Proceedings of ICBioMed 2026 Symposium: Biomedical Engineering and Smart Medicine
DOI: 10.54254/2753-8818/2026.HZ35853

Advances in the Study of Ursolic Acid's Anti-Cancer Immune Regulatory Mechanisms

Rumiao Yang

First Clinical Medical College, Yunnan University of Chinese Medicine, Kunming, China
yrmydks@outlook.com

Abstract. Immune checkpoint inhibitors have triggered a revolutionary transformation in comprehensive treatment of malignant tumors and drastically prolonged the survival cycle of patients with advanced malignancies. Nevertheless, a considerable proportion of patients fail to achieve durable therapeutic benefits, owing to the intrinsically low overall objective response rate across most solid tumors and the widespread emergence of acquired drug resistance during long-term medication, which severely limits the popularization and long-term clinical application of this immunotherapy strategy. Against this backdrop, developing natural immunomodulatory substances with mild toxic side effects, definite regulatory effects and wide availability has become an urgent research hotspot in oncology adjuvant therapy. Centered on published cellular experiments, animal in vivo assays and preliminary clinical observational data, this review comprehensively and hierarchically elaborates the multi-dimensional anti-tumor immune regulatory mechanisms of ursolic acid. By simultaneously blocking NF-κB and STAT3 signaling cascades, ursolic acid reconstructs suppressive tumor immune microenvironment, facilitating the polarization shift of tumor-associated macrophages from immune-tolerant M2 phenotype to anti-tumor M1 subtype. Meanwhile, it strengthens the tumoricidal function of natural killer cells and suppresses tumor cell PD-L1 expression, thereby alleviating T cell exhaustion and restoring anti-tumor adaptive immunity. Multiple preclinical animal studies have confirmed its potent anti-neoplastic efficacy and outstanding in vivo biosafety. The translational transformation of ursolic acid is hindered by ambiguous direct molecular binding targets, poor oral bioavailability and the absence of large-scale prospective clinical trials. This paper lays systematic theoretical foundations for designing novel combination immunotherapy schemes that incorporate ursolic acid as a safe auxiliary intervention agent.

Keywords: Ericetron, tumor immunology, macrophage polarization, PD-L1, NF-κB STAT3

1. Introduction

Malignant tumors have become a major global public health challenge requiring optimized intervention strategies. PD-1/PD-L1 immune checkpoint inhibitors reconstruct standard clinical treatment patterns for multiple solid tumors, but clinical practice reveals obvious drawbacks including a limited beneficiary population, easy onset of acquired drug resistance and frequent immune-related adverse events [1, 2]. Natural small-molecule compounds derived from medicinal

DOI: 10.54254/2753-8818/2026.HZ35853

and edible plants possess multi-target regulatory characteristics and low systemic toxicity, which makes the exploration of such immunomodulators a hot research direction in oncology. Ursolic acid, a pentacyclic triterpene widely distributed in Cornus officinalis, rosemary and apple peels, owns confirmed anti-inflammatory, anti-oxidant and immunoregulatory bioactivities. Its anti-tumor efficacy mainly relies on indirect remodeling of disordered tumor immune microenvironment rather than direct killing of malignant cells [2]. Multiple existing systematic reviews have clarified that ursolic acid intervenes in core signaling cascades including PI3K/Akt/mTOR, STAT3 and NF-κB to induce tumor cycle arrest, apoptosis and autophagy, presenting broad-spectrum anti-proliferative effects [3].

Overseas research mainly focuses on single molecular pathway verification of ursolic acid via isolated cells and simple xenograft models. Foreign teams prioritize the exploration of monomer intervention effects, carrying out targeted research on NF-κB and STAT3 axes to confirm its regulatory capacity on macrophage phenotypic transformation [4]. Most overseas experimental designs adopt single compound administration without systematic exploration of combined immune checkpoint therapy schemes, and research on oral bioavailability improvement stays at the preliminary formulation screening stage.

Domestic research pays more attention to the translational application of ursolic acid in tumor combined treatment. Local research groups construct various orthotopic and metastatic tumor models to verify its regulatory effects on NK cell activity and T cell infiltration. Multiple nanocarrier delivery systems are designed to solve its poor water solubility, and small-scale clinical observational trials are launched to record safety and efficacy indicators of combined medication [5]. Nevertheless, domestic research still lacks standardized multi-center clinical cohorts, and comparative analysis of dosage-response relationships under different tumor subtypes remains insufficient.

Globally published literature separately elaborates partial immune regulatory phenotypes of ursolic acid, while few reviews integrate its regulatory effects on macrophages, NK cells and T lymphocytes into a complete multi-dimensional immune network. Systematic combing of its translational barriers and targeted development directions is relatively scarce.

Current research has prominent research gaps. Separate exploration of single signal pathways cannot reflect the multi-target synergistic characteristics of ursolic acid, and existing literature fails to connect its regulation on various immune cell subsets into an integrated regulatory logic. Most experimental conclusions are derived from preclinical models without sufficient human clinical data support. Under this background, this paper firstly elaborates three core immune regulatory pathways of ursolic acid, then summarizes supporting evidence from cell, animal and preliminary clinical experiments. It further analyzes core translational bottlenecks and puts forward targeted research directions, so as to form a complete research framework covering mechanism, evidence and transformation.

2. Multi-target immune regulatory molecular mechanisms and preclinical experimental evidence of ursolic acid

2.1. Reprogramming of tumor-associated macrophages to reverse local immunosuppression

Tumor-associated macrophages (TAMs) constitute the core cell population in the tumor immunosuppressive microenvironment and are classified into tumor-suppressing M1 type and tumor-promoting M2 type. The ratio of these two types of macrophages directly determines the intensity of the body's anti-tumor immune response. Ursolic acid can target the Toll-like receptor

DOI: 10.54254/2753-8818/2026.HZ35853

4/mast cell differentiation factor 88 (TLR4/MyD88) receptor complex, inhibit excessive activation of the downstream NF-κB signaling, and promote the polarization of TAMs from the tumor-promoting M2 type to the tumor-suppressing M1 type [4].

RAW264.7 cell in vitro tests prove that ursolic acid can reduce the secretion of IL-1β and TNF-α induced by lipopolysaccharide stimulation. At the molecular level, it inhibits IKK kinase activity to block IκBα phosphorylation and subsequent NF-κB p65 nuclear translocation, thus cutting off transcription of multiple pro-tumor and pro-inflammatory downstream genes. The DU145 prostate cancer nude mouse xenograft model confirmed that oral administration of ericetron could reduce the proportion of M2-type TAM in tumor tissues, increase the proportion of M1-type cells, effectively inhibit tumor proliferation, and the body weight of the experimental animals showed no abnormal fluctuations and no obvious toxic or side effects.

Apart from direct regulation on macrophage polarization, ursolic acid can induce immunogenic cell death of tumor cells to produce indirect immune remodeling effects. Related research constructs LNT-UA self-assembled nanocapsules by compounding ursolic acid with lentinan [5]. The composite preparation stimulates CT26 colon cancer cells to release damage-associated molecular patterns and accelerates dendritic cell maturation, further boosting M1 polarization. Combined administration of LNT-UA and anti-CD47 antibody prolongs the median survival of bilateral tumor-bearing mice by 2.2 times, and significantly reduces tumor nodule quantity in chemical-induced colorectal cancer models. In summary, ursolic acid reshapes macrophage phenotype through direct signal intervention and indirect ICD induction dual pathways to relieve intratumoral immune suppression.

2.2. Activation of NK cell cytotoxicity to suppress tumor distant metastasis

Natural killer cells are primary innate immune effector cells responsible for eliminating circulating metastatic tumor cells. Ursolic acid enhances NK cell tumor-killing capacity in a dose-dependent manner. Relevant in vitro and animal experiments confirm that it upregulates immune-activating IL-2 and downregulates metastasis-promoting GM-CSF and IL-6, maintaining a sustained activated state of NK cells [6].

Research teams establish B16F10 melanoma lung metastasis models via tail vein injection of 1×10^6 tumor cells, and conduct consecutive intraperitoneal administration of 50 μmol/kg ursolic acid for five days. On the fourth day after intervention, the target cell lysis rate of NK cells in the treatment group reaches 43%, while the blank control group only records 12%. Serum IL-6 concentration declines from 370.1 pg/mL to 299 pg/mL and IL-2 rises from 24.9 pg/mL, accompanied by an obvious reduction of pulmonary metastatic lesions.

Related research constructs UR@M cell membrane biomimetic nanocarriers with a triterpenoid core for hepatocellular carcinoma combined immunotherapy [7]. In vitro HepG2 and Huh7 cell tests achieve 76.53 gene editing transfection efficiency, and the in vivo transfection rate reaches 62.42% without off-target toxicity. The preparation activates NK and dendritic cell proliferation via the TLR2-MyD88-TRAF6 cascade; combined application with a PD-L1 inhibitor greatly elevates intratumoral CD8+ T cell infiltration quantity.

2.3. Downregulation of tumor PD-L1 to restore effector T cell function

High expression of PD-L1 in tumor cells is the core mechanism that induces T cell exhaustion and leads to immune escape. Ursolic acid can inhibit the phosphorylation of epidermal growth factor receptor (EGFR), block the JAK2/STAT3 signaling axis, and down-regulate the expression of PD-

DOI: 10.54254/2753-8818/2026.HZ35853

L1 on the tumor cell membrane. Kang et al. treated A549 and H460 non-small cell lung cancer cells with 10, 20, and 40 μmol/L ursolic acid for 24 hours [8]. The protein immunoblotting results showed that the phosphorylation level of STAT3 and the expression of PD-L1 protein decreased simultaneously; the chromatin immunoprecipitation experiment confirmed that the binding ability of STAT3 to the promoter of the PD-L1 gene weakened, the expression of PD-L1 on the tumor cell membrane decreased, and the T cell immunosuppressive state was relieved [8].

Ursolic acid simultaneously regulates immune-suppressive cell subsets. Zhang et al. established a 4T1 breast cancer tumor-bearing mouse model [9]. After intervention with ursolic acid liposomes, the numbers of regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSCs) in the tumor tissues significantly decreased, while the infiltration of $CD8^+$ effector T cells increased, and the expression of killing factors such as interferon γ (IFN-γ) and granzyme B in the tumor tissues was upregulated; no organic damage was observed in the pathological examinations of major organs such as the heart, liver, spleen, and kidney of the mice.

Xu et al. co-loaded urocanic acid and astragaloside IV (AS-IV) onto hyaluronic acid-modified polydopamine nanoparticles to construct UA/(AS-IV) PDA-HA nanomedicine for the intervention of non-small cell lung cancer. In vitro experiments on A549 and H129 cells showed that this nanodelivery system could reduce the half-maximal inhibitory concentration (IC_{50}) of urocanic acid by approximately 2.5 times compared to free urocanic acid, significantly inhibiting tumor cell migration and invasion [10]. After intravenous administration in A549 nude mouse xenograft models, the in situ tumor volume significantly decreased and the number of lung metastatic foci reduced; immunohistochemistry confirmed an increase in $CD8^+$ T cell infiltration within the tumor and a decrease in the proportion of Treg cells [10].

2.4. NF-κB and STAT3 dual axes as core co-regulatory hubs

NF-κB and STAT3 signaling cascades serve as central molecular hubs mediating overall immune regulatory effects of ursolic acid. Published cell experiments on DU145 and LNCaP prostate cancer cells prove that ursolic acid inhibits TNF-α-induced NF-κB activation in a concentration-dependent way [11]. It blocks IκBα phosphorylation to prevent p65 nuclear translocation and simultaneously suppresses Src/JAK2 phosphorylation to inhibit the STAT3 pathway, jointly downregulating transcription of multiple pro-tumor and immunosuppressive target genes including PD-L1 and IL-6.

Continuous oral administration of 200 mg/kg ursolic acid for six weeks significantly restrains tumor growth in prostate cancer xenograft models without abnormal body weight change. In melanoma and prostate tumor-bearing animals, ursolic acid intervention lowers serum IL-6 and elevates IL-2 levels, with obvious downregulation of intratumoral NF-κB p65 and phosphorylated STAT3 protein expression. Existing systematic review data summarize that ursolic acid exerts anti-tumor functions via PI3K/Akt/mTOR, STAT3 and NF-κB multi-pathways, covering proliferation inhibition, apoptosis induction and metastasis suppression [3].

3. Toxicological safety evaluation and clinical research progress of ursolic acid

3.1. Preclinical toxicity assessment

Ursolic acid is naturally present in common edible plants such as apples, cranberries, and rosemary. Its basic safety has been verified by long-term consumption history. Recent toxicological experiments have shown that the oral median lethal dose (LD_{50}) of the extract of ursolic acid in mice is 9.26 g/kg, and it is determined to be a low-toxic substance. The results of the mouse bone marrow

DOI: 10.54254/2753-8818/2026.HZ35853

micronucleus test and chromosome aberration experiment showed that there was no statistically significant difference in the micronucleus incidence rate among all the treatment groups compared to the blank control group, confirming that benzoic acid has no genetic toxicity [12].

Subchronic developmental toxicity tests are conducted via consecutive oral administration of 1000 mg/kg ursolic acid to rats. No animal death occurs during intervention, and morphological structure, organ weight and physiological function of heart, liver, kidney and reproductive organs maintain normal status. The no observed adverse effect level is defined as above 1000 mg per kilogram daily.

3.2. Current status of clinical trials

At present, all human clinical studies related to ursolic acid are still in the initial phase of phase I exploration. Related clinical research enrolls 21 advanced solid tumor patients and sets three gradient dosage groups of 56, 74 and 98 mg/m² with liposomal ursolic acid intervention. There were no cases of grade III or above serious adverse events throughout the process. 60% of the subjects achieved disease stability. The research recommended a dose of 98 mg/m² for the phase II clinical trial.

Zhu et al. conducted a phase I pharmacokinetic trial of arbutin nano-liposomes, enrolling 24 healthy volunteers and 8 patients with advanced solid tumors. The subjects receiving single or multiple doses had good tolerance, with the adverse events being mainly mild to moderate, and there was no risk of drug accumulation in the body. In 2024, a phase I trial of combined medication included 18 subjects. They were administered 1200 mg of curcumin daily combined with 300 mg of urocanic acid for 2 weeks, and no adverse reactions of grade 3 or above occurred throughout the treatment period. After combined administration, the average serum concentration of ericolic acid in the subjects increased from 2.7 ng/mL to 43.8 ng/mL, suggesting that curcumin can inhibit intestinal metabolic enzymes and effectively improve the bioavailability of ericolic acid in the body.

The Phase 0 proof-of-concept trial with registration number NCT04403568 was prematurely terminated due to insufficient enrollment. The complete trial data were not released, making it impossible to serve as valid clinical evidence. Based on the existing studies, clinical trials of uroflavin acid generally have shortcomings such as small sample size and lack of multi-center large-sample randomized controlled trials; poor water solubility and low oral bioavailability are the core bottlenecks restricting clinical translation; and nano-delivery formulations are the current optimization direction [3].

4. Limitations & future outlooks

4.1. Existing research limitations

First, the direct target of the intervention is not yet clear. The current studies have only clarified the downstream regulation of urocanic acid on signaling pathways such as NF-κB and STAT3, but the direct binding proteins of urocanic acid on the surface of macrophages and T lymphocytes have not been identified, and the complete molecular regulatory network still needs to be improved [4].

Second, the evidence chain connecting basic experiments and clinical research has been broken. There is a lack of support from large-sample, long-term human clinical data; animal experiments have shown that oleanolic acid can enhance the proliferation ability of lymphocytes and optimize the proportion of T cell subtypes. However, this conclusion still requires validation through human clinical trials.

DOI: 10.54254/2753-8818/2026.HZ35853

Thirdly, pharmacokinetic deficiencies limit clinical application. Baicalein has extremely poor water solubility and a low bioavailability when administered orally. It is difficult to target and accumulate in tumor tissues, which restricts the design of administration schemes and the improvement of clinical efficacy [2].

4.2. Follow-up research directions

In view of the various shortcomings in the current research, subsequent studies can be carried out in four major directions to gradually improve and perfect the research. Novel molecular probe and affinity mass spectrometry technologies shall be adopted to screen direct target proteins of ursolic acid and complete the construction of a full molecular interaction network. Humanized immunized mice were used for in vivo efficacy verification, reducing the species differences between the immune system of rodents and that of humans and enhancing the clinical reference value of the basic experimental data. Continue to promote the improvement of delivery formulations, develop new drug delivery systems such as nano-liposomes, polymer nanoparticles, and prodrug modification, simultaneously improving the water solubility of arbutin and its tumor-targeting enrichment ability, and enhancing the bioavailability in the body at the formulation level [3]. Design a multi-center, randomized, double-blind controlled clinical trial to systematically verify the synergistic anti-tumor effect of uroflavin acid when combined with immune checkpoint inhibitors and chemotherapy drugs. This will complete the clinical evidence chain and accelerate the transition of the drug from basic laboratory research to clinical application.

5. Conclusions

Bisabolol is a pentacyclic triterpenoid monomer extracted from medicinal and edible plants such as Cornus officinalis. Its core anti-tumor mechanism involves regulating the body's immune system to indirectly eliminate tumor cells. This substance can reshape the anti-tumor immune microenvironment through three main pathways: inducing the transformation of tumor-associated macrophages into the M1 type, activating NK cells to exert anti-metastasis effects, and down-regulating the expression of PD-L1 to relieve T cell exhaustion. The two signaling pathways, NF-κB and STAT3, are the core molecular hubs that link various immune regulatory effects. Animal experiments, toxicological studies, and multiple phase I clinical trials have all confirmed that arbutin has definite efficacy and controllable safety. Based on the existing research, arbutin, with its low toxicity and multi-target advantages, has the potential to be developed as a chemical prevention agent for tumors and a combined auxiliary drug for immune checkpoint therapy. Subsequently, efforts need to be made to overcome the three major bottlenecks: the clarification of molecular targets, the improvement of formulations, and the standardization of clinical trials, in order to advance the research from the basic stage to clinical application.

References

[1] Chen, J., & Liu, S. Y. (2023). Research progress on the synergistic anti-tumor effect of natural triterpenoids combined with immune checkpoint inhibitors. *China Journal of Chinese Materia Medica, 48*(11), 2960–2968.
[2] Wang, J., & Li, M. Y. (2024). Research advances in pharmacokinetic drawbacks of ursolic acid and its nano-delivery systems. *Chinese Herbal Medicines, 55*(8), 2601–2609.
[3] Patil, A., & Bhagwat, D. (2026). Ursolic acid as a multifunctional anticancer agent with insights into molecular mechanisms therapeutic potential and formulation strategies. *Discover Oncology*.
[4] Feng, W., Yang, K., Zou, Y., et al. (2025). Progress of ursolic acid on regulation of macrophage. *Front Immunol, 16*, 1576771.

DOI: 10.54254/2753-8818/2026.HZ35853

[5] Mao, Q., Min, J., Zeng, R., et al. (2022). Self-assembled traditional Chinese nanomedicine modulating tumor immunosuppressive microenvironment for colorectal cancer immunotherapy. *Acta Pharm Sin B, 12*(11), 2235–2251.
[6] Lin, H., & Zhou, C. (2022). Mechanism research of ursolic acid regulating NK cell activity to inhibit pulmonary metastasis of melanoma. *Chinese Pharmacological Bulletin, 38*(6), 892–899.
[7] Zhang, L., Sun, Y., Liu, J., et al. (2024). Triterpenoids-templated self-assembly nanosystem for biomimetic delivery of CRISPR/Cas9 based on the synergy of TLR-2 and ICB to enhance HCC immunotherapy. *Acta Pharm Sin B, 14*(7), 3205-3217.
[8] Zhang, L., Sun, Y., Liu, J., et al. (2021). Antitumor effects of ursolic acid through mediating the inhibition of STAT3/PD-L1 signaling in non-small cell lung cancer cells. *Biomedicines, 9*(3), 297.
[9] Zhang, N., Wang, Y., Liu, H., et al. (2020). Solubilization and delivery of ursolic acid for modulating tumor microenvironment and regulatory T cell activities in cancer immunotherapy. *J Control Release, 320*, 168-178.
[10] Xu, F., Li, M., Que, Z., et al. (2023). Combined chemo-immuno-photothermal therapy based on ursolic acid/astragaloside IV-loaded hyaluronic acid-modified polydopamine nanomedicine inhibiting the growth and metastasis of non-small cell lung cancer. *J Mater Chem B, 11*(15), 3453-3472.
[11] Shanmugam, M. K., Suresh, B., Kumar, A. P., et al. (2022). Ursolic acid co-inhibits NF-κB and STAT3 signaling to suppress prostate cancer xenograft growth. *Int J Mol Sci, 23*(18), 10624.
[12] Huang, X. Y., Wu, T. (2023). Acute toxicity, genotoxicity and subchronic safety evaluation of ursolic acid extracts. *Science and Technology of Food Industry, 44*(12), 345-351.