REVIEW
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Research progress on the anti-tumor effect of *Codonopsis pilosula*

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Author contributions

Han X devised the project and the main conceptual ideas. Yin XL devised proof outline, wrote the manuscript, revised the article and drew the mechanism diagram. Han X, Gu RJ edited and proofread the article.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

CP, *Codonopsis pilosula*; TCM, traditional Chinese medicine; CPP, CP polysaccharide.

Citation

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Abstract

Currently, the mortality rate of malignant tumors ranks second globally, surpassed only by cardiovascular and cerebrovascular diseases. The treatment of malignant tumors poses a formidable challenge to both modern medicine and traditional Chinese medicine (TCM). To date, TCM has developed a substantial foundational theoretical understanding and accumulated significant clinical experience in combating tumors. According to TCM foundational theories, "Qi deficiency" is a critical symptom associated with cancer, and "fortifying the body's vitality while expelling pathogens" is the cornerstone of TCM's approach to tumor treatment and bodily balance. *Codonopsis pilosula* (CP), a Qi-invigorating herb, is known to invigorat the spleen, benefit the lungs, nourish the blood, and promote bodily fluids. It is often employed as a substitute for ginseng in clinical settings. Prolonged clinical observations have identified key active constituents of CP, such as *Codonopsis* polysaccharides, isoimperatorin, saponins, lobetyolin, sesquiterpene lactones, and muscone. These ingredients exhibit various therapeutic properties, including anti-tumor, immunomodulatory, anti-infective, antioxidant, and hematopoiesis-enhancing effects. Additionally, when CP is combined with other TCM herbs like *Astragalus* and *Atractylodes macrocephala*, it bolsters the body's vital energy and rejuvenates both Qi and blood. CP can be used in combination with chemotherapy agents to mitigate the adverse effects of radiotherapy and chemotherapy. Moreover, CP demonstrates potential in preventing precancerous lesions. This review summarizes recent research findings on the anti-tumor properties of CP, elucidates the anti-tumor effects and molecular mechanisms of its active components, provides a basis for promoting the utilization of CP resources and its active constituents, and offers insights for the research and development of new anti-tumor drugs.

Keywords: *Codonopsis pilosula*; anti-tumor; molecular mechanism; *Codonopsis* polysaccharides; isoimperatorin; saponins

Background

Malignant tumors have long posed a significant threat to human life and health, making the advancement of tumor treatment and the alleviation of related symptoms a critical and challenging area in both modern medicine and traditional Chinese medicine (TCM) research. The inherent ease of metastasis and diffusion are fundamental characteristics of tumors. The progression of this disease is often associated with complex pathogenic mechanisms, including inflammation and oxidative stress, disturbances in microenvironment and cellular function, obesity, and environmental factors [1]. In modern medicine, radiotherapy, chemotherapy, and surgical interventions can particularly inhibit tumor grows. However, despite improving patient survival rates, radiotherapy and chemotherapy significantly diminish the quality of life for patients. Therefore, the prognosis of tumor treatment and the maintenance of patient survival are central focuses in tumor research.

Through continuous clinical practice, TCM therapy has amassed a wealth of practical experience. Significant progress has been made in the study of Chinese herbal medicines, prescriptions, and their active ingredients with anti-tumor effects. TCM posits that the deficiency of vital energy (Zheng Qi) (Chinese medical term, a driving force behind the body's vital activities with the ability to fight disease) accompanies tumor development, while the accumulation of internal heat toxins that obstruct the flow of Qi (Chinese medical term, functional vigour of all tissues and organs in the human body) is considered the key pathological mechanism. For instance, the inflammation associated with lung cancer can be explained by the TCM pathogenesis of phlegm, blood stasis, and the accumulation of cancer toxins. Tumor-related pathological products, such as phlegm, blood stasis, and cancer toxins, accumulate and intertwine over time, generating heat and leading to inflammation [2]. Therefore, under the guidance of TCM theory, the main therapeutic principle is to support the vital energy and eliminate pathogenic factors (Fu Zheng Qu Xie) (nourish the internal organs, strengthen resistance to disease, reduce disease symptoms and eliminate disease-causing factors), employing a combination of attack and reinforcement methods throughout the treatment process [3].

Codonopsis pilosula (CP) is a traditional Chinese medicinal herb categorized under the category of tonifying herbs. *Intergrating Chinese And Western Medicine* indicates that the ancient *Panax ginseng* mentioned in medical classics is believed to be today's CP, originating from Shangdang. The *Classic of Herbal Medicine* describes *Panax ginseng* as sweet, never bitter. Modern CP is sweet, while *Panax ginseng* from Liaoning is slightly sweet and bitter. This suggests that the ancient *Panax ginseng* is equivalent to today's CP." Scholar Zhang Xichun argues that the "sweet taste" and "originating from Shangdang" point to CP being the *Panax ginseng* in ancient prescriptions. *The Divine Farmer's Materia Medica* describes CP as "having a sweet and slightly cold taste, mainly supplementing the five organs, calming the spirit, settling the ethereal soul, stopping palpitations, expelling pathogenic factors, improving vision, opening the heart, and benefiting the intellect; when taken for a long time, it lightens the body and prolongs life. grown in the valleys of Shangdang Mountain." Compared with other types of ginseng, CP has milder properties and exerts effects of invigorating the spleen, nourishing the lungs, and generating fluids. Clinically, it is used to boost the immune function of cancer patients and alleviate treatment-induced fatigue. Modern medical research has identified that the *Codonopsis* polysaccharides, isoimperatorin, saponins, lobetyolin, sesquiterpene lactones, and muscone ect. found in CP can effectively exert anti-tumor effects and improve the prognosis of tumors. Polysaccharides are one of the main contributors to the biologically activity in *C. pilosula* roots, which for instance immunomodulatory, anti-hepatoma, hepatoprotive, antioxidant and anti-inflammatory [4–7]. Among the over 40 species of *Codonopsis*, the main medicinal CP varieties in the market are White CP from Longxi, Lu CP from Shanxi, and Wen CP from Wenxian. In clinical anti-tumor practice, Lu CP and Wen CP are the main research and application targets.

Xie Danfeng et al.'s research indicates that CP ranks seventh among the top ten most frequently used anti-tumor drugs [3]. Esteemed TCM practitioners are adept at distinguishing between various types of ginseng in clinical tumor treatment. In many well-known formulas for treating tumors, such as Xiao Chaihu Decoction with modifications, Liu Junzi Decoction with modifications, and Qing Qi Hua Tan Decoction with modifications. CP is often used as a substitute for *Panax ginseng* to treat patients with weakened constitution, especially those experiencing deficiency of vital energy after radiotherapy or chemotherapy. For instance, in the case of recurrent thyroid cancer post-surgery, the renowned herbalist Wang Sanhu modified the prescription of Xiao Chaihu Decoction by replacing *Panax ginseng* with CP to stabilize the postoperative therapeutic effect. Despite its prevalent use, current research on the clinical anti-tumor mechanisms and drug compatibility of CP is still insufficient and lacks comprehensive scientific exploration.

This paper provides a comprehensive review of the active ingredients of *Codonopsis pilosula* (CP) and its role in combination therapies with other anticancer drugs, along with their corresponding molecular mechanisms. The review synthesizes findings from both domestic and international research literature. By integrating fundamental theories of TCM, the paper explores the application principles and strategies of CP in tumor treatment. The discussion aims to offer a theoretical foundation for the optimal utilization of CP resources and to promote innovation in TCM-based anticancer clinical therapies.

Antitumor effects and molecular mechanisms of active ingredients in CP

Enhancement of immune function and maintenance of immune balance

The active components of CP, primarily *Codonopsis* polysaccharides, exhibit significant immunological effects on tumors at the mechanistic level. Modern pharmacological experiments demonstrate that *Codonopsis* polysaccharides can enhance both humoral and cellular immunity. A study revealed that CP polysaccharide (CPP) could inhibit the proliferation of H22 in tumor-bearing mice by enhancing host immunity [8]. *In vitro* cultures have shown that CP extracts can increase the phagocytic capacity and activity of macrophages, assisting or activating cytotoxic lymphocytes and NK cells to lyse and destroy mutant tumor cells, thereby playing a role in immune surveillance [9]. The research by Hongxu Liu et al. uncovered that the glycopeptide dCP1 has the efficacy to regulate the polarization of M2-like tumor-associated macrophages (TAM) to the M1 phenotype in simulated tumor microenvironment (TME) [10]. Additionally, magnetically treated CP solutions have been shown to promote phagocytic function of the mononuclear macrophage system in mice; in the study of the immunological function of the effective components in Lu CP oral liquid, Mao Zhujun et al. found that CP polysaccharide could activate anti-tumor cells such as NK cells, macrophages, and LAK cells, induce tumor cell death, and rapidly rebuild and repair the damaged immune system, which is beneficial to the treatment of tumor; through injecting sheep red blood cells (SRBC) and ovalbumin as antigens and subsequently administering CP polysaccharides to mice, Yang Guang et al. discovered that CP polysaccharides could enhance antibody production in normal mice [11–13]. Li-Xia He et al. discovered that small molecule oligopeptides from sea cucumber (*Codonopsis pilosula*) (SOP) could enhance immune functions in mice, possibly through augmenting cell-mediated immunity, humoral immunity, macrophage phagocytosis, and NK cell activity [14]. Used *Codonopsis pilosula* glucofructan (CPG) as an immunomodulatory, Yuting Fan et al. found that administration of CPG at 100 mg/kg effectively inhibited tumor growth in mice, with an inhibition rate of 45.37% [15]. Moreover, CPG significantly increased the expression of Interleukin-2 (IL-2), Interferon-γ (IFN-γ), and Tumor Necrosis Factor-α (TNF-α). Furthurmore, CP essence and polysaccharides have also been shown to have a weight-increasing

effect on the spleen and thymus of mice [16]. Experiments by Liu Hongxu et al. demonstrate that crude polysaccharides of CP could significantly reduce the number of CD68 macrophages in tumors and prolong the survival period of melanoma-bearing mice [17]. Research by Zou Yuanfeng et al. found that β-d-(1→4)-Galactan chains in *Codonopsis* polysaccharides play a crucial role in the expression of immunomodulatory activity both *in vitro* and *in vivo* [18]. According to Chen Min et al., higher concentrations of DSPS (a strain of endophytic bacteria isolated from CP and used to isolate extracellular polysaccharides) at 5 mg/mL could activate macrophages *in vitro*, promoting macrophage polarization to the M1 phenotype, which is valuable for macrophage-mediated cancer treatment immunotherapy [19]. In a transplant tumor model study, Wang Meng found that isoimperatorin, discovered in the root bark of *Codonopsis pilosula*, at a specific dose, could mitigate cyclophosphamide-induced damage to the thymus and spleen of mice, thereby protecting the immune organs of the mice [20].

The research on the immune-related effects of the active components of CP predominantly focuses on *Codonopsis* polysaccharides, with most experiments conducted on mice. There is a notable absence of clinical trials involving tumor patients taking CP. The active components, mainly *Codonopsis* polysaccharides, have demonstrated the capability to rebuild and repair the damaged immune system and inhibit tumor immune responses. From the perspective of TCM, this falls under the category of "supporting the body's vital energy". Additionally, the effective ingredients in CP can enhance both humoral and cellular immunity, which aligns with the TCM concept of "expelling pathogenic factors". Therefore, from the viewpoint of TCM theory, it can be concluded that CP effectively participates in critical anti-tumor processes.

Influencing the cell cycle, inhibiting cancer cell migration, and inducing apoptosis

Two water-soluble *Codonopsis* polysaccharides (CPP1a and CPP1c) were isolated and purified by Bai Ruibin et al., who discovered that both could affect the morphology of human liver cancer cells (HepG2 cells) *in vitro* [21]. These polysaccharides influenced the G2/M phase of the cell cycle, inhibited cell migration, and induced apoptosis. Besides, CPP1b exerts significant cytotoxicity on human lung adenocarcinoma A549 cells in a dose- and time-dependent manner [22]. Chen Min et al. demonstrated that extracellular polysaccharides isolated from the strain 14-DS-1 (DSPS) in CP inhibited the migration of cancer cells (breast cancer, cervical cancer cells) *in vitro*, inducing S phase arrest and apoptosis [19]. Immunofluorescence staining revealed spindle orientation and positioning defects as the underlying mechanism. The molecular mechanism of the anti-metastatic ability of CP polysaccharide fraction (CLPS) was studied by Liu Yanqiu et al., revealing that CLPS could disrupt the β1 integrin-mediated migration of B16F10 melanoma cells [23]. CLPS decreased the affinity between β1 integrin and ligand protein GST-FNIII, weakened adhesive adhesion dependency, blocked the β1 integrin/FAK/paxillin signaling axis, and effectively inhibit melanoma cell migration in mice. Liu Hongmei et al. found that a certain dose of total saponins from CP inhibited the proliferation of breast cancer cells MCF-7 and promoted apoptosis, though exact mechanism remains to be determined [24]. Oleanolic acid A, a major triterpenoid saponin extracted from the roots of CP, was found by An Zhihui et al. to significantly inhibit the migration and invasion of matrix metalloproteinases (MMPs)-9 and (MMPs)-3 in ovarian cancer A2 and SKOV9 cells [25]. This inhibition was achieved by activating the ROS-mediated p38 pathway to suppress MMP expression and cancer cell invasion, thereby achieving an anti-metastatic effect. Lobetyolin (LBT) has shown the ability to assist in drug-induced apoptosis and tumor growth inhibition [26]. Studies have indicated that LBT can effectively inhibit mRNA and protein expression, downregulating glutamine metabolism, to promote drug-induced apoptosis and tumor growth inhibition. The synergistic action of lobetyolin and lobetyol exhibits activity against cancer cells [27]. *Codonopsis* extract D6 has been shown to selectively inhibit tumor cell growth and migration. Tang Xiaolong et al. conducted experiments on the resistance of EGFR tyrosine kinase inhibitors (EGFR-TKIs) targeting activated EGFR mutations in non-small cell lung cancer (NSCLC) [28]. Using D6-1 to mimic natural products isolated from *Codonopsis* roots, they cultured D6NCI-H 1975 cells . Through cell diffusion analysis, they found D6 inhibited tumor cell adhesion. In NCI-H 1975 cells, D6 regulated the levels of two adhesive kinases (SRC and FAK), thereby modulating cell adhesion and spreading.

In the experiments, no significant decrease in cell viability was observed. Codonolactone (CLT), one of the major active components of *Atractylodes macrocephala*, also found in CP, has shown significant potential in cancer treatment. It was demonstrated by Fu Jianjiang et al. that CLT can inhibit the epithelial-mesenchymal transition (EMT) both *in vitro* and *in vivo*, effectively reducing the motility of metastatic breast cancer cells [29]. Furthermore, Wang Wei et al. elucidated the underlying mechanisms, finding that codonolactone significantly inhibited the activity and expression of MMP-9 and MMP-13, thereby weakening the binding ability of Runx2 to the MMP-13 promoter sequence [30]. Complementary *in vitro* studies by Yu Yaping et al. verified that syringing, extracted from CP, significantly inhibited the phosphorylation of MAPK-JNK and Akt (Thr308), upregulated the expression of the key regulatory gene ESR1, and enhanced its capacity to inhibit cell viability and migration, while promoting apoptosis [31]. Lin Cheng et al. elucidated that lobetyolin exerts anti-cancer properties by attenuating cell proliferation and promoting cell apoptosis through the downregulation of ASCT2 in GC [32]. Additionally, research by Luan Yunpeng et al. identified cordifoliketone A as a potential candidate for preventing the proliferation and metastasis of pancreatic ductal adenocarcinoma cells, possibly through mechanisms involving the induction of apoptosis, reduction cancer cell viability, and inhibition inhibiting invasion and migration [33]. The various active components of CP possess significant research value regarding their mechanisms of action on different tumor cells. Over the past decade, these related studies have gained increasing attention. Clarifying these mechanisms will facilitate the clinical application of CP's active components and provide new perspectives for anti-tumor treatment. Additionally, genes such as MMP-9 and MMP-13 can serve as markers for assessing breast cancer metastasis in subsequent research.

Direct inhibitory effects on cancer cells

It was found that CPPS-II + DOX could synergistically exert a direct killing effect on tumour cells [34]. CPPI significantly inhibited the growth of A2780 cells *in vitro* [35]. Moreover, when combined with tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), CPP synergistically inhibited the proliferation of HCT116 cells. He Rupu et al. investigated the impact of CP on protein metabolism and found that CP CP improved gastric mucosal injury and selectively inhibited the proliferation of rat gastric without affecting normal cells, thereby exerting anti-gastric precancerous lesion effects [36]. *In vitro* examinations conducted by Tao Xin et al. found that *Codonopsis* polysaccharides significantly inhibited the invasion and migration potential of human epithelial ovarian cancer HO-8910 cells and exerted a notable anti-proliferative effect on these tumor cells [37]. Additionally, *Codonopsis* polysaccharides reduced the expression of HO-8910 on HO-44 cells, which may involve the inhibiting tumor cell invasion, migration, adhesion, and downregulating CD44, an adhesion molecule, thereby effectively slowing tumor metastasis. *In vitro* experiments, Ning Li et al. found that *Codonopsis pilosula* may inhibit the growth of hepatocellular carcinoma by suppressing CDK1 and impacting the PDK1/β-catenin signaling axis, thereby restricting cell EMT and decreasing cell stemness [38]. Wang Meng utilized a transplantable tumor model and found that isoimperatorin from the root bark of CP exhibited a significant inhibitory effect on mouse liver cancer H22 across various doses [20]. In studies concerning the direct inhibitory effects of CP on cancer cells, the specific mechanisms remain largely unclear. The MMPs through which the active components of CP exert their inhibitory effects still require further investigation. This will provide additional pathways and targets for

tumor treatment.

Prevention of Tumor deterioration through antioxidant pathways
Reactive oxygen species (ROS) generated by oxidative stress can damage DNA, proteins, and lipids, and producing toxic and mutagenic metabolites that alter the biological behavior of tumors, leading to malignant phenotypes. Pectic polysaccharides were obtained from Clematis and *Codonopsis* roots through hot water extraction and column chromatography, as reported by Zou Yuanfeng et al [39]. They found that pectic polysaccharides from different species of Clematis roots could serve as potential natural sources of antioxidants. Xiong Yuanjun et al. discovered that Xinjiang *Codonopsis* polysaccharides exhibit *in vitro* effect on anti-free radical metabolism, thereby reducing bodily damage and enhancing endogenous superoxide dismutase (SOD) activity [40]. Tang Yanan et al. investigated the effects of heating and the addition of honey on the appearance, chemical composition, and *in vitro* antioxidant activity of *Codonopsis* decoctions, noting significant alterations [41]. Further research has shown that *Codonopsis* polysaccharides can be modified by sulfate molecules to enhance antioxidant activity, providing significant protection against acute oxidative stress [42]. *Codonopsis* polysaccharides are the primary components responsible for its antioxidant effects. The methods of decoction and medicinal compatibility influence the degree of its antioxidant properties, thereby affecting its efficacy in preventing tumor progression. This provides insights for adjusting medicinal compatibility and selecting decoction methods when prescribing *Codonopsis*-containing anti-tumor formulations in clinical practice. However, there is still a lack of research on the *in vivo* antioxidant mechanisms of *Codonopsis*' active components.

CP in combination with other drugs for antitumor effects

Anti-tumor effects of cp combined with radiotherapy and chemotherapy
Various clinical studies have demonstrated that combining CP with chemotherapy drugs can protect normal cells, enhance immunity, and mitigate the toxic side effects of radiotherapy and chemotherapy, thereby improving clinical efficacy. This combination therapy has the potential to replace some chemotherapy regimens. Mao Zhujun et al. found that CP can correct the imbalance in the cellular information transmission system and inhibit the transcription of tumor cell genetic factors [12]. These effects enable CP to enhance clinical outcomes effectively when used alongside radiotherapy and chemotherapy, facilitating the clearance of tumor cells. Additionally, CP can alleviate the toxic side effects of radiotherapy and chemotherapy. For instance, oral administration of Lu CP oral liquid can activate the body's complement system and reticuloendothelial system, promote antibody production, accelerate the clearance of tumor cells, thereby complementing radiotherapy and chemotherapy and avoiding damage to normal cells. Additionally, Lu Dangshen oral liquid can accelerate the growth of bone marrow hematopoietic growth factors through immune cell reconstruction, preventing a decrease in white blood cells. It also aids in clearing useless metabolites from the liver, adjusting gastrointestinal function, and improving the surface state of the gastric mucosa. These effects significantly alleviate adverse reactions such as decreased white blood cells, gastrointestinal reactions, and liver function damage caused by radiotherapy and chemotherapy. Through sensitivity analysis, Tan Ying et al. found that CP, along with six other herbal medicines, has the potential to improve the response of advanced gastric cancer (AGC) tumors to oxaliplatin-based chemotherapy [43]. Zhuang Shuxian et al. found that the application of RG-CMH (a herbal compound of rose geranium and Clematis extracts) to patients undergoing chemotherapy/radiotherapy could delay or alleviate the decrease in white blood cell and neutrophil levels experienced by treatment [44]. Herbal extracts, including soy sterols (active extracts of CP), were discovered by Zhang Zhiyi et al. to exhibit a good binding capacity with proteins involved in steroid hormone response, thereby enhancing the efficacy of hormone-based chemotherapy for pancreatic ductal adenocarcinoma [45]. Luan Yunpeng et al. found that CP inhibits cell proliferation and promotes apoptosis in a dose-dependent manner, with the high-dose CP effect on colon cancer cells (inhibiting autophagy) being similar to that of oxaliplatin [46]. Zeng Xiaolan et al. applied Lu *Codonopsis* ointment to 33 lung cancer patients and 32 esophageal cancer patients undergoing radiotherapy and found that Lu *Codonopsis* ointment reduced damage to patients' immune function and IgM to a certain extent [37]. These experimental results indicate that CP and its anti-tumor components, when used in combination with radiotherapy and chemotherapy, have shown certain advantages in both basic research and clinical observations. However, the mechanisms underlying its synergistic and detoxifying effects require further investigation.

Synergistic antitumor mechanism of *Codonopsis* polysaccharides combined with cyclophosphamide. Wu Hongmei et al. found that *Codonopsis* polysaccharides exhibit a synergistic effect with cyclophosphamide in combating mouse tumors [47]. They speculated that this synergistic effect is attributed to the ability of *Codonopsis* polysaccharides to regulate serum cytokines, such as interleukin-2 and interleukin-4 (IL-2, IL-4). This regulation promotes the activation and proliferation of immune cells, thereby enhancing both specific and non-specific cytotoxicity of immune cells against tumor cells. The underlying mechanisms require further exploration, and clinical observations can also be further refined.

CP and *Astragalus* extracts combined with paclitaxel inhibit tumor angiogenesis. Using transplanted tumor volume, tumor tissue microvascular density, number of lung metastatic tumors, and mouse survival time as observation indicators, Bai Changqing et al. found that the combination of paclitaxel with CP and *Astragalus* extracts significantly inhibited the density of microvessels within the transplanted tumor compared to paclitaxel treatment alone [48]. This combination also reduced the number of lung metastatic tumors and significantly prolonged the survival time of mice. These findings suggest that CP and *Astragalus* extracts enhance the inhibitory effects of paclitaxel on tumor angiogenesis and the metastasis of transplanted tumors. It is suggested that tumor patients undergoing paclitaxel chemotherapy can be treated with traditional Chinese medicine containing CP and *Astragalus*. This combination can further inhibit tumor growth and metastasis by suppressing tumor angiogenesis.

***Codonopsis* polysaccharides stabilize selenium nanoparticles for selective anticancer activity.** Hu Nua et al. discovered that polysaccharides from CP, specifically CPW1, can effectively stabilize selenium nanoparticles (SeNPs) [5]. Their study demonstrated that CPW1-stabilized SeNPs (CPW1-Se) exhibit selective anticancer activity against liver cancer cells, promoting cancer cell apoptosis and inhibiting proliferation, while having no adverse effects on normal cells. This selective activity highlights the significant potential of CPW1-Se in liver cancer treatment.

CP combined with other traditional Chinese medicines for anticancer effects

CP combined with *astragalus* for anticancer effects. *Astragalus* is known for its effects of replenishing Qi, raising yang, stabilizing the exterior and stopping sweating, generating fluids and nourishing blood circulation and relieving pain, detoxifying and draining pus, and contracting wounds and generating flesh. CP can replenish the spleen and nourish the lungs, as well as nourish blood and generate fluids. The combination of *Astragalus* and CP is a commonly used herbal pair in TCM clinical practice and frequently appears in anticancer formulas. In their study, Xie Danfeng et al. conducted data mining and statistical analysis, and discovered that among the 296 anticancer formulas collected, the combination of CP and *Astragalus* appeared 46 times, ranking fourth among the most commonly used anticancer herbal pairs [3]. The basic rationale for this combination is that *Astragalus* and CP can replenish Qi and blood, aligning with the TCM principle of tonifying the righteous Qi. Utilizing network pharmacology and integrated modern pharmacological research findings, Wen Fang et al. predicted that the mechanism of action of

the *Astragalus*-CP pair in treating gastric cancer is mainly through mediating PI3K-Akt, MAPK, NF-κB [49]. These pathways regulate biological processes such as tumor cell proliferation, apoptosis, migration, anoikis, kinase activity, and angiogenesis, thereby exerting therapeutic effects.

CP combined with *Tricholoma matsutake* for anticancer Effects. Shen Zhiai et al. found that MECI (*Codonopsis pilosula* extract) and METM (*Tricholoma matsutake* methanol extract) can increase the expression of Bak protein, thereby inhibiting cancer cell growth and inducing apoptosis [50]. This combination was particularly effective in inhibiting the growth of HSC-2 oral cancer cells.

Anticancer compound formulations containing CP. In traditional Chinese medicine, CP is often used in combination with other drugs [51]. The formula called Weikang Keli (made from roots of *C. pilosula* and five other plants) was found to induce autophagic cell death of SGC-7901 gastric cancer cells and to reduce tumor growth *in vivo* [52]. The medication patterns of 904 TCM prescriptions for the treatment of primary liver cancer were analyzed by Pan Shumao [53]. Among these prescriptions, the four herbs *Atractylodes macrocephala*, CP, *Poria cocos*, and *Glycyrrhiza uralensis* were the most commonly used in clinical practice, which correlates with the deficiency of righteous Qi in patients with primary liver cancer. Among those, CP combined with one or two of *Atractylodes macrocephala*, *Glycyrrhiza uralensis*, *Poria cocos*, *Bupleurum chinense*, *Plantago asiatica*, or *Calculus Bovis* are more common. The analysis reveals that combinations of CP with *Atractylodes macrocephala*, *Bupleurum chinense*, *Poria cocos*, *Ampelopsis radix*;; *Atractylodes macrocephala*, *Glycyrrhiza uralensis*, *Bupleurum chinense*, *Plantago asiatica*; *Calculus Bovis*, *Atractylodes macrocephala*, *Glycyrrhiza uralensis*, *Bupleurum chinense* have extremely high confidence levels (above 0.96), indicating that they are relatively common combination types. The core drug combinations among these are the *Glycyrrhiza uralensis*, CP, *Bupleurum chinense* combination and the *Atractylodes macrocephala*, *Poria cocos*, *Glycyrrhiza uralensis*, CP combination. CP and its combinations are widely used in clinical situations with pathogenic patterns such as phlegm and blood stasis intermingled (e.g., the combination of CP, *Glycyrrhiza uralensis*, and *Bupleurum chinense*), deficiency of righteous Qi and blood stasis (e.g., the combination of Citrus reticulata, *Atractylodes macrocephala*, and CP), blood stasis in the liver and spleen (e.g., the combination of CP, *Glycyrrhiza uralensis*, *Bupleurum chinense*, and *Ampelopsis radix*), and stagnation of liver Qi (e.g., the combination of CP, *Poria cocos*, and *Atractylodes macrocephala*). Shi Wenbo et al. found, based on network pharmacology and metabolomics, that the compound Ejiao decoction (*Colla Corii Asini*, *Panax ginseng*, *Rehmannia glutinosa*, CP, and *Crataegus pinnatifida)* may improve gastric mucosal injury in rats with precancerous gastric lesions by regulating gastrointestinal hormones and inhibiting inflammation [54]. Its mechanism of action is related to the inhibition of excessive activation of the PI3K/AKT/HIF-1α signaling pathway and the regulation of energy metabolism disorders in the body. The above studies indicate that the combination of CP with other traditional Chinese medicines can be tailored to the specific TCM syndrome differentiation of the patient, showing potential in preventing precancerous lesions [44]. However, further research is needed to determine the appropriate dosages, the selection of compatible Chinese medicines, the mechanisms of action, and the effects on various types of tumors.

CP extracts as adjuvants for cancer vaccines

In their research, Zhang Weiting et al. discovered that the polysaccharide CP extracted from CP can effectively replace bacterial lipopolysaccharides as an efficient adjuvant in the preparation of dendritic cell-based cancer immunotherapeutic vaccines [55]. This adjuvant enhances the anti-metastatic activity of dendritic cells against breast cancer, thereby boosting the efficacy of cancer immunotherapy. This research provides insights into exploring the potential of *Codonopsis* polysaccharides and other active components as vaccine adjuvants.

Other therapeutic roles of *Codonopsis* in clinical oncology

Over the past few years, research on the development of biocompatible carriers based on hydroethanolic physical gels for effectively encapsulating and delivering hydrophobic drug molecules has been continuously progressing. CPP-G, comprised of a random physically crosslinked network formed by the hydrophobic association of CPP chains, exhibits good mechanical strength, higher shear-thinning sensitivity, and rapid, highly efficient self-recovering characteristics. It demonstrates outstanding performance in constructing injectable and self-recovering drug-loaded gels [56].

Potential adverse effects of cp and related herbs on specific cancers at certain dosages

In a study by Zhang et al., relevant prostate cancer (PCa) models *in vitro* and *in vivo* were used to study the effects of 21 selected Chinese herbal medicines on tumor proliferation and growth [57]. They found that Epimedii Folium (EF) and *Codonopsis* Radix (CNR) significantly increased the protein expression of LNCaP cells and 22Rv1 cells . Further experiments showed that EF or CNR could reduce the bioavailability of abiraterone acetate (ABI) by activating the PI3K/AKT and Rb/E2F pathways, simultaneously enhancing the anti-tumor effect of ABI by increasing AR expression [58]. This finding suggest that CP-related components can promote the proliferation of certain tumor-associated cells in specific diseases, and this promotion effect is achieved by enhancing the expression of androgen receptors. Therefore, the authors conclude that from the perspective of clinical experience and specific types of disease pathophysiology, the above experiments cannot overturn the arguments in this review.

Conclusion and outlook

As a traditional tonic herbal medicine widely used in China, CP and its primary components, such as *Codonopsis* polysaccharides, isoimperatorin, saponins, lobetyolin, sesquiterpene lactones, and muscone--have demonstrated therapeutic effects against various malignancies, including lung, colorectal, gastric, liver, colon and breast cancers [5, 36, 46, 53, 55, 59–61]. The anticancer mechanisms of CP and its combined therapies primarily involve: 1. enhancing immune function and maintaining immune balance; 2. influencing the cell cycle; 3. inhibiting migration; 4. inducing apoptosis. The mechanism is illustrated in Figure 1. As the molecular mechanisms underlying the anticancer effects of CP continue to be elucidated, the holistic therapeutic approach and the multi-target mechanism of action characteristic of traditional Chinese medicine are gradually becoming more evident. However, further in-depth investigations at the microscopic level, such as genetic studies, are still needed to fully understand the anticancer effects of CP and its components. Additionally, the mechanisms of action of its herbal combinations and classical anticancer prescriptions remain to be explored. This has profound implications for the development of targeted anticancer preparations containing effective components of CP and the optimization of anticancer prescriptions. Furthermore, systematic exploration of comparative studies and statistical analyses on the use of CP and other ginseng-like herbs in anticancer prescriptions is lacking. It is also noteworthy that at certain dosages, CP may have adverse effects on specific cancers, such as prostate cancer, suggesting that caution should be exercised when prescribing CP-related formulations to patients with prostate cancer and similar conditions.

In summary, the role of CP in the field of cancer treatment requires a substantial experimental data and research findings as theoretical support. Therefore, continuing to conduct in-depth research on the anticancer activities of CP and its components is of great significance for promoting the development and utilization of CP resources, the research and development of new anticancer drugs, and the optimization of clinical herbal combinations.

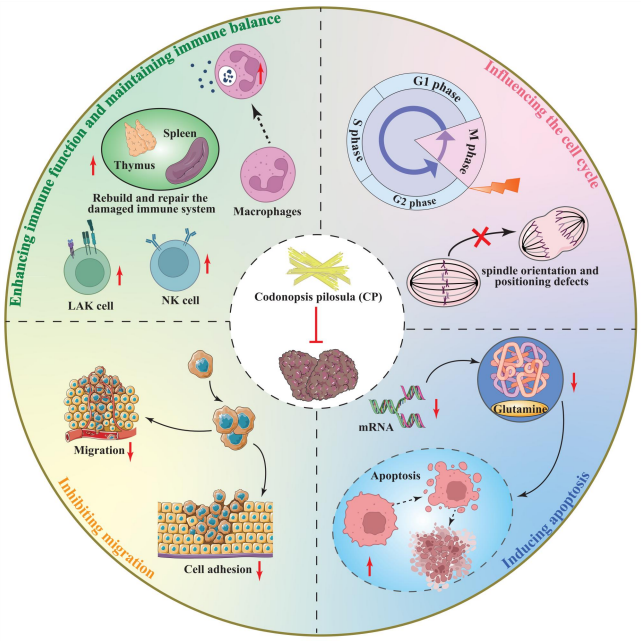

Figure 1 Four main anti-tumour mechanisms of CP

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