferation of H1975 cells (72). Autophagy-related gene 5 (ATG5) plays a pivotal role in autophagy by participating in the formation of autophagic complexes and autophagosomes, thus amplifying the autophagic response and offering potential therapeutic avenues (73,74). Mutations in ATG5 have been linked to various pathologies. Notably, inhibition of ATG5 via chloroquine (CQ) or siRNA enhances UA's anti-proliferative effects by suppressing autophagy, suggesting that autophagy may serve as a protective mechanism in cancer cells under UA treatment (75).

Cell proliferation involves the biosynthesis of macromolecules such as proteins, lipids and nucleic acids, as well as an increase in cell size and mass. Aberrant regulation of cell proliferation and division contribute to tumor development. Wu *et al* (76) demonstrated that UA suppresses NSCLC cell proliferation by inducing phosphorylation of stress-activated

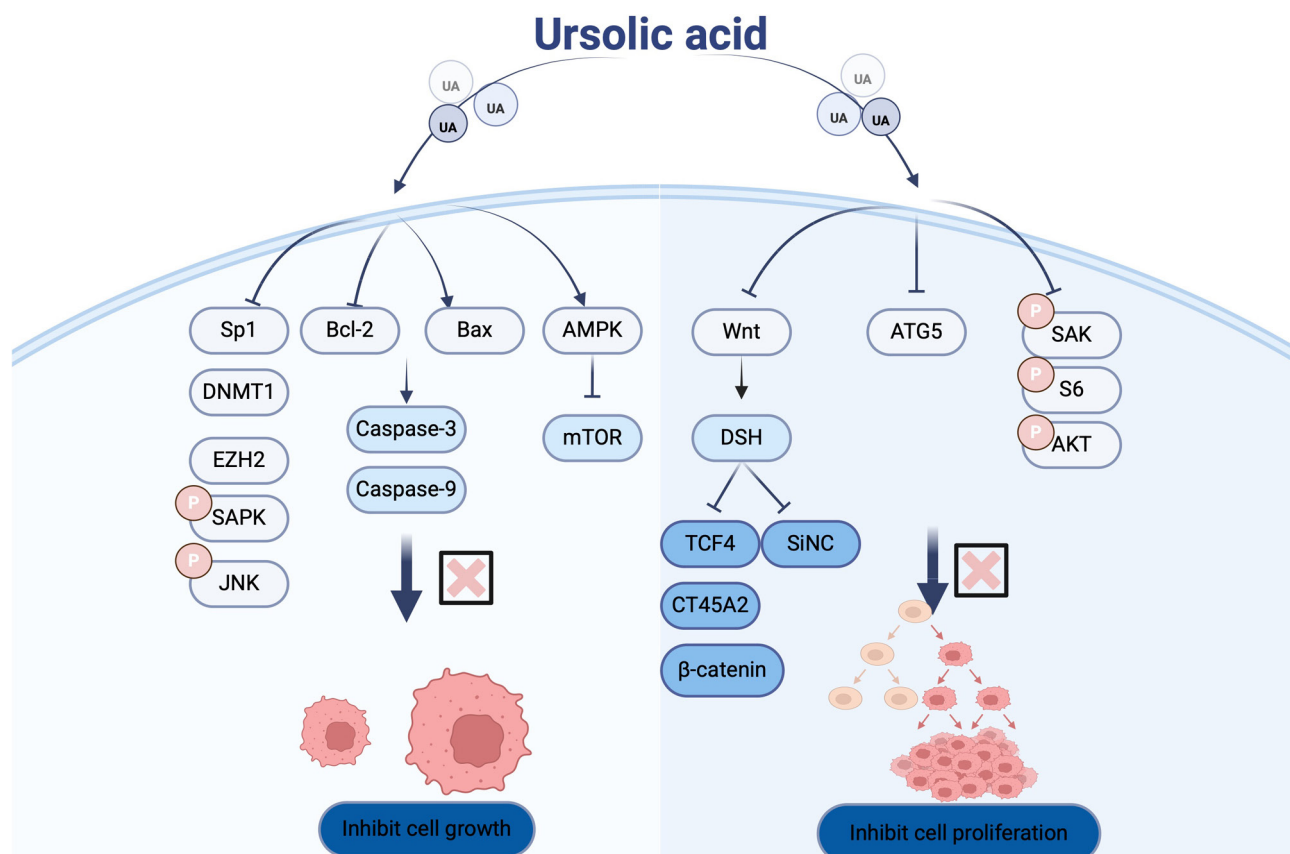


Figure 3. Molecular targets regulated by UA and their effects on cell proliferation. UA, ursolic acid. Figure created using Adobe Illustrator 2024 (v28.0), Adobe Inc.

protein kinase/c-Jun N-terminal kinase and subsequently downregulating Sp1 expression. Furthermore, Way *et al* (49) reported that UA inhibits LC cell proliferation through modulation of key signaling proteins, including mTOR and AMPK. Their findings indicate that UA activates AMPK in a dose- and time-dependent manner, which in turn suppresses mTOR activity—a central regulator of protein synthesis and cellular proliferation (Fig. 3).

Combination with other anticancer drugs. Chemotherapy remains a cornerstone in the treatment of LC (77,78). However, the emergence of drug resistance constitutes a significant barrier to successful chemotherapy outcomes (79). Cisplatin resistance, in particular, is a major cause of therapeutic failure in patients with LC (80). Recently, UA has attracted increasing attention for its potential to overcome cisplatin resistance in LC (Fig. 4).

Fan *et al* (81) utilized the A549 human LC cell line as a model for cisplatin-resistant cells and demonstrated that UA treatment inhibited the activation of the Janus kinase 2/signal transducer and activator of transcription 3 (Jak2/Stat3) signaling pathway. This inhibition led to downregulation of pluripotency-associated transcription factors and suppression of CSC enrichment, thereby attenuating chemoresistance.

To improve UA delivery and targeting, Li *et al* (82) developed a hydrogel-based drug delivery system co-loaded with UA and cisplatin. This platform enhances the targeting of UA to LC cells by facilitating its binding to the LC-specific

membrane protein TMEM16A, effectively inhibiting lung adenocarcinoma progression. The hydrogel system thus provides a promising strategy to potentiate UA's therapeutic efficacy in resistant LC.

Furthermore, Chen *et al* (83) identified the miRNA-149-5p/MyD88 signaling axis as a critical mediator of chemoresistance in NSCLC cells. Their study revealed that UA suppresses this signaling pathway, thereby reducing cancer stemness, overcoming chemotherapy resistance, and ultimately enhancing treatment efficacy in LC.

4. Novel drug carriers

Currently, most anticancer drugs have the drawback of poor targeting, which can cause irreversible damage to the body during treatment. New drug delivery systems aimed at ensuring drug safety and efficient therapy may become key to enhancing the efficacy of anticancer drugs (84). Research indicates that nanoparticle-based drug delivery systems (Nano-DDS) could potentially resolve the challenges associated with drug administration in cancer therapy (85).

In an experiment by Wu *et al* (79), a biomimetic red blood cell membrane (RBCM) nano-carrier, UA-loaded NPs coated with RBCM, was developed. This novel biomimetic drug delivery platform enhanced the tumor targeting, stability and biocompatibility of the UA NPs. It addressed the clinical limitations of UA and improved its bioavailability. This innovative biomimetic delivery system

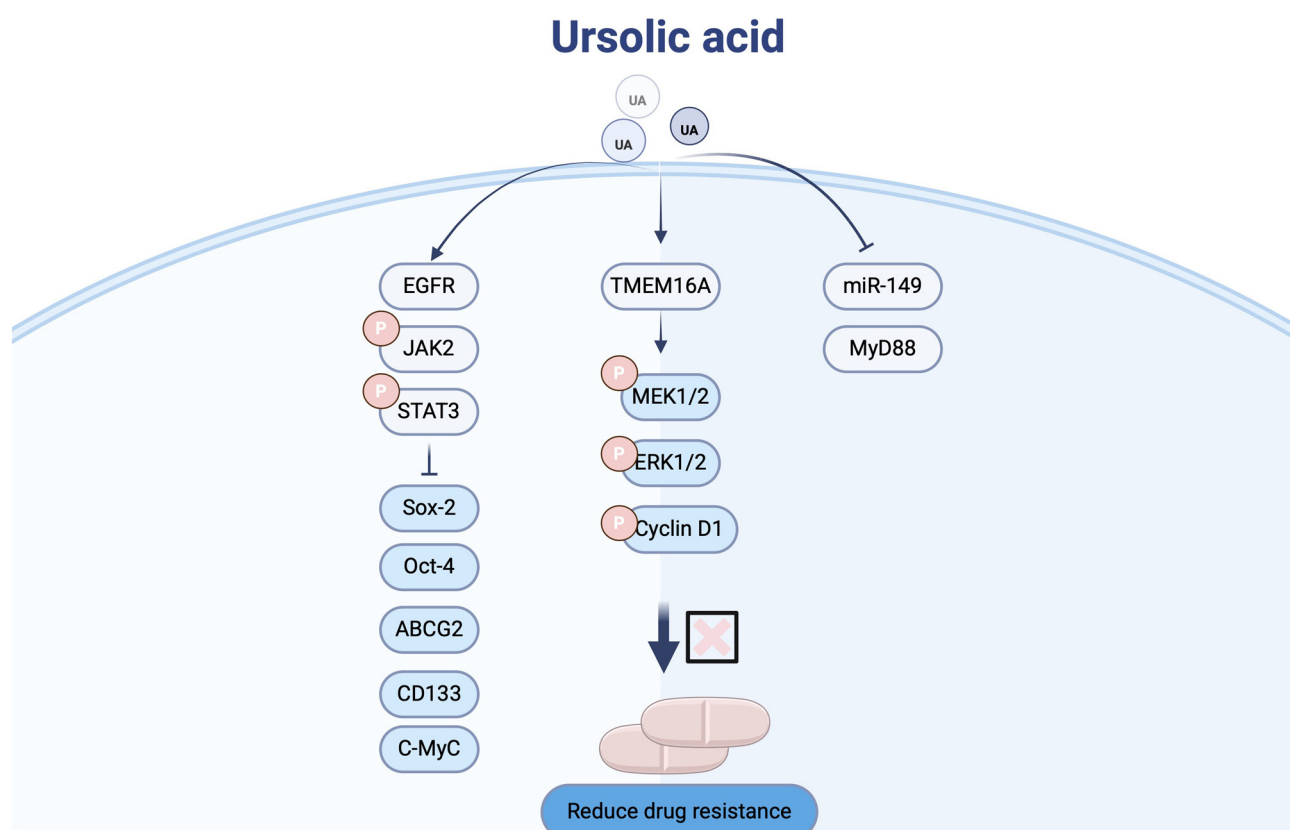


Figure 4. Molecular targets regulated by UA and their impact on attenuating drug resistance. UA, ursolic acid; miR, microRNA. Figure created using Adobe Illustrator 2024 (v28.0), Adobe Inc.

significantly improved the anticancer efficacy in advanced NSCLC model, offering a promising strategy for enhancing UA-based treatments. In addition, Xu *et al* (66) developed a HA-modified UA/AS-IV-loaded polydopamine (PDA) nanomedicine (UA/(AS-IV)[@]PDA-HA). This nanomedicine effectively enhanced the water solubility and targeting ability of UA. It allows UA to specifically bind to the overexpressed cluster of differentiation 44 on the surface of NSCLC cells. Moreover, the modified nanomedicine significantly improved the cytotoxicity mediated by UA and enhanced its ability to inhibit NSCLC cell proliferation and metastasis. These findings suggest that UA has great potential as an effective targeted anticancer drug for LC therapy. Novel drug delivery systems have greatly enhanced the ability of UA to target LC, enabling precise control that reduces systemic toxicity and improves anticancer efficacy. However, the integration and interaction between targeted therapies and UA in addition-related oncogenes of NSCLC remain unclear and require further investigation.

5. Pharmacokinetics of UA

According to the Biopharmaceutics Classification System (BCS), UA is classified as a Class IV drug, characterized by low solubility and low permeability. Although UA demonstrates unique advantages in the treatment of cancers such as LC, its pharmacological efficacy is limited. Due to its lipophilic nature, UA exhibits poor oral bioavailability and has difficulty penetrating biological membranes, thereby reducing

its therapeutic effectiveness against tumors (86). To overcome these challenges, Antonio *et al* (87) developed chitosan (CS)-modified polylactic acid NPs encapsulating UA. Their study showed that this nanoparticle system reduced the average particle size and promoted the amorphous transformation of UA, enabling sustained release. This significantly reduced cytotoxicity in tumor cells and enhanced UA's oral absorption, clearance rate and metabolic efficiency in rat models. Furthermore, Yang *et al* (88) demonstrated that amorphous UA NPs prepared using the supercritical antisolvent technique effectively improved UA's supersaturation, solubility and absorption. In another study, Yu *et al* (89) formulated a supra-molecular co-amorphous system combining UA and piperine. Through differential scanning calorimetry and scanning electron microscopy, it was confirmed that the co-amorphous system significantly enhanced UA's oral bioavailability and solubility in physiological media compared to its crystalline form.

Regarding drug absorption, high-performance liquid chromatography-mass spectrometry was used to analyze the tissue distribution of UA in rats 1 h after oral administration. The study revealed that UA concentrations were highest in the lungs, followed by the spleen, liver, brain, heart and kidneys, in descending order (90). Additionally, Wang *et al* (91) found that a novel CS-coated UA liposome achieved significantly higher accumulation at tumor sites in mice compared with conventional UA liposomes and free UA. These findings offer new insights and strategies for enhancing UA's therapeutic efficacy against LC.

Table I. Mechanism of action of ursolic acid in lung cancer.

First author/s, year	Disease	Real modules (Animal/Cell/Patient)	Possible mechanisms	Targets	Doses	Treatment period	(Refs.)
Kang <i>et al</i> , 2021	Lung cancer	Cell: A549, H460	Inducing apoptosis, inhibiting cell proliferation, and concentrating on blocking the cell cycle.	MMP2↓, MMP3↓, MMP9↓, PD-L1↓, CDK4↓, CCND1↓, CCNE1↓, CDKN1A↑, CDKN1B↑, VEGF↓, pSTAT3↓	10 μM, 20 μM	24 h	(52)
Way <i>et al</i> , 2014		Cell: A549, H460	Induces apoptosis and inhibits cell proliferation.	Caspase-3↑, Caspase-9↑, Bax↑, Bcl-2↓, p-mTOR↓, FASN↓	30 μM	24; 48 h	(49)
Lai <i>et al</i> , 2007		Cell: H460	Induces apoptosis of tumor cells.	MMP-1↑, MMP-2↑, MMP-3↑, MMP-9↑, MMP-10↑, Caspase-3↑	10 μM	24 h	(51)
Gou <i>et al</i> , 2020		Cell: H460, A549	Induces apoptosis by activating the endoplasmic reticulum stress pathway, arresting the cell cycle.	CHOP↑, Cyclin D1↓, CDK4↓p-PERK↑, p-eIF2α↑, eIF2α↑	0-50 μM	24, 48, 72 h	(45)
Chen <i>et al</i> , 2019		Cell: NCI-H292	Induces apoptosis through mitochondrial-dependent pathway.	AIF↑, Endo G↑, BCL-Xs↑	3, 6, 9, 12 and 15 μM	Respectively 24, 48 h	(54)
Ma <i>et al</i> , 2023		Cell: A549	Induces mitochondrial apoptosis, create HA-Lipo/UA delivery system.	ARTS↑, p53↑, ascapase-3↑, Cyto-C↑, Bcl-2↓, Bax↑	20 μg/ml	24 h	(55)
Castrejon-Jimenez <i>et al</i> , 2019		Cell: A549	Induces apoptosis, induces mitochondrial phagocytosis.	P62↑, Parkin↑	10 μg/ml	24, 48 h	(56)
Song <i>et al</i> , 2017		Cell: H1299	Induces cell death, enhances cell radiosensitivity.	GSH↓, HIF-1α↓	50, 80 μg/ml	24 h	(57)
Kim <i>et al</i> , 2015		Cell: A549	Induces apoptosis and impedes DNA damage repair capability.	53BP1 foci↓, α-p-CREB↓, α-H3 p-Ser10↓	50 μM	12 h	(62)
Lamouille <i>et al</i> , 2014		Cell: HNB, A549, H3255 and Calu-6	Reduces cell invasion, reduce cell migration, reduces cell activity.	MMP-9↑, MMP-2↑, protein kinase C↓	2, 4, 8, 16 μMol/l	48 h	(68)

Table I. Continued.

First author/s, year	Disease	Real modules (Animal/Cell/Patient)	Possible mechanisms	Targets	Doses	Treatment period	(Refs.)
Liu <i>et al.</i> , 2013		Cell: H1975	Inhibits cell invasion and migration.	EMT↓, MMP-2↓, MMP-9↓, Integrin αvβ5↓	0, 1, 5, 10, 15, 20, 25, 50, 100 ng/l	24 h	(70)
Jesudason <i>et al.</i> , 2000		Cell: A549 and H1975	Inhibits cell metastasis and EMT	AEG-1↓, E-cadherin↑, N-cadherin↓, vimentin↓	5, 10, 20, 30, 40 μM	24 h	(71)
Higgins <i>et al.</i> , 2009		Cell: PC9, H1299, A549, H1650, H358 and H1975	Inhibits cell proliferation.	Sp1↓, DNMT1↓, EZH2↓, SAPK/JNK↓	30 μM	48 h	(77)
Way <i>et al.</i> , 2014		Cell: A549, H460	Inhibits cell proliferation.	AMPK↑, mTOR↓, Caspase-3↓, Caspase-9↓, Bcl-2↓, Bax↑	30 μM	24, 48 h	(49)
Changotra <i>et al.</i> , 2022		Cell: H1975	Inhibits cell proliferation.	CT45A2↓, transcription factor/β-catenin↓, TCF4↓, siNC↓	25 μM	24, 48, 72 h	(73)
Wu <i>et al.</i> , 2015		Cell: H460, H1975, A549, H1299, H520, H82 and H446	Inhibits cell proliferation and autophagy-related genes.	ATG5↓, p-SAK↓, p-S6↓, p-AKT↓	10 μM, 15 μM	24, 48, 72 h	(76)
Li <i>et al.</i> , 2024		Cell: A549	Reduces cell resistance and inhibits the enrichment of tumor stem cells.	Oct-4↓, Sox-2↓, c-Myc↓, Jak2↑, Stat3↑	10, 20, 30, 40 μM	48 h	(82)
Chen <i>et al.</i> , 2020		Cell: LA795	Inhibits neural pathways, induces DNA damage and cell membrane damage, and design hydrogel drug delivery systems to enhance targeting ability.	TMEM16A↓, p-MEK1/2↓, p-ERK1/2↓, Cyclin D1↓	5, 10, 15, 20, 30, 50 μM	24, 48, 72 h	(83)
Perez-Herrero <i>et al.</i> , 2015		Cell: NSCLC, A549	Reduces chemical resistance, inhibits miRNA, weakens stemness of cells.	miR-149↓, MyD88↓	5, 10, 20 μM	24, 48, 72 h	(84)

p-, phosphorylated; miRNA or miR, microRNA; CHOP, C/EBP-homologous protein; AIF, apoptosis-inducing factor; Endo G, endonuclease G; ARTS, apoptosis-related protein in the TGF-β signaling pathway; HIF-1α; hypoxia-inducible factor 1 alpha; GSH, reduced glutathione; EMT, epithelial-mesenchymal transition; AEG-1, astrocyte-elevated gene-1; CT45A2, Cancer/Testis Antigen Family 45 Member A2; TCF4, transcription factor 4; si-, small interfering; NC, negative control; ATG5, autophagy-related gene 5; SAPK/JNK, stress-activated protein kinase/c-Jun N-terminal kinase.

Mechanisms associated with the chemoprotective effect of UA for the treatment of lung cancer

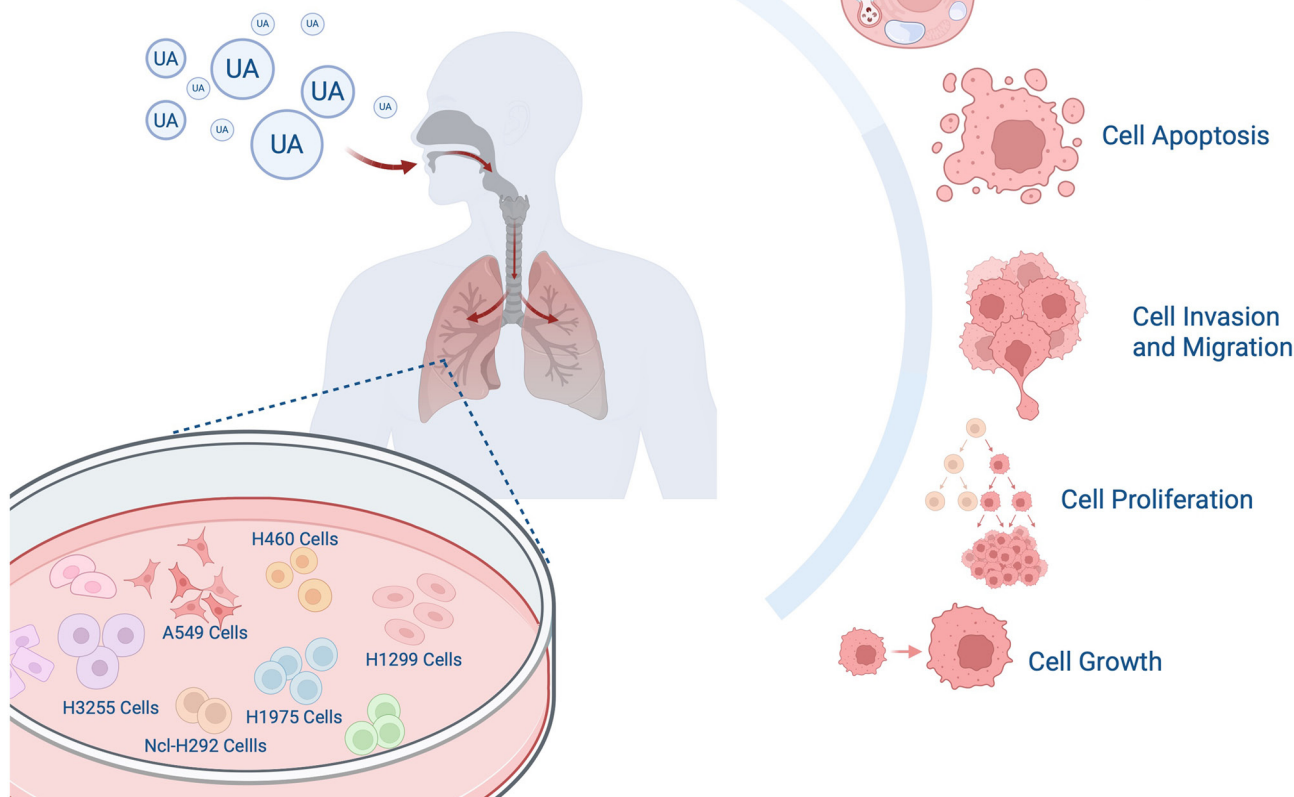


Figure 5. Mechanisms associated with the chemoprotective effect of UA for the treatment of lung cancer. UA, ursolic acid. Figure created using Adobe Illustrator 2024 (v28.0), Adobe Inc.

In terms of drug metabolism and excretion, research on UA remains relatively limited. Available studies indicate that UA is primarily metabolized in the human body by the hepatic cytochrome P450 (CYP450) enzyme system, along with phase II conjugation reactions. In Caco-2 cells, CYP3A4 and CYP2C9 play key roles in UA metabolism, and the PXR-RXR α pathway has been shown to significantly upregulate CYP2C9 expression, thereby promoting UA biotransformation (92).

In summary, although UA shows promising pharmacokinetic behavior, further studies are needed to fully elucidate its absorption, metabolism and elimination profiles, which will be essential for advancing its clinical application.

6. Conclusion and outlook

LC, a malignant tumor originating from lung tissue, is one of the most common cancers worldwide and a leading cause of cancer-related mortality (93,94). UA plays a significant role in the treatment of LC, with mechanisms that include inhibiting cell proliferation, invasion and migration, and reducing drug resistance. These effects involve signaling pathways such as β -catenin, β -catenin/TCF4/CT45A2, NF- κ B, Jak2/Stat3, and the regulation of related genes such as ATG5, CT45A2, MMP and AEG-1, as well as the expression of proteins such as Bcl-2, Bax, upregulation of E-cadherin, downregulation of N-cadherin, vimentin, mTOR and sp1, alongside the

involvement of proteases and kinases such as caspase-3, caspase-9, urokinase, cathepsin B, AMPK and VRK1 (Table I).

Due to the limited water solubility, poor targeting ability, and drug resistance of UA (95), the development of novel DDS, including Nano-DDS and hydrogel-based delivery systems, has greatly addressed these issues. These innovations significantly enhance the delivery efficiency, targeting ability and bioavailability of UA, improving the effectiveness of monotherapy and boosting the antitumor effect through synergistic strategies. Furthermore, Ram Kumar Pandian *et al* (96) found that polyhydroxybutyrate NPs could deliver UA, enhancing its stability and bioactivity, thus improving the treatment of tumors. In another study by Sharma *et al* (97), HA-UA conjugates were used to prepare PTX-loaded HA-UA NPs, which significantly inhibited tumor cell proliferation in experimental models, offering new ideas and methods for combined chemotherapy delivery. If these two delivery systems are applied to the treatment of LC, they might yield unforeseen effects and become a new direction for future research. In addition, smoking as an important factor affecting LC is detrimental to the whole process of carcinogenesis. It has been identified that polycyclic aromatic hydrocarbons in cigarettes can affect the metabolism of drugs by key drug-metabolizing enzymes of cytochrome P450 and isoforms of the glucuronosyltransferase family, shortening the duration of drug action by accelerating the metabolism of related drugs and thus affecting therapeutic

efficacy (98). In addition, Zevin *et al* (99) found that smoking significantly upregulated CYP2E1 activity, increasing the rate of metabolizing drugs while activating carcinogens and increasing the risk of disease. Whether smoking affects the metabolism and utilization of natural active ingredients, such as UA, has not been confirmed by relevant experiments, and the authors will further explore this issue in future studies.

Although UA shows remarkable therapeutic potential in LC treatment, there are still some limitations: First, low bioavailability: Its poor water solubility results in low absorption and bioavailability in the body. Second, lack of clinical trial data: Most studies on UA in LC remain at the laboratory stage, lacking large-scale clinical trials to support its safety and efficacy. In particular, clinical evidence for UA combination chemotherapy in non-small cell carcinoma remains low and a distant dream. Third, Dose and administration challenges: In clinical application, determining the appropriate dose is crucial. A very low dose may result in ineffective treatment, while a very high dose could cause toxicity. Further experimental research is needed to optimize dosing and administration methods. Fourth, drug interactions: UA may interact with other drugs, influencing their metabolism and therapeutic effects. Identifying interactions with other drugs is one of the future research directions. Fifth, side effects and toxicity: While UA is considered a relatively safe natural compound, high doses or prolonged use may still produce toxicity and side effects, which need further investigation. Sixth, individual differences: Patients may have different responses to UA based on factors such as genetic background, tumor type, stage and overall health. Hence, it is essential to avoid generalizing treatment approaches.

In conclusion, while UA has made significant progress in non-clinical research, some issues and limitations remain. In the future, the authors will focus research on the cultivation of real animal cells, to deepen the analysis of their multi-target regulatory networks and develop efficient delivery systems, to promote the clinical translation of UA and its derivatives, and ultimately to realize the leap from cellular evidence to human disease intervention (Fig. 5).

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Availability of data and materials

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Authors' contributions

ZL wrote the manuscript and drew the pictures. QC and ZC collected and organized literature. TP and JB proofread the manuscript. FM are fully responsible for the study designing, research fields, drafting, and finalizing the manuscript. All

authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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