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Review Article

Application and mechanism of *Pleione bulbocodioides* traditional Chinese medicine for antitumor treatment

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Abstract: Objectives: To provide a comprehensive overview of the antitumor mechanisms of *Pleione bulbocodioides (P. bulbocodioides)* extract and offer insights for future research in this field. Methods: The antitumor activity of *P. bulbocodioides* was investigated using a combination of network pharmacology, *in vitro* cellular assays, and *in vivo* animal models. Results: The antitumor effects of *P. bulbocodioides* are likely mediated through multiple mechanisms, including cytotoxicity, induction of apoptosis, inhibition of tumor cell proliferation, suppression of tumor angiogenesis, prevention of tumor invasion and metastasis, modulation of immune responses, and synergistic interactions with conventional antitumor drugs. Conclusions: *P. bulbocodioides* exhibits a complex chemical composition and exerts antitumor effects through diverse mechanisms. However, the precise molecular pathways underlying these effects remain insufficiently understood. Despite increasing interest in its antitumor therapeutic potential, further systematic studies are needed to elucidate its mechanisms and validate its antitumor efficacy.

Keywords: *P. bulbocodioides,* tumor, chemical composition, mechanism, immune modulation

Introduction

Traditional Chinese medicine (TCM), including herbs such as ginseng, astragalus, licorice, angelica, and Shancigu (*Pleione*), has been practiced in China for thousands of years and has shown promising effects in disease prevention and treatment. Shancigu is derived from plants of the genus *Pleione* (Orchidaceae), which are primarily distributed in Yunnan, Sichuan, and Taiwan. These plants have a long history of medicinal use and exhibit a wide range of biological activities, including antioxidant, anti-inflammatory, antibacterial, immunomodulatory, and antitumor effects. Among them, *Pleione bulbocodioides (P. bulbocodioides) and Pleione yunnanensis* are listed as the official source plants of the crude drug "Shancigu" in the Chinese Pharmacopoeia (2010 edition) [1-3]. In addition, the dried pseudobulbs of these two *Pleione* species, together with those of *Cremastra appendiculata*, constitute the traditional medicinal materials of Shancigu.

P. bulbocodioides is an important TCM plant, in which the dried pseudobulb is used as the medicinal part. It was first documented in the Bencao Shiyi (Supplement to Materia Medica by Chen Cangqi) during the Tang Dynasty. According to traditional descriptions, it is characterized as sweet, slightly pungent, cool in nature, and slightly toxic. Since the 1990s, its chemical constituents and pharmacological activities have been systematically investigated [4]. Various compounds, including phenanthrenes, bibenzyls, terpenoids, steroids, and flavonoids, have been isolated and identified from this plant; many of these occur in glycosylated forms, alongside various free sugars [5-8]. These constituents confer multiple pharmacological effects, such as antitumor, antihypertensive, hypoglycemic, hypolipidemic, and antibacterial activities, among which the antitumor effect is particularly prominent [9, 10].

Extracts of *P. bulbocodioides* have been documented to exert antitumor effects against a

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variety of tumors, including breast, colorectal, lung, and gastric cancers. In addition, these extracts can enhance tumor sensitivity to chemotherapeutic agents while reducing associated side effects. The underlying mechanisms may involve direct cytotoxicity, induction of apoptosis, inhibition of tumor cell proliferation, suppression of tumor neovascularization, prevention of tumor invasion and metastasis, modulation of immune responses [11, 12], and synergistic antitumor effects with conventional antitumor drugs. This review systematically summarizes recent advances in the chemical components and antitumor mechanisms of *P. bulbocodioides*, aiming to provide a theoretical basis for its clinical application and to support the further development of novel antitumor agents.

Chemical composition and antitumor effects of *P. bulbocodioides*

To date, a total of 280 natural products have been identified from *P. bulbocodioides*, including 122 newly discovered compounds with promising biological activities. In addition, 152 patents related to *P. bulbocodioides* have been filed in China, of which 88.8% focus on its pharmacological applications against various cancers, including breast, lung, liver, gastric, and colorectal cancers. These findings are consistent with numerous studies demonstrating the significant antitumor potential of *P. bulbocodioides* [13].

According to the current literature, the antitumor activities of *P. bulbocodioides* and other components of Shancigu (including *Pinus yunnanensis* and *C. appendiculata*) have been primarily investigated in liver, colorectal, and breast cancer models. Li et al. isolated a series of compounds from *P. bulbocodioides* (designated as compounds 1-30 in **Table 1**) [2, 3, 14, 15], among which five exhibited notable antitumor activity. Among these, bulbocodioidin A (9R) and bulbocodioidins D (10R) showed significant cytotoxic effects in a panel of human cancer cell lines, based on the evaluation of newly isolated phenanthrenequinones. In addition to antitumor activity, several compounds demonstrated hepatoprotective effects. Specifically, M-bulbocodioidin E, pleionoside C, and pleionoside E exhibited protective effects in an *in vitro* model of *N*-acetyl-*p*-aminophenol (APAP)-induced HepG2 cell injury. At a concentration of 10 μM, these compounds yielded cell survival rates of 31.89%, 31.52%, and 31.97%, respectively, which were comparable to that of the positive control bicyclol (31.90%) [15].

P-bulbocodioidin H, identified as a phenanthrene/bibenzyl atropisomer, exhibited cytotoxic activity against HCT-116 (colorectal cancer), HepG2 (liver cancer), and MCF-7 (breast cancer) cell lines, with IC_{50} values of 7.6, 3.8, and 3.4 μM, respectively. Additionally, compound 59 demonstrated cytotoxic activity against MCF-7 cells, with an IC_{50} value of 5.4 μM [14].

Furthermore, pleionosides K and L, two phenylpropanoid glycosides, demonstrated moderate hepatoprotective activity against APAP-induced HepG2 cell injury *in vitro* [3]. Collectively, these findings suggest that *P. bulbocodioides* possesses potential therapeutic value in cancer treatment, although further verification through preclinical and clinical studies is still required.

Dong and Cui isolated numerous compounds from 70-95% ethanolic extracts of *P. yunnanensis* tubers [16-19] (**Table 1**). At a concentration of 10 μmol/L, compared to the model group (bicyclol, 9%), pleionoside P and pleionoside U exhibited moderate hepatoprotective activity against APAP-induced toxicity in HepG2 cells, increasing cell viability by 16% and 12%, respectively [20].

Moreover, various compounds have been isolated from *C. appendiculata* [21-29], as summarized in **Table 1**. Previous studies have systematically evaluated the bioactivity of these compounds against multiple cancer cell lines, including HCT-8 (human colorectal cancer), Bel7402 (hepatoma), BGC-823 (gastric cancer), A549 (lung adenocarcinoma), MCF-7 (breast cancer), and A2780 (ovarian cancer) [24]. Among these, only two compounds - cirrhopetalanthrin and (+)-24,24-dimethyl-25,32-cyclo-5α-lanosta-9(11)en-3β-ol - exhibited notable activity, showing non-selective and moderate cytotoxicity. However, these compounds demonstrated relatively selective cytotoxic effects in human breast cancer cell lines. As shown in **Table 1**, compounds 106-108 exhibited potent cytotoxicity against HCT-116 and MDA-MB-231 cell lines, whereas compounds

Table 1. Names of chemical components in *P. bulbocodioides* associated with antitumor activities and their main functional descriptions

No.	Molecular	Functional description	References
1	Bulbocodin D (BD)	This compound belongs to the bibenzyl class (with p-hydroxyphenyl groups substituted at the C-2 and C-4 positions). It can significantly inhibit the proliferation, colony formation, migration, and invasion of lung cancer cells; induce apoptosis and G2/M cell cycle arrest in A549 lung cancer cells; exert its anticancer activity by specifically targeting STAT3; and can serve as a key candidate compound for breast cancer therapy, with the involved signaling pathways including PI3K-AKT, MAPK, etc.	[39-41]
2	Bulbocodin C (BC)	This compound, belonging to the bibenzyl class, bears p-hydroxyphenyl groups at the C-2 and C-4 positions. It can significantly inhibit the proliferation, colony formation, migration, and invasion of lung cancer cells, and may exert its anticancer activity by specifically targeting STAT3.	[39, 40]
3	2-methoxy-9,10-dihydrophenanthrene 4,5-diol	A major active components of Cremastra appendiculata/Pleione bulbocodioides, which participates in the mechanisms related to breast cancer therapy. It can target estrogen, androgen, and other core genes, regulate the p53 signaling pathway, inhibit cell proliferation, and promote cell apoptosis.	[46]
4	9,10-Dihydrophenanthrene	A structural type of phenanthrene derivatives contained in Cremastra appendiculata/Pleione bulbocodioides. The derivatives (e.g., phenanthraquinone enantiomers) exhibit significant cytotoxicity, which constitutes an important structural category of the antitumor active components in these two plant species.	[2, 14]
5	Stigmasterol	One of the major active components of Cremastra appendiculata/Pleione bulbocodioides. It participates in the mechanisms associated with breast cancer therapy, can target core genes, regulate relevant signaling pathways, inhibit cell proliferation and promote cell apoptosis.	[46]
6	β-sitosterol	Extracted component of Cremastra appendiculata/Pleione bulbocodioides can exert inhibitory effects on lung cancer and breast cancer by suppressing VEGF synthesis; participates in the mechanisms associated with breast cancer therapy and regulate the signaling pathways related to cell proliferation, apoptosis, invasion, and metastasis.	[46, 48]

109-114, 117, and 134-139 showed moderate to weak cytotoxicity against HCT-116, MCF-7, MDA-MB-231, and HeLa cell lines. These findings suggest that these compounds may serve as potential candidates for further investigation in targeted antitumor therapies. In addition, compounds 141-187 were evaluated for cytotoxicity against A549 and Bel7402 cell lines. Among them, compound 88 displayed moderate cytotoxic activity against A549 cells, with an IC_{50} value of 16.0 μM, while no significant activity was observed against Bel7402 cells (IC_{50} > 50 μM). These results highlight the potential of compound 88 [30-33], although further studies are required to confirm its therapeutic relevance.

Recent studies on the biological activities of these compounds have contributed to a deeper understanding of the pharmacological mechanisms of *P. bulbocodioides* and its potential for translational application. Several constituents with promising activity profiles have been identified as lead candidates for drug development. However, systematic preclinical and clinical studies are still needed to evaluate their efficacy and safety *in vivo*, as current evidence is largely based on *in vitro* experiments. In particular, investigations in the antitumor properties of these active constituents provide important evidence supporting their role in cancer therapy, including validation of their cytotoxic effects and a foundation for the development of novel anticancer agents.

Nevertheless, the precise molecular mechanisms underlying these effects remain poorly elucidated, despite consistent evidence supporting the antitumor activity of *P. bulbocodioides* and its constituents. This review summarizes current knowledge of the tumor-inhibitory mechanisms associated with *P. bulbocodioides*, with the aim of providing a structured framework to guide future mechanistic and translational research.

Antitumor mechanisms of *P. bulbocodioides*

Induction of tumor cell apoptosis

Zhifan et al. reported that the pro-apoptotic effect of *P. bulbocodioides* extract was mediated through the regulation of key apoptosis-related proteins, particularly members of the caspase and Bcl-2 families [34]. This treatment significantly increased the activities of caspase-3 and caspase-9, while markedly reducing Bcl-2 expression in tumor cells, thereby promoting apoptotic cell death and highlighting the therapeutic potential of the extract.

Further mechanistic studies have provided additional insights into this regulatory network. Wang Yang et al. found that the extract could downregulate AEG-1 protein expression, leading to decreased Bcl-2 levels and increased Bax expression. These changes ultimately inhibited the proliferation of SW480 cells and induced apoptosis [35]. Similarly, Yu et al. confirmed that the extract suppressed proliferation and induced apoptosis in HT29 colorectal cancer cells by regulating the expression of cytochrome C, BCL-2, Bax, and caspase-3 [36]. Collectively, these findings indicate that *P. bulbocodioides* extracts exert antitumor effects by modulating key pathways involved in cell proliferation and programmed cell death.

Another study investigated the pro-apoptotic effects of the ethyl acetate extract of *P. bulbocodioides* in leukemia cells, supporting its potential as an anti-leukemic therapeutic agent [37]. In K562 and HL-60 cells, treatment with the extract induced a concentration-dependent upregulation in pro-apoptotic proteins, including Bax, cleaved PARP, and cleaved caspase-3, along with a reduction in the anti-apoptotic protein Bcl-2. Moreover, cytochrome c (CytC) and apoptosis-inducing factor (AIF), key mediators of the mitochondrial apoptotic pathway, were increasingly released into the cytosol in a dosedependent manner. These results suggest that the extract primarily induces apoptosis via the mitochondrial pathway. The conclusion is supported by the observed protein expression profile, characterized by increased Bax, cleaved PARP, cleaved caspase-3, and cytosolic CytC/AIF levels, along with reduced Bcl-2 expression (**Figure 1**). These findings provide valuable mechanistic insights into the anti-leukemic effects of *P. bulbocodioides*.

Ye et al. [38] demonstrated that treatment of HGC-27 gastric cancer cells with *P. bulbocodioides* extract led to a concentration-dependent reduction in the p-Akt/Akt ratio, indicating inhibition of Akt activity. Accordingly, the antiproliferative effect of the extract may be mediated through inactivation of the PI3K/Akt signaling pathway. Bulbocodin D (BD) and Bulbocodin C

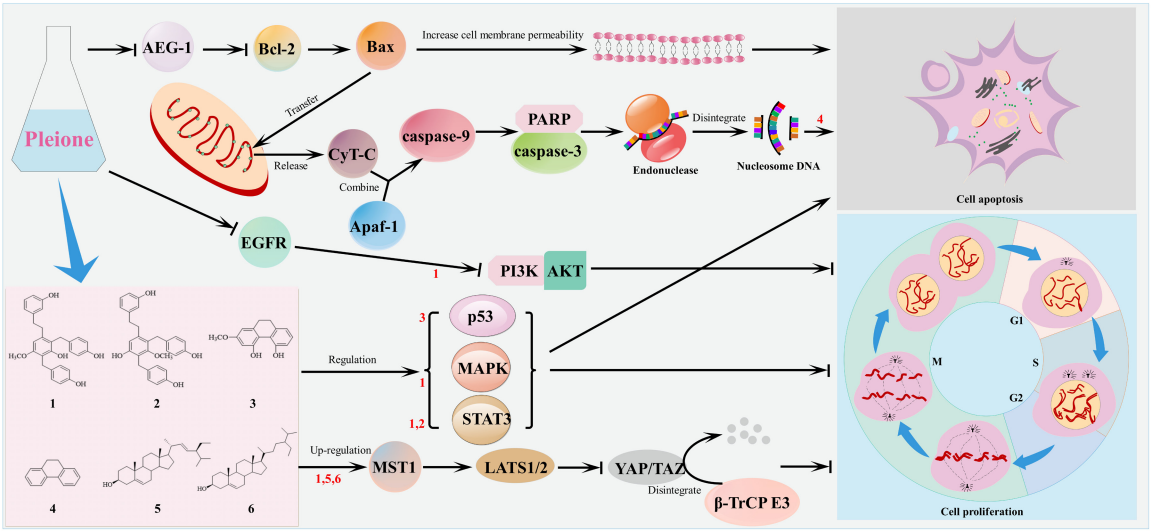

Figure 1. Direct antitumor mechanism of *P. bulbocodioides*. Names of chemical components: 1, Bulbocodin D (BD); 2, Bulbocodin C (BC); 3, 2-methoxy-9,10-dihydrophenanthrene 4,5-diol; 4, 9,10-Dihydrophenanthrene; and 5, Stigmasterol; 6, β-sitosterol.

(BC), two bibenzyl compounds isolated from *P. bulbocodioides*, are characterized by p-hydroxyphenyl substituents at the C-2 and C-4 positions [39]. Both compounds significantly inhibited lung cancer cell proliferation, colony formation, migration, and invasion. Notably, BD induced apoptosis and G2/M phase cell cycle arrest in A549 cells. Mechanistically, the antitumor effects of BD and BC are primarily associated with inhibition of STAT3 signaling, highlighting their potential as promising therapeutic candidates [36].

Complementing these experimental findings, network pharmacology analysis identified 108 potential targets associated with the anti-breast cancer effects of *P. bulbocodioides*, including 23 core targets such as TP53, MAPK3, MAPK1, RELA, AKT1, FOS, ESR1, tumor necrosis factor (TNF), interleukin-6 (IL-6), and MAPK14. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis further revealed that these targets were involved in key signaling pathways, including PI3K-AKT, MAPK, proteoglycans in cancer, AGE-RAGE, IL-17, TNF, apoptosis, and HIF-1. Overall, these findings underscore the multi-target and multi-pathway mechanisms underlying the anti-breast cancer activity of *P. bulbocodioides* [40, 41].

Yuxin Cao et al. [42] reported that BQZC (an extract of *P. bulbocodioides*) inhibited lung cancer cell growth while inducing both protective autophagy and apoptosis through activation of the AMPK-mTOR-ULK1/BMF signaling pathway. These findings suggest the potential of *P. bulbocodioides*-derived preparations for further development as antitumor therapies.

In summary, *P. bulbocodioides* extracts induce cancer cell apoptosis by modulating multiple signaling pathways (e.g., PI3K/Akt, MAPK, and oxidative stress-related pathways) and key regulatory proteins (e.g., caspase and Bcl-2 family members). Through these coordinated mechanisms, the extracts exert significant antitumor effects, supporting their potential as promising candidates for antitumor therapy.

Cell cycle arrest and inhibition

The cell cycle is a fundamental regulatory process governing cellular growth, division, and replication, and its dysregulation is a hallmark of tumor proliferation. *P. bulbocodioides* extracts have been shown to inhibit tumor cell growth primarily by interfering with cell cycle progression. For instance, Liu et al. [43] demonstrated that the extract significantly inhibited proliferation and induced apoptosis in mouse 4T1 breast cancer cells. Similarly, Xiaoyu et al. [44] and Chun [45] reported that an aqueous decoction of *P. bulbocodioides* induced G2-phase cell cycle arrest, thereby suppressing proliferation and promoting apoptosis in MDA-

MB-231 and T-47D human breast cancer cells. These effects may be associated with key bioactive constituents, such as β-sitosterol, stigmasterol, and 2-methoxy-9,10-dihydrophenanthrene-4,5-diol, which act through multiple interconnected pathways [46]:

1. Targeting core genes, including estrogen, androgen, and progesterone receptors, and prostaglandin G/H synthase 2, to suppress proliferation and promote apoptosis.

2. Upregulating the p53 signaling pathway and prostaglandin G/H synthase 2, thereby disrupting angiogenesis and cellular differentiation.

3. Downregulating vascular endothelial growth factor (VEGF) and matrix metalloproteinase-9 (MMP-9) expression, and inhibiting the Wnt pathway, to suppress breast cancer cell invasion and metastasis.

Collectively, these findings highlight the multitarget antitumor effects of *P. bulbocodioides* extracts in breast cancer.

Furthermore, serum containing bioactive components of *P. bulbocodioides* has been reported to inhibit the proliferation of SK-BR-3 breast cancer cells in a concentration-dependent manner [47]. The inhibitory effect was most pronounced at a 20% serum concentration, with greater suppression observed at higher concentrations. Fluorescence-based assays further confirmed that treatment with the *P. bulbocodioides*-containing serum induced apoptosis in SK-BR-3 cells. Besides, wound healing assays confirmed a marked reduction in cell migration into the scratch area, indicating impaired tumor cell motility.

In summary, *P. bulbocodioides* suppresses tumor cell proliferation, at least in part, through disruption of the cell cycle. This effect involves modulation of key regulatory proteins and induction of cell cycle inhibitors, providing a mechanistic basis for the development of *P. bulbocodioides*-derived antitumor agents.

Anti-angiogenic and anti-metastatic effects

The active constituents of *P. bulbocodioides* also exhibit significant anti-angiogenic and anti-metastatic activities. For example, Zhang et al. [48] reported that β-sitosterol, a major component of *P. bulbocodioides*, inhibited tumor growth in lung and breast cancer models by reducing VEGF production.

Additional evidence from the chick chorioallantoic membrane assay demonstrated that *P. bulbocodioides* extract markedly inhibited both the proliferation of human umbilical vein endothelial cells and angiogenesis [49]. Consistently, Xuelian et al. [50] found that the extract downregulated the expression of hypoxia-inducible factor-1α (HIF-1α), VEGF-A, and VEGFR-2 in human breast cancer cells, thereby blocking angiogenic signaling pathways. Furthermore, an aqueous extract of *P. bulbocodioides* has been shown to markedly reduce VEGF expression in breast cancer tissues, leading to inhibition of tumor angiogenesis and contributing to its overall antitumor efficacy [51].

Additionally, components of *P. bulbocodioides* can interfere with tumor cell migration and metastasis. This effect may be mediated, at least in part, by downregulating the expression of key membrane-associated proteins involved in tumor cell adhesion and transendothelial migration.

Immunomodulatory mechanisms

Immune dysfunction plays a critical role in tumorigenesis and progression, making immunomodulation an important strategy in antitumor therapy. Emerging evidence suggests that *P. bulbocodioides* exhibits significant immunoregulatory activity (**Figure 2**). For instance, Nan investigated the ethyl acetate extract of Shancigu (*Cremastra appendiculata*, CrAp) in a 4T1 breast cancer model. CrAp suppressed 4T1 cell proliferation *in vitro* and tumor growth *in vivo*, improved the general condition of tumorbearing mice, and increased their body weight *in vivo*. These effects were associated with increased levels of IL-2 and interferon-γ (IFN-γ), along with decreased levels of TNF-α and IL-10 in tumor tissues. Furthermore, CrAp could enhance the antitumor and immunomodulatory effects of doxorubicin (ADM) [52].

Consistent with these findings, Zhang et al. reported that CrAp modulated the tumor microenvironment by increasing IL-2 and IFN-γ levels while reducing TNF-α and IL-10 expression. Notably, the combined treatment of CrAp and

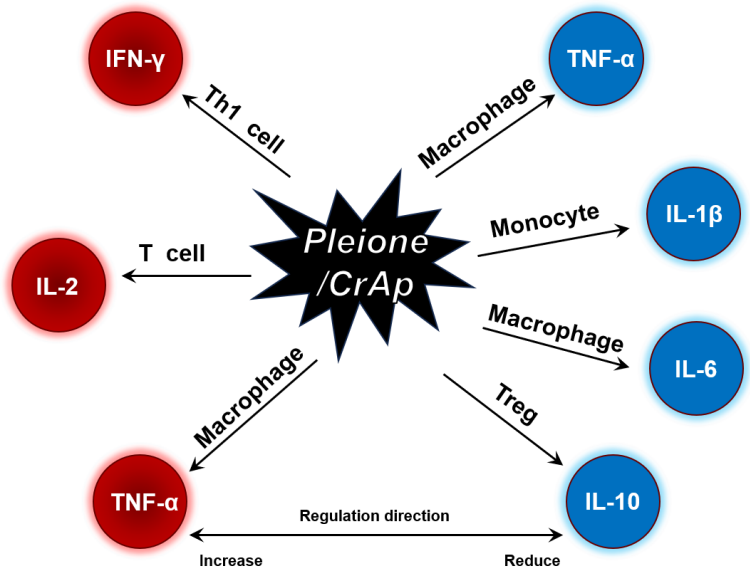

Figure 2. Immune regulation of *P. bulbocodioides.* Abbreviations: IL-1β, Interleukin-1 beta; IL-2, Interleukin-2; IL-6, Interleukin-6; IL-10, Interleukin-10; TNF-α, Tumor Necrosis Factor-alpha; IFN-γ, Interferon-gamma.

ADM exhibited stronger immunoregulatory effects than either treatment alone [53].

Similar mechanisms have also been observed in studies of related polysaccharides. Xu et al. found that polysaccharides derived from *P. yunnanensis* prolonged survival in tumor-bearing mice, likely through increased IL-2 production and enhanced overall immune function [54]. Jiang et al. further demonstrated that the antitumor effects of Pseudobulbus *Cremastrae seu Pleiones* polysaccharide were closely associated with immune enhancement. These effects included increased lymphocyte proliferation and macrophage phagocytic activity, inhibition of tumor growth in S180-bearing mice, elevated spleen and thymus indices, increased $CD4^+$ and $CD8^+$ T-cell counts, and higher serum levels of IL-2, TNF-α, and IFN-γ [55].

Additionally, Tang et al. reported that a water decoction of Shancigu could reduce the secretion of TNF-α, IL-6, and IL-1β in SMMC-7721 tumor cells, thereby modulating the tumor microenvironment and inhibiting cell proliferation [56].

In summary, *P. bulbocodioides* and its related extracts exhibit multifaceted immunomodulatory and antitumor activities. These effects are likely mediated through regulation of the tumor microenvironment, enhancement of immune cell function, and modulation of key cytokine networks. Therefore, *P. bulbocodioides* represents a promising candidate for immunotherapeutic strategies in antitumor treatment.

Synergy with antitumor agents

CrAp has demonstrated inhibitory effects on tumor growth. Notably, the combination of CrAp with ADM achieved a superior tumor inhibition rate than either agent alone. This finding suggests a synergistic interaction between the two agents, which not only enhances therapeutic efficacy against breast cancer but may also reduce the adverse effects commonly associated with ADM [57].

The application of TCM in antitumor treatment has gained increasing attention, with growing evidence supporting its clinical value. For instance, Wang Xuanxuan et al. [58] analyzed 11,293 prescriptions from 3,234 lung cancer patients at Hubei Cancer Hospital and identified a core prescription consisting of 16 key herbs, including Shancigu.

Among various antitumor TCM formulations, those containing Shancigu exhibit several advantages, including favorable safety profiles, demonstrated efficacy, and relatively mild side effects. These formulations may enhance host resistance by modulating immune function, reduce cancer recurrence, and prolong patient survival. Accordingly, they can be used either as standalone therapies or as adjuvant treatments in combination with chemotherapy and radiotherapy.

In summary, TCM formulations containing Shancigu show considerable potential as important adjuncts in comprehensive antitumor treatment strategies.

Future perspectives on the antitumor effects of *P. bulbocodioides*

As a medicinal plant, *P. bulbocodioides contains* a wide range of bioactive compounds and shows promising potential in antitumor

therapy. This review systematically summarizes its chemical constituents and antitumor activities. Current evidence indicates that *P. bulbocodioides* inhibits tumor growth through multiple mechanisms. Moreover, it may enhance the efficacy of conventional therapies when used in combination, while potentially reducing treatment-related toxicity. Furthermore, *P. bulbocodioides* appears to exhibit a favorable safety and tolerability profile, with relatively few serious adverse effects reported. Collectively, these findings provide a strong foundation for its further development as an antitumor agent. However, several limitations remain. The underlying molecular mechanisms and clinical applications of *P. bulbocodioides* require further investigation to provide a stronger scientific basis for its integration into antitumor treatment strategies.

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Disclosure of conflict of interest

None.

Abbreviations

ADM, Adriamycin (doxorubicin); AIF, Apoptosis-inducing factor; APAP, N-acetyl-p-aminophenol; BC, Bulbocodin C; BD, Bulbocodin D; CytC, Cytochrome C; IFN-γ, Interferon-γ; IL-2, Interleukin-2; *P. bulbocodioides, Pleione Bulbocodioides;* TNF-α, Tumor necrosis factor-α; VEGF, Vascular endothelial growth factor.

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