

## Research and Application Progress of *Corydalis yanhusuo* in Tumor and Its Adjuvant Therapy

Hanqing Yu <sup>1,\*</sup>, Jianfeng Wang <sup>2</sup>

<sup>1</sup> School of Pharmacy, Zhejiang Chinese Medical University, 311499 Hangzhou, Zhejiang, China

<sup>2</sup> Xingzhi College, Zhejiang Normal University, 321004 Jinhua, Zhejiang, China

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### \* Correspondence

Hanqing Yu,

School of Pharmacy, Zhejiang

Chinese Medical University, 311499

Hangzhou, Zhejiang, China

E-mail: 3362213779@qq.com

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### Abstract

The global incidence of malignant tumors keeps rising year-on-year. Although surgery, radiotherapy, chemotherapy, targeted therapy and immunotherapy are widely adopted in clinical practice, major challenges including tumor proliferation and metastasis, radiochemotherapy-triggered organ toxicity, and tumor-mediated immune suppression still greatly impair cancer patients' prognosis and quality of life. *Corydalis yanhusuo* W. T. Wang, a well-known traditional Chinese medicinal herb, promotes blood circulation, resolves blood stasis and relieves pain, and has long been applied for treating stasis-associated masses. Modern pharmacological studies suggest that its rich isoquinoline alkaloids possess diverse anti-tumor properties: tumor-growth inhibition, cancer-pain alleviation, radiochemotherapy-related detoxification, reversal of drug resistance, and tumor immune modulation. Recent pre-clinical evidence indicates that its key bioactive alkaloids (levo-tetrahydropalmatine, dehydrocorydaline, glaucine, and isocorydine) can hamper tumor progression via modulating cell-cycle arrest, apoptosis, autophagy, epithelial-mesenchymal transition, oncogenic signaling, angiogenesis, and the immunosuppressive tumor microenvironment. In clinical settings, *Corydalis yanhusuo* can safely alleviate graded cancer pain, lower opioid dependence, mitigate cardiac, renal and gastrointestinal injuries induced by radiochemotherapy, reverse multidrug resistance, and boost immunotherapeutic effects across peri-operative, radiochemotherapeutic, rehabilitative and palliative care phases. This review systematically summarizes the bioactive constituents, pre-clinical anti-tumor mechanisms, and comprehensive clinical applications of *Corydalis yanhusuo*. It further discusses existing research limitations and puts forward translational perspectives, hoping to offer supporting evidence for developing this herb into a promising botanical adjuvant anti-tumor agent and facilitate integrated Chinese-Western therapeutic strategies against malignant tumors.



*Corydalis yanhusuo* W. T. Wang, a well-known ancient medicinal herb for pain relief, belongs to the Papaveraceae family. Also known as Xuanhu or Yanhusuo, it is one of the famous "Eight Zhejiang Medicinal Herbs", mainly produced in Dongyang and Pan'an of Zhejiang Province. *Corydalis yanhusuo* exerts marked analgesic, sedative and hypnotic effects. It shows favorable clinical efficacy in the treatment of various diseases such as coronary heart disease, arrhythmia and gastric ulcer, and is also widely applied in the adjuvant therapy of tumors. Owing to its remarkable therapeutic effects and extensive clinical application, nearly 30% of the formulated preparations recorded in the 2025 edition of the Chinese Pharmacopoeia contain *Corydalis yanhusuo*.

1 Material basis of anti-tumor pharmacodynamics of *corydalis yanhusuo*

The chemical constituents of *Corydalis yanhusuo* are dominated by isoquinoline alkaloids. More than 80 alkaloids have been isolated and identified to date. It also contains auxiliary active components such as polysaccharides, flavonoids, and coumarins. Among these constituents, isoquinoline alkaloids serve as the core substances responsible for anti-tumor, analgesic, and toxicity-attenuating effects [1]. Levo-tetrahydropalmatine(l-THP) is specified by the Chinese Pharmacopoeia as the indicator component

for the content determination of *Corydalis yanhusuo*, serving as the core marker for the quality control of this medicinal material [2]. Table 1 shows the pharmacodynamic material basis of *Corydalis Rhizoma* against tumors.

From the perspective of traditional Chinese medicine, tumor-related blood-stasis syndrome corresponds to multiple modern pathophysiological alterations in malignant tumors. Clinically, tumor-associated blood stasis is manifested as hypercoagulable state, excessive epithelial-mesenchymal transition (EMT), intratumoral hypoxia, aberrant pathological angiogenesis, and local tumor-microenvironment immunosuppression. These pathological changes jointly drive tumor invasion, metastasis, and refractory cancer pain, which match the TCM understanding that "stasis forms masses". As the core material basis for the classic effect of *Corydalis yanhusuo* to "activate blood circulation and resolve stasis", isoquinoline alkaloids act on these interconnected pathological links. They can inhibit EMT-mediated metastatic potential, suppress pathological angiogenesis, relieve hypoxic stress, and remodel immunosuppressive tumor microenvironment. Such multi-component and multi-target pharmacological characteristics partially interpret the modern biological connotation of TCM blood-stasis-resolving therapy for malignant tumors.

Table 1 Material basis of anti-tumor pharmacodynamics of *Corydalis yanhusuo*.

| No. | Active ingredients       | Core efficacy                                                    | Mechanism of action                                                        | Research models / Application scenarios                                                                                                                                                    | References |
|-----|--------------------------|------------------------------------------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| 1   | Levo-tetrahydropalmatine | Tumor suppression, analgesia, immunomodulation, organ protection | Regulates AMPK/mTOR, TGF-β/Smad, PI3K/AKT, glycolysis-associated molecules | In vitro models of liver cancer, gastric cancer, breast cancer, and prostate cancer; intervention of bone metastatic cancer pain; development of chemotherapeutic organ protective agents. | [3-6]      |

|   |                   |                                                                                                                             |                                                                                      |                                                                                                                                  |        |
|---|-------------------|-----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|--------|
| 2 | Dehydrocorydaline | Inhibition of tumor proliferation, blockade of invasion and metastasis, interruption of inflammation-driven oncogenic cycle | ↓ Cyclin D1, CDK4, Bcl-2, MMP2/MMP9, NLRP3; ↑ Caspase-3/9                            | Significant tumor-inhibitory effects in colorectal cancer and lung cancer models                                                 | [7]    |
| 3 | Glaucine          | Reversal of multidrug resistance, inhibition of tumor angiogenesis                                                          | ↓ P-gp, MRP1                                                                         | Reversal of chemotherapy resistance in breast cancer and non-small cell lung cancer; blockade of nutrient supply in solid tumors | [8]    |
| 4 | Isocorydine       | Regulation of tumor metastasis, immune checkpoint modulation                                                                | HCG18/miR-380-5p axis; ↓ PD-L1                                                       | Synergizes with PD-1 immune checkpoint inhibitors to enhance anti-tumor responses in breast cancer models                        | [9,10] |
| 5 | Corynoline        | Inhibition of tumor neovascularization                                                                                      | ↓ VEGF-A/VEGFR2 axis                                                                 | Combined with protopine to synergistically inhibit in-situ growth of melanoma and glioma                                         | [8]    |
| 6 | Protopine         | Inhibition of tumor distant metastasis                                                                                      | Modulates tumor cell adhesion-related molecules                                      | Combined with corynoline to synergistically inhibit in-situ growth of melanoma and glioma                                        | [7]    |
| 7 | Polysaccharides   | Immunomodulation, enhancement of anti-tumor immunity                                                                        | ↑ NK cells, CD8 <sup>+</sup> T cells; ↓ Treg cells, myeloid-derived suppressor cells | Regulation of host anti-tumor immunity                                                                                           | [11]   |
| 8 | Flavonoids        | Antioxidation, alleviation of oxidative damage induced by radiotherapy and chemotherapy                                     | Regulates oxidative-stress-related molecules                                         | Protection against radiotherapy and chemotherapy-induced oxidative damage                                                        | [1]    |

## 2 Molecular mechanisms of corydalis rhizoma monotherapy against tumors

Pre-clinical studies, including cellular assays, tumor-bearing mouse models, and chick embryo chorioallantoic membrane (CAM) angiogenesis assays, provide preliminary evidence that total alkaloids and bioactive monomers of *Corydalis yanhusuo* can produce broad-spectrum anti-tumor activities. Six

major underlying mechanisms have been proposed: cell-cycle arrest to restrain tumor proliferation, mitochondrial-dependent apoptosis induction, AMPK/mTOR-dependent autophagy for tumor metabolic reprogramming, inhibition of the TGF- $\beta$ /STAT3 axis to reverse epithelial-mesenchymal transition (EMT) and metastatic capacity, suppression of VEGF-driven neovascularization, and remodeling of

the tumor microenvironment to alleviate immune exhaustion [1].

### 2.1 Cell cycle arrest and inhibition of unrestrained tumor cell proliferation

Dysregulated cell cycle is the key to sustained tumor proliferation. I-THP and dehydrocorydaline upregulate cyclin-inhibitory proteins p21 and p27, while downregulating Cyclin D1, CDK4/6, and proto-oncogene c-Myc, thereby arresting hepatocellular carcinoma and prostate cancer cells at the G0/G1 phase and suppressing DNA replication and clonogenic formation [3,7].

### 2.2 Activation of Mitochondrial Pathway for Dual Induction of Tumor Apoptosis

It triggers mitochondrial-dependent apoptosis as the core event and concurrently activates the death receptor pathway. I-THP elevates mitochondrial reactive oxygen species levels in tumor cells, disrupts mitochondrial membrane potential, promotes cytochrome C release, and activates the caspase cascade. It upregulates the pro-apoptotic protein Bax and downregulates the anti-apoptotic protein Bcl-2, exerting tumor-selective cytotoxicity with negligible toxicity toward normal hepatocytes and epithelial cells [12].

### 2.3 Modulation of the AMPK/mTOR Autophagy Pathway and Reprogramming of Tumor Metabolism

Tumors rely on aerobic glycolysis for energy supply. I-THP activates the AMPK- ULK1 axis to trigger protective autophagy, inhibits the mTOR complex, reduces the glycolytic rate and mitochondrial oxidative phosphorylation in tumor cells, and consequently induces energy exhaustion. Seahorse metabolic assays suggest that blockade of autophagic flux completely abolishes its antitumor efficacy, verifying that metabolic reprogramming serves as a core antitumor mechanism [4].

### 2.4 Inhibition of the TGF- $\beta$ /STAT3 Pathway to Reverse EMT and Block Invasion and Metastasis

EMT is a prerequisite for tumor distant metastasis. I-THP downregulates TGF-  $\beta$  1, p- Smad2/3 and STAT3, upregulates the epithelial marker E- cadherin, and downregulates the mesenchymal markers N- cadherin and Vimentin. It suppresses MMP2/MMP9 to attenuate cell invasive capacity [3].

### 2.5 Down- regulation of the VEGF Family to Suppress Tumor Neovascularization

Solid tumor growth relies on nutrients delivered by newly formed blood vessels. Alkaloids from *Corydalis yanhusuo* down-regulate VEGF- A, VEGFC and KDR and inhibit endothelial tube-like structure formation. Tumor-bearing mice treated with these alkaloids show obvious reduction in microvessel density (MVD), accompanied by smaller primary tumor mass and fewer pulmonary and hepatic metastatic lesions. Early foundational work suggested the anti-angiogenic potential of *Corydalis yanhusuo* alkaloids [8]. More recent pre-clinical studies further suggest that corynoline and total alkaloids suppress endothelial tube formation via the VEGF-A/VEGFR2 axis and downstream ERK/STAT3 signaling, providing new mechanistic insights into its anti-angiogenic properties [13]. Topical application can relieve vascular endothelial inflammation and protect against chemotherapy-induced extravasation phlebitis [14].

### 2.6 Remodeling of the Tumor Immune Microenvironment and Reversal of Immune Exhaustion

Abundant infiltration of myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) within the tumor microenvironment drives local immunosuppression. *Corydalis yanhusuo* exerts multi-faceted immunomodulatory effects: ① down-regulates tumor PD-L1 to recover CD8<sup>+</sup> T-cell cytotoxicity; ② suppresses G-CSF production to limit

MDSC differentiation; ③ rebalances Th1/Th2 homeostasis and increases the abundance of NK, CD4<sup>+</sup> and CD8<sup>+</sup> T-cells; ④ reduces levels of pro-inflammatory cytokines such as TNF- $\alpha$  and IL-6.

Early work indicated that this herb could modulate T-cell-related immune responses [11,13]. More recent in-vivo breast-cancer model data suggest that *Corydalis yanhusuo* constituents can block MDSC accumulation via the G-CSF-ARG-1-STAT3 axis. This

effect mitigates spleen-originated immunosuppression and rescues CD8<sup>+</sup> T-cell cytotoxicity, providing new mechanistic clues for tumor microenvironment (TME) regulation [15]. In 4T1 breast-cancer-bearing mice, combining *Corydalis yanhusuo* powder with cyclophosphamide yields better anti-tumor effects than chemotherapy monotherapy [13]. Figure 1 is a schematic diagram of the anti-tumor molecular mechanism of *Corydalis Rhizoma* as a single agent.

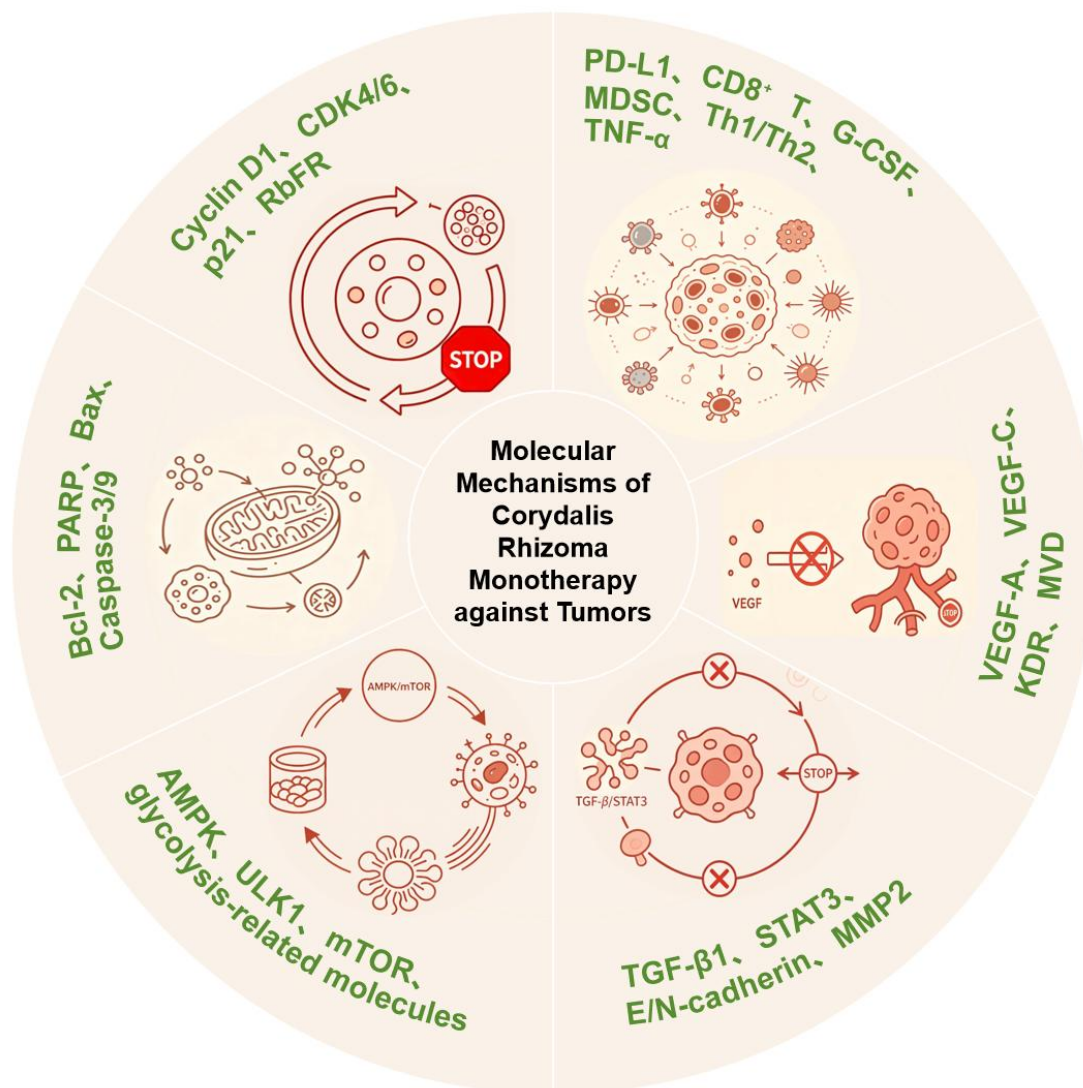


Figure 1 Molecular Mechanisms of *Corydalis Rhizoma* Monotherapy against Tumors.

### 3 Basic experimental evidence of corydalis rhizoma against tumors in different systems

#### 3.1 Digestive system tumors (Liver cancer, gastric cancer, colorectal cancer)

Digestive-system malignancies belong to the relatively high-sensitive tumor types for *Corydalis yanhusuo* alkaloids in pre-clinical investigations. For liver cancer, I-THP produces prominent anti-tumor phenotypes when applied alone or combined with sorafenib in cell

and xenograft models [3,4]. Network-pharmacology prediction supports its potential adjuvant application for hypochondriac pain in advanced-stage liver cancer [16]. In addition, I-THP exerts anti-proliferative effects against hepatocellular carcinoma via AMPK-dependent metabolic switching [17].

Gastric cancer displays background-dependent responsiveness to alkaloid treatment. More prominent pre-clinical inhibitory effects are observed for EBV-positive gastric cancer, while moderate cytotoxic activity can be detected in Hp-associated gastric cancer settings [18]. Recent work further suggested that I-THP could synergize cytotoxic CD8<sup>+</sup> T-cell-mediated antitumor response and trigger ferroptosis in gastric cancer [19].

Colorectal cancer responds well to total alkaloids of *Corydalis Rhizoma*. Pre-clinical observations show reduced malignant phenotypes related to cancer-stem-cell features and decreased recurrence tendency. Beyond tumor-suppressing effects, its intrinsic gastrointestinal-mucosa-protective property represents a unique tissue-specific advantage for colorectal tumor models, which helps relieve chemotherapy-provoked abdominal discomfort and intestinal injury [20].

### 3.2 Breast and reproductive- system tumors

Sensitivity of breast cancer to *Corydalis yanhusuo* active constituents is subtype-dependent. Both triple-negative and hormone-positive breast cancer show treatment responsiveness, yet distinct monomers contribute to different pharmacological outcomes. Isocorydine and dehydrocorydaline mainly restrain tumor progression, whereas glaucine stands out for reversing paclitaxel chemoresistance [9]. The herb-pair combination of *Chelidonium majus-Corydalis yanhusuo* can further improve its drug-resistance-reversal efficacy [21]. For hormone-positive breast cancer, I-THP achieves therapeutic effects by promoting ER  $\alpha$  protein

degradation [22]. Moreover, I-THP can enhance cisplatin sensitivity in human ovarian cancer cells through the microRNA-93/PTEN/Akt signaling cascade [23].

In breast-cancer in-vivo models, *Corydalis Rhizoma* powder alleviates immunosuppressive cell infiltration and lowers pulmonary-metastasis burden; clinically it is used to ameliorate postoperative chest-wall stabbing pain and chemotherapy-related breast distending pain [13].

Prostate-cancer responsiveness is independent of androgen status: inhibitory effects are observed for both androgen-dependent and castration-resistant prostate tumors. A distinct tissue-specific merit lies in its capacity to relieve bone-metastasis-associated pain in advanced disease [24].

### 3.3 Other Solid Tumors, including Lung Cancer and Glioma

Non-small-cell lung cancer presents moderate overall drug sensitivity. Glaucine shows prominent potency in reversing cisplatin- and gefitinib-associated chemoresistance. Apart from direct tumor-related phenotypes, I-THP brings extra tissue-specific benefit by mitigating radiation-pneumonitis-caused injury and associated thoracic symptoms.

Glioma constitutes a special case limited by physiological blood-brain-barrier restriction. Among all tested alkaloid monomers, only I-THP possesses satisfactory blood-brain-barrier-penetrating capacity, which enables intracranial tumor intervention and relief of tumor-caused intractable headache and vomiting. Other alkaloids display limited intracranial efficacy due to poor central nervous-system penetration [7].

## 4 Clinical adjuvant application of corydalis rhizoma throughout the whole tumor cycle

Relying on its four major advantages of analgesia,

toxicity alleviation, therapeutic sensitization, and body- resistance reinforcement, *Corydalis Rhizoma* covers all therapeutic stages: pre-operation, chemoradiotherapy, post-operation, and advanced-stage palliative care.

#### 4.1 Standardized adjuvant palliative therapy for cancer-related pain

The core pathogenesis of cancer pain includes blood- stasis obstruction and qi- stagnation, and *Corydalis Rhizoma* is a priority Chinese medicinal herb for pain relief.

1.Mild- to- moderate cancer pain: 6 – 12 g alone combined with *Paeoniae Radix Alba* and *Glycyrrhizae Radix et Rhizoma* to reduce gastrointestinal and renal injury induced by non-steroidal anti-inflammatory drugs [5].

2.Moderate- to- severe cancer pain (three-ladder combined therapy): I-THP produces synergistic analgesia with opioids, which can lower the dosage of morphine and oxycodone by 30%–40%, and reduce risks of constipation, nausea, and drug addiction [5].

3.Special- type pain: internal administration combined with external application for bone- metastasis-caused stabbing pain, postoperative incision pain, chemotherapy-induced phlebitis, and radiation-provoked pleuritic pain. The externally applied "Jingyan ' an" wet compress, composed of *Corydalis Rhizoma*, *Rhei Radix et Rhizoma*, and *Typhae Pollen*, prevents chemotherapy- extravasation-induced phlebitis with superior efficacy compared with magnesium sulfate wet compress [14].

Mechanistic studies on bone pain suggest that I-THP inhibits the TNF-  $\alpha$ /uPA/PAR2/TRPV1 axis: it blocks substance- P release at the early stage to decrease macrophage infiltration, and promotes anti-inflammatory M2- polarization of macrophages at the later stage, thus achieving long-term

bidirectional analgesia [25]. Moreover, it targets the Nav1.7 channel to ameliorate morphine tolerance and resolve the efficacy decline of long-term analgesic medication for cancer pain [26].

#### 4.2 Efficacy enhancement and toxicity reduction for chemoradiotherapy

##### 4.2.1 Reversal of chemotherapeutic multidrug resistance

Glaucine and corynoline dually inhibit P- gp and MRP1 efflux transporters, elevate intracellular chemotherapeutic- drug concentration in tumor cells, and restore the sensitivity of breast, lung and gastric cancers to doxorubicin, cisplatin and paclitaxel. It enhances therapeutic responses while lowering chemotherapeutic dosage and consequent organ toxicity. Existing reviews summarize that multiple alkaloids derived from *Corydalis Rhizoma* serve as high- quality natural multidrug- resistance reversers with low- toxicity features [27].

##### 4.2.2 Organ- protection against Chemotherapy- induced Injury

Cardioprotection: it suppresses Nox2 oxidase and the NLRP3 inflammasome, mitigates anthracycline-triggered myocardial oxidative damage, reduces risks of arrhythmia and heart failure, and stabilizes left- ventricular ejection fraction. Animal experiments verify its capacity to decrease cardiomyocyte apoptosis after chemotherapy. Small- sample clinical observations reveal that *Corydalis Rhizoma*-containing formulas reduce the incidence of chemotherapy-related myocardial injury [5].

Renoprotection: I-THP inhibits the tubular OCT2 transporter, reduces cisplatin accumulation in kidney tissues, alleviates chemotherapy-provoked renal injury and ototoxicity without compromising the antitumor effect of cisplatin. Relevant preparation patents have been published [28].

Gastrointestinal protection: it regulates gastrointestinal qi movement, lowers the incidence of chemotherapy-induced nausea, vomiting, and intestinal erosion, and guarantees complete chemotherapy cycles. Combined with Astragali Radix and Angelicae Sinensis Radix, it ameliorates chemotherapy-caused leukopenia and thrombocytopenia. Multiple clinical observations imply that such compatibility effectively relieves chemotherapy-related myelosuppression and gastrointestinal adverse reactions [29].

#### 4.2.3 Relief of Local Radiotherapy-Induced Injury

Oral administration alleviates burning pain induced by radiation pneumonitis and esophagitis; external application alleviates radiation-provoked skin erythema and ulceration and improves radiotherapy tolerance. Compound formulas containing this herb are widely adopted in clinical practice [29].

#### 4.3 Synergy with Immunotherapy / Targeted Therapy and Reduction of Immune-related Adverse Events

PD-1/PD-L1 inhibitors are limited by unsatisfactory clinical efficacy as well as adverse events such as immune-mediated hepatitis and thyroiditis. On one hand, *Corydalis yanhusuo* down-regulates tumor-cell PD-L1, restores the cytotoxic function of CD8<sup>+</sup> T cells, and improves anti-tumor potency. On the other hand, it suppresses excessive systemic inflammation and lowers the risk of immune-related adverse events. It is frequently included in clinical herbal formulas for immunotherapy against liver and lung cancers [10].

#### 4.4 Perioperative Rehabilitation Intervention

Pre-operation: combined with Cyperi Rhizoma and Curcumae Radix to soothe liver-qi, relieve tumor-related anxiety and hypochondriac distending pain, stabilize host immunity, and mitigate surgical stress injury.

Postoperative: it facilitates absorption of thoracic- and

abdominal cavity blood stasis, alleviates intractable incision stabbing pain, reduces postoperative analgesic consumption, accelerates gastrointestinal peristalsis, and lowers risks of intestinal adhesion and peritoneal effusion. Such clinical application conforms to the traditional therapeutic principle of activating blood, moving qi, and resolving stasis, and is supported by clinical retrospective studies [30].

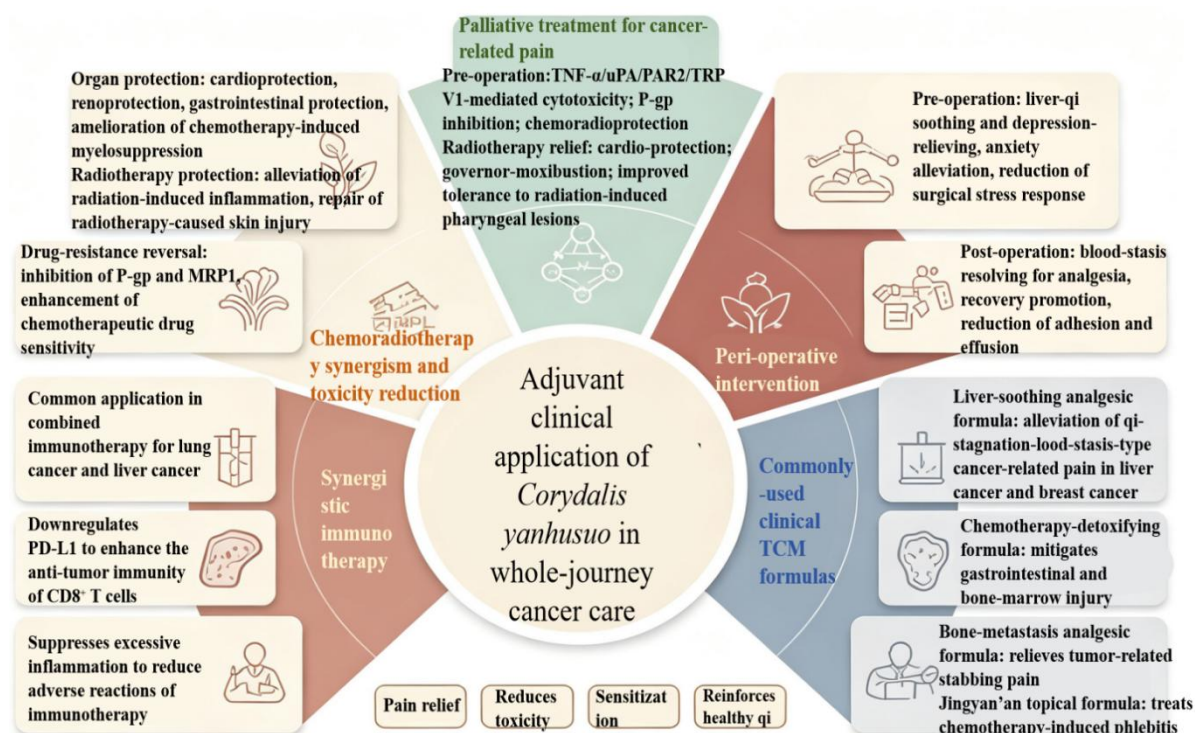
#### 4.5 Commonly-used Clinical Compatibility Formulas

1.Liver- soothing analgesic formula (for liver / breast cancer): Corydalis Rhizoma, Toosendan Fructus, Curcumae Radix, Paeoniae Radix Alba, Hedyotidis Diffusae Herba. Indicated for qi- stagnation- blood- stasis- type hypochondriac pain and breast distending pain, applied for intervention of mild- to- moderate pain in advanced tumors [16].

2.Chemotherapy- detoxifying and body- reinforcing formula: Corydalis Rhizoma, Astragali Radix, Angelicae Sinensis Radix, Ophiopogonis Radix, Poria cocos. Ameliorates myelosuppression and gastrointestinal injury; multiple clinical observations imply that it downgrades the severity of chemotherapy- related adverse reactions [29].

3.Bone- metastasis analgesic formula: Corydalis Rhizoma, Olibanum, Myrrha, Psoraleae Fructus. Relieves persistent stabbing pain from bone metastasis via multi-pathway analgesic mechanisms of its alkaloid constituents [25].

4.Externally- used Jingyan'an wet- compress formula: Corydalis Rhizoma, raw Rhei Radix et Rhizoma, Typhae Pollen, Platycladi Cacumen. Prevents chemotherapy-induced phlebitis and drug- extravasation injury; controlled trials provide its superiority over conventional magnesium- sulfate wet compresses [14]. Figure 2 is a schematic diagram of clinical adjuvant applications of Corydalis Rhizoma in the full-cycle management of tumors.



**Figure 2** Schematic diagram of clinical adjuvant applications of *Corydalis Rhizoma* in full-cycle tumor management.

## 5 Current Limitations of Existing Studies

1. Most basic-research studies are confined to in-vitro cell experiments and conventional tumor-bearing mouse models, while validations using transgenic tumor models and large-mammalian models remain scarce. Most investigations focus on single signaling pathways, lacking multi-dimensional dynamic regulatory-network analysis based on single-cell and spatial proteomics, and the application of cutting-edge multi-omics approaches is insufficient.

2. Weak clinical evidence: available observations are mostly single-center, small-sample retrospective studies; large-sample, multi-center, randomized, double-blind controlled trials are lacking. Therapeutic evaluations mainly rely on pain scores and adverse-event records, whereas hard endpoints such as objective response rate (ORR), progression-free survival (PFS), and survival time are rarely adopted, leading to low-level evidence in evidence-based medicine [1].

3. Deficiencies in pharmaceutical preparations: I-THP

features a short half-life and low oral bioavailability. Research on novel drug-delivery systems, including nanoliposomes and sustained-release microspheres, is limited, and the development of injectable and long-acting topical preparations lags behind, restricting its clinical translation [31].

4. Incomplete safety evidence: Short-term animal experiments have not revealed obvious hepatorenal toxicity. Nevertheless, systematic long-term toxicological evaluations and a clearly defined maximum tolerated dose are still lacking. Potential drug-drug interactions between *Corydalis yanhusuo* alkaloids and commonly used antitumor agents, including chemotherapeutics, opioids and immune-checkpoint inhibitors, have not been adequately evaluated.

From the TCM perspective, *Corydalis yanhusuo* promotes blood circulation and resolves stasis. Integrated with modern pharmacological evidence, pregnant women and patients with hemorrhagic diseases are contraindicated for this herb. Patients with severe qi-deficiency require cautious

administration. At present, quantitative safe-dose windows, monitoring indicators and standardized treatment courses for these special populations are still lacking. The Chinese Pharmacopoeia only provides general warnings for blood-activating herbs, lacking tumor-population-oriented safety evidence to guide clinical practice [2].

5. Ambiguous mechanisms of compound formulas: the molecular interaction mechanisms underlying synergistic anti-tumor and toxicity-alleviation effects of multi-component compound formulas remain unclear. Integrated multi-omics analysis for compound-formula regulatory networks is scarce. Most mechanistic explorations are performed merely on single monomers, ignoring the holistic characteristics of traditional Chinese medicine compound formulas [1].

## 6 Summary

Mounting pre-clinical and clinical evidence suggests that isoquinoline alkaloids from *Corydalis yanhusuo* produce broad-spectrum direct anti-tumor activities. They suppress multiple systemic solid tumors via multiple pathways including cell-cycle arrest, induction of apoptosis and autophagy, inhibition of EMT and angiogenesis, and remodeling of anti-tumor immunity [1]. Meanwhile, they serve as adjuvant interventions throughout the whole tumor cycle: they achieve stratified and safe cancer-pain control and reduce opioid dependence; additionally, they reverse chemotherapy resistance, alleviate cardiac, renal and gastrointestinal injuries induced by chemoradiotherapy, and produce synergistic efficacy-enhancing and toxicity-reducing effects combined with immunotherapy. These properties conform to the integrated Chinese-western-medicine concept of comprehensive tumor management: "tumor suppression, vital-qi protection, analgesia and toxicity alleviation".

Nevertheless, current studies still have drawbacks including monotonous animal models, insufficient clinical evidence, lagging pharmaceutical translation and inadequate long-term safety data. Future research can be deepened from four perspectives:

① Integrate cutting-edge multi-omics, such as single-cell sequencing and spatial proteomics, together with transgenic tumor animal models to systematically decipher the dynamic molecular mechanisms by which *Corydalis Rhizoma* monomers and compound formulas modulate the tumor microenvironment and immune networks, and explore novel anti-tumor targets to overcome the limitations of existing single-pathway studies.

② Conduct multicenter, large-sample randomized controlled clinical trials, adopt objective response rate, progression-free survival, and immune-function indicators as primary endpoints, establish standardized adjuvant-medication regimens of *Corydalis Rhizoma* for tumors, and upgrade the level of clinical evidence.

③ Modify *Corydalis Rhizoma* alkaloids based on nano-delivery and sustained-release carrier technologies to improve oral bioavailability, and develop novel oral, intravenous, and topical adjuvant preparations for tumors, so as to resolve the shortcomings of poor absorption and short half-life of existing monomers [31].

④ Perform systematic long-term toxicological assessments and safety evaluations for combined Chinese-Western-drug therapy, clarify the dosage, treatment courses, and contraindications for special populations at different tumor stages, formulate standardized clinical medication guidelines, and supplement tumor-specific safety references uncovered by the Pharmacopoeia [2].

With continuous advances in mechanistic research and clinical translation, *Corydalis Rhizoma* holds promise

for developing novel natural adjuvant drugs with combined anti-tumor, analgesic, and chemoradioprotective functions, and provides innovative insights for precision integrated Chinese-Western- medicine therapy of malignant tumors.

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### Conflicts of Interest

The authors declare that there is no conflict of interests.

### Author Contributions

Conceptualization: hanqing Yu; Methodology: hanqing Yu; Writing-original draft preparation: hanqing Yu; Supervision: jianfeng Wang. All authors have read and approved the final version of the manuscript.

### Ethics Approval and Consent to Participate

Not applicable. This is a narrative review based on published literature; no human participants or animal experiments were performed in this study.

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### Availability of Data and Materials

The data presented in this study are available on request from the corresponding author.

### Supplementary Material

Not applicable.

### References

- [1] Zhang YY, Wei JH. Research progress on chemical constituents and anti-tumor activities of *Corydalis yanhusuo*. *Chinese Herbal Medicines* 2025; 56(12): 3890-3898.
- [2] Chinese Pharmacopoeia Commission. Pharmacopoeia of the People's Republic of China (Volume I ). *Pharmacopoeia of the People's Republic of China (Volume I )*; China Medical Science Press: Beijing, China, 2020; pp.1462-1463.
- [3] Ding XM, Zeng JQ, Huang TH, et al. Tetrahydropalmatine inhibits migration and invasion of hepatocellular carcinoma cells via TGF- $\beta$ 1/Smads signaling pathway. *Chinese Journal of Experimental Traditional Medical Formulae* 2024; 30(8): 121-127.
- [4] Li T, Wang J. Levo-tetrahydropalmatine suppresses HCC via AMPK - mediated autophagy and metabolic reprogramming. *Phytomedicine* 2023; 108: 154762.
- [5] Luo LM. Review on dual pharmacological effects of tetrahydropalmatine: analgesia and tumor intervention. *Chinese Journal of Applied Physiology* 2016; 32(2): 228-231.
- [6] Yang K. Experiment on protective effect of total alkaloids of *Corydalis yanhusuo* against chemotherapy - induced myocardial injury. *Chinese Journal of Clinical Research* 2016; 29(9): 1057-1061.
- [7] Liu C. Analysis of tumor-apoptosis-intervention targets of active ingredients from *Corydalis yanhusuo* based on network pharmacology. *Journal of Liaoning University of Traditional Chinese Medicine* 2020; 22(10): 112-116.
- [8] Gao JL, Shi JM. *Corydalis yanhusuo* alkaloids inhibit endothelial angiogenesis for tumor intervention. *Oncology Research* 2009; 17(12): 519-526.
- [9] Ding M, Li X, Wang L. Isocorydine suppresses breast cancer invasion and metastasis via regulating HCG18/miR-380-5p axis. *Chinese Archives of Traditional Chinese Medicine* 2025; 43(12): 156-161.
- [10] Shu YY, Xu X. Regulatory effects of blood - activating alkaloids on tumor immune microenvironment. *China Journal of Chinese Materia Medica* 2023; 48(16): 4275-4282.
- [11] Li S, Chen Y, Zhang L, et al. Structural characterization of *Corydalis yanhusuo* polysaccharides and its bioactivity in vitro. *Journal of Ethnopharmacology* 2025; 312: 116487.
- [12] Yin XZ, Liu ZJ, Wang J. Tetrahydropalmatine induces apoptosis of hepatocellular carcinoma cells by regulating

energy metabolism through mitochondrial ROS. *China Journal of Chinese Materia Medica* 2025; 50(18): 4723-4730.

[13] Mao YE. Xuanhusuo powder has an anti-breast cancer effect by inhibiting myeloid - derived suppressor cell differentiation in the spleen of mice through down-regulating granulocyte colony stimulating factor. *Chinese Journal of Immunology* 2024; 40(7): 1425-1430.

[14] Feng LX, Wang HQ, He J. Experimental study on Corydalis yanhusuo mixture for prevention and treatment of chemotherapy-induced phlebitis. *Chinese Journal of Clinical Oncology* 2012; 39(15): 1073-1077.

[15] Li W, Zhao Y, Zhang Q, et al. Alkaloid extract of Corydalis yanhusuo inhibits angiogenesis via targeting vascular endothelial growth factor receptor signaling. *BMC Complement Altern Med* 2019; 19(1): 359.

[16] Zhang T, Li J. Network pharmacological analysis of Toosendan - Fructus - Corydalis - Yanhusuo herb pair against hepatocellular carcinoma. *Journal of Clinical Hepatology* 2021; 37(9): 2122-2128.

[17] Yin X, Li W, Zhang J, et al. AMPK-Mediated Metabolic Switching Is High Effective for Phytochemical Levo - Tetrahydropalmatine (l - THP) to Reduce Hepatocellular Carcinoma Tumor Growth. *Metabolites* 2021; 11(12): 811.

[18] Wang JN, Chen C. Corydalis yanhusuo inhibits immune escape of EBV-positive gastric cancer through CXCL17/AMPK pathway. *Journal of China Medical University* 2024; 53(5): 418-423.

[19] Zhou L, Wei Y, Lin K, et al. L - Tetrahydropalmatine synergizes cytotoxic CD8+ T mediated antitumor and ferroptosis in gastric cancer. *Cell Death Discovery* 2025; 11(1): 541.

[20] Pu ZH, Li T. Correlation mechanism of total alkaloids from Corydalis yanhusuo in activating blood circulation to dissipate blood stasis and anti - tumor activity. *Food and Fermentation Science & Technology* 2025; 61(1): 102-107.

[21] Zou X, Zhang XR, Yu JH, et al. Pharmacodynamic substances of Chelidonium majus - Corydalis yanhusuo herb pair reversing adriamycin resistance in breast cancer. *Chinese Herbal Medicines* 2024; 55(7): 2259-2270.

[22] Xia X, He J, Liu B, et al. Targeting ERα degradation by L - Tetrahydropalmatine provides a novel strategy for breast cancer treatment. *International Journal of Biological Sciences* 2020; 16(12): 2192-2204.

[23] Gong J, Xing C, Wang LY, et al. L-Tetrahydropalmatine enhances the sensitivity of human ovarian cancer cells to cisplatin via microRNA - 93/PTEN/Akt cascade. *Journal of BUON* 2019; 24(2): 701-708.

[24] Chen Y, Zhang H. Corydalis yanhusuo extract inhibits prostate cancer EMT via miR - 192 - 5p/STAT3 axis. *International Journal of Molecular Sciences* 2025; 26(15): 6721.

[25] Zheng G. Tetrahydropalmatine relieves bone cancer pain via TNF - α/uPA/PAR2/TRPV1 signaling in dorsal root ganglia. *Journal of Translational Medicine* 2025; 23(1): 397.

[26] Sun JF. Study on tetrahydropalmatine targeting Nav1.7 to inhibit morphine tolerance in cancer pain. *Journal of Shenyang Pharmaceutical University* 2024; 41(8): 942-948.

[27] Liu YJ, Cao YH. Research progress on traditional Chinese medicine reversers for tumor multidrug resistance. *Chinese Pharmaceutical Journal* 2024; 59(7): 561-570.

[28] State Intellectual Property Office of P.R.China. Application of tetrahydropalmatine in preparing drugs against cisplatin-induced nephrotoxicity. China Patent: CN106551930A, 2017.

[29] Zhou LC, Wen TT. Clinical observation of compound prescriptions containing Corydalis yanhusuo for ameliorating adverse reactions of tumor radiotherapy and chemotherapy. *Shenzhen Journal of Integrated Traditional Chinese and Western Medicine* 2021; 31(17): 55-57.

[30] He J, Hao XB. Study on Corydalis yanhusuo improving postpartum blood stasis and regulating tumor - related inflammatory pathways. *Modern Journal of Integrated Traditional Chinese and Western Medicine* 2022; 31(22): 3100-3105.

[31] Xu SB, Fu RC, Su JJ, et al. Research progress on novel drug delivery systems of tetrahydropalmatine. *Journal of Liaocheng University (Natural Science Edition)* 2026; 39(5): 737-745.