Research Progress on the Chemical Components and Anti-tumor Effects of Cremastrae Pseudobulbus Pleiones Pseudobulbus (CPPP)

Jiawei LIU, Chunhui LIU*, Zeyu WU, Qin WANG, Yanbin LI, Hanrui BAI

Inner Mongolia Medical University, Hohhot 010010, China

Abstract This article systematically reviews the chemical components of Cremastrae Pseudobulbus Pleiones Pseudobulbus (CPPP), as well as their mechanisms of action against various cancers, including lung, breast, liver, and thyroid cancers. These compounds exerts therapeutic effects through multiple signaling pathways, such as inhibiting tumor proliferation, invasion, and migration, promoting cell apoptosis, and regulating immune responses. Current research mainly focuses on cellular and animal experiment levels, with limited progress in clinical translation and full-chain studies of "component, product, and application". Future investigations should use molecular network analyses and strategies integrating traditional Chinese and Western medicine to thoroughly explore synergistic targets, toxicity reduction, and efficacy enhancement, thereby facilitating the efficient translation of basic research achievements into clinical applications.

Key words Cremastrae Pseudobulbus Pleiones Pseudobulbus (CPPP), Chemical component, Anti-tumor activity, Research progress

1 Introduction

Cremastrae Pseudobulbus Pleiones Pseudobulbus (CPPP) refers to the dried pseudobulb of the orchid family plants *Cremastra appendiculata*, *Pleione bulbocodioides*, or *Pleione yunnanensis*. The earliest document of CPPP appears in the *Bencao Shiyi* (*Supplement to the Compendium of Materia Medica*) from the Tang Dynasty. It is primarily used for the treatment of abscesses, sores, fistulas, scrofula, tuberculosis, and related conditions. When ground with vinegar and applied topically, it is also reported to alleviate symptoms described as "illness black". The plant is described as growing in mountainous wetlands and is commonly known as the golden lantern flower. Its leaves are noted to resemble those of *Plantago asiatica*, while its roots are similar to those of *Sagittaria trifolia*[1]. It has a sweet, slightly pungent, and cooling taste and is associated with the liver and spleen meridians. Its therapeutic functions include clearing heat, detoxification, resolving phlegm, and dispersing nodules. It is commonly used in the treatment of abscesses, furunculosis, scrofula, phlegm nodules, snake and insect bites, as well as abdominal masses and lumps[2]. The recommended clinical dosage ranges from 3 to 9 g. The main chemical components of CPPP include phenanthrenes, bibenzyls, flavonoids, terpenoids and lignans, *etc.*[3]. A large number of studies have confirmed that CPPP has anti-tumor, immunomodulatory, antihypertensive, and neuroprotective effects[4]. This article provides a comprehensive review of the research progress on the chemical components and anti-tumor effects of CPPP, aiming to offer a foundational basis and theoretical framework to support basic research and the further development of clinical compatibility theories for the application of this drug in tumor treatment.

2 Chemical components

Due to the diverse botanical origins of CPPP, *C. appendiculata*, *P. bulbocodioides*, and *P. yunnanensis*, documented in the *Chinese Pharmacopoeia* (2020 Edition), were selected as the subjects of this study. To date, researchers at home and abroad have identified nearly 234 compounds from CPPP extracts, including 92 phenanthrene compounds, 35 bibenzyl compounds, and 14 ketone compounds[5]. The common chemical components of these three plant species are discussed in detail below.

2.1 *C. appendiculata* *C. appendiculata*, a medicinal plant, has been extensively investigated by contemporary researchers, revealing a complex and diverse chemical composition. The main chemical components are detailed in Table 1.

2.2 *P. bulbocodioides* *P. bulbocodioides*, a source of the traditional Chinese medicinal herb CPPP, contains complex and diverse chemical components. Recent research has revealed its significant biological activities. The primary chemical components are detailed in Table 2.

2.3 *P. yunnanensis* At present, there are relatively few studies on the chemical properties of *P. yunnanensis*. Wang Jing *et al.*[6] employed ultra-performance liquid chromatography coupled with quadrupole electrostatic field orbital-well high-resolution mass spectrometry to extract and identify 42 chemical components, including 13 benzyl succinate glycosides, 4 phenolic glycosides, 3 alkaloids, 1 flavonoid, 7 aromatic compounds, 1 carbohydrate compound, 3 bibenzyl compounds, and 10 other types of compounds.

Received: April 18, 2026 Accepted: June 20, 2026

Supported by National Natural Science Foundation of China (82060908); Natural Science Foundation of Inner Mongolia Autonomous Region (2024MS08033); Project of the Health Commission of Inner Mongolia Autonomous Region (202202140); Joint Fund of the Affiliated Hospital of Inner Mongolia Medical University (2023NYFYLHZD010).

Jiawei LIU, bachelor's degree. * Corresponding author. Chunhui LIU, doctoral degree, professor.

Table 1 Common chemical components of *Cremastra appendiculata*

Chemical component	Chemical formula	Reference
Phenanthrenes	Isohircinol	[6]
	2-Hydroxy-4, 7-dimethoxyphenanthrene	[6]
	4-Methoxy-2, 3, 7-trihydroxyphenanthrene	[7]
	4, 7, 4', 9'-Tetramethoxy-[1, 1'-biphenanthrene]-2, 2', 7, 7'-tetrol	[7]
	4, 4' -Dimethoxy-[1, 1' -biphenanthrene]- 2, 2', 7, 7'-tetrol	[7]
Bibenzyls	3, 5, 3'-Trihydroxybibenzyl	[6]
	3, 3'-Dihydroxy-2-(4-hydroxybenzyl)-5-methoxybibenzyl	[7]
	3, 5-Dimethoxy-3'-hydroxybibenzyl	[8]
Lignans	Pinoresinol-β-D-glucopyranoside	[8]
	Matairesinol-4'-O-glucoside	[8]
Flavonoids	Quercetin	[8]
	Genkwanin	[8]
	5, 7-Dihydroxy-3-(3-hydroxy-4-methoxybenzyl)-6-methoxychroman-4-one	[9]
	Quercetin-3'-O-β-D-glucopyranoside	[10]
Alkaloids	Aurantiamide acetate	[11]
Terpenoids and steroid compounds	(-)-Cadin-4,10(15)-dien-11-oic acid	[12]
	(-)-Ent-12β-hydroxykaur-16-en-19-oicacid, 19-O-β-D-xylopyranosyl-O-β-glucopyranoside	[13]

Table 2 Common chemical components of *Pleione bulbocodioides*

Chemical component	Chemical formula	Reference
Phenanthrenes	2-Hydroxy-4, 7-dimethoxy-phenanthrene	[13]
	4, 7-Dihydroxy-2-methoxy-9, 10-dihydro-phenanthrene	[14]
Flavonoids	Flavanthrinin	[14]
Bibenzyls	Batatasin III	[15]
	3', 5-Dihydroxy-2-(4-hydroxybenzyl)-3-methoxybibenzyl	[15]
	3, 3'-Dihydroxy-2, 6-bis(p-hydroxybenzyl)-5-methoxybibenzyl	[15]
Benzyl ester glycosides	Bletistroside C	[16]

3 Anti-tumor effects

According to traditional Chinese medicine (TCM), tumor development is attributed to internal factors such as "deficiency of vital energy", "blood stasis", and "toxicity". The therapeutic approach primarily emphasizes "strengthening the body's constitution", "enhancing circulation", and "eliminating toxins"[7]. CPPP is believed not only to clear heat and detoxify but also to promote blood circulation and disperse nodules, thereby facilitating "the expulsion of pathogenic factors". Contemporary research has demonstrated that chemical components in CPPP extracts show inhibitory effects on tumor proliferation, invasion, and neovascularization, while also promoting apoptosis and modulating immune responses in tumor treatment[8].

3.1 Anti-lung cancer In recent years, lung cancer has emerged as a malignant tumor with extremely high incidence and mortality rates in China, and this trend continues to increase[9]. TCM scholars classify lung cancer under the categories of "lung accumulation", "pulmonary mass", and "carcinomatosis". Although the clinical manifestations of the disease are varied, the pathogenesis, as described in the *Essential Readings for Medical Professionals*, is attributed to the accumulation of vital energy. Specifically, when the body's vital energy is deficient, pathogenic factors predominate and contribute to disease development. Li Candong[10] proposed that most non-small cell lung cancers (NSCLCs) were characterized by the coexistence of phlegm and blood stasis. His therapeutic approach involved treating the lung, spleen, and liver to regulate the qi movement within the lung and liver, protect the vital energy of the spleen and stomach, and thereby achieve the resolution of phlegm and removal of blood stasis. CPPP was commonly used as a single medicinal ingredient in his clinical practice and was frequently preferred as a primary choice among medicines with a cold nature. Zhang Shunan[12] advocated for an integrative treatment approach for pulmonary micronodules, combining TCM and Western medical practices. Western medicine addresses the pathological basis of pulmonary nodules, whereas TCM primarily emphasizes lung tonification and the promotion of blood circulation to eliminate blood stasis. Among the 10 core medicinal ingredients identified, CPPP was the most

frequently used, with a usage rate of 66.18%, and demonstrated favorable clinical efficacy. Zhang Yu *et al.*[11] summarized the clinical experience and established formulation of the Kangai Fuzheng Prescription for the treatment of NSCLCs at Jinhua Hospital of Traditional Chinese Medicine. They believed that lung cancer is a consumptive disease that depletes qi and blood extensively. The therapeutic approach should focus on clearing heat and detoxification, tonifying qi and nourishing yin, as well as enhancing the body's resistance while eliminating pathogenic factors. Among the core 8 Chinese medicines, CPPP is recognized for its significant role in detoxification. Li Yangzhi *et al.*[13] conducted a comprehensive analysis of the diagnostic and therapeutic approaches employed by numerous national TCM masters in the treatment of lung cancer through syndrome differentiation. Their findings revealed that the chi-square value for the use of CPPP in treating cancer toxin syndrome was 38.097, indicating its widespread application among national TCM masters. Xiao Kai *et al.*[16] investigated the treatment of advanced NSCLCs using a combination of TCM and Western medicine. They administered the Western pharmaceutical icotinib hydrochloride alongside the TCM Shancigu Decoction, achieving a high clinical remission rate and demonstrating improvements in patient prognosis and recovery.

Cai Kan[14] conducted a summary analysis of 1 800 outpatient cases and found that CPPP was used 620 times, accounting for 34.44% of the total dosage. In clinical treatment, the maximum administered dose reached 25 g. Since prolonged use of CPPP may result in cumulative toxicity, careful consideration should be given to the duration of its use in clinical practice. Cao *et al.*[15] integrated the spectral-effect relationship with the theory of serum pharmacochemistry to identify a combination of 11 bioactive components with anti-lung cancer efficacy for the first time. Their study showed that the AMPK-mTOR-ULK1/BMF signaling pathway not only inhibited the proliferation of lung cancer cells but also induced protective autophagy and apoptosis in these cells. The research further revealed that BMF played a critical role in modulating the interplay between autophagy and apoptosis. Qian Wei *et al.*[17] identified potential active compounds, including 2-methoxy-9, 10-dihydrophenanthrene-4, in CPPP through network pharmacology and molecular docking analysis, which exhibited significant regulatory functions. They also determined that multiple targets, such as CASP3 and JUN, may serve as key targets of CPPP in the treatment of lung cancer. These targets were predominantly enriched in pathways related to cancer and estrogen signaling. Guan Dingkun *et al.*[18] elucidated the mechanisms underlying the effects of CPPP and Spina Gleditsiae on lung cancer using network pharmacology. They identified two common active compounds, β-sitosterol and stigmasterol, from which 202 potential targets and 20 key gene targets associated with lung cancer were screened. These targets primarily functioned through the IL-17 signaling pathway, MAPK signaling pathway, and VEGF signaling pathway. The mechanism of action may include the inhibition of tumor cell proliferation and growth, suppression of angiogenesis in the tumor microenvironment, and regulation of tumor metastasis.

3.2 Anti-breast cancer Breast cancer, a malignant tumor, poses a significant threat to women's health worldwide. In TCM literature, it is commonly referred to as "mammary cancer"[19], with its earliest mention found in Ge Hong's *Emergency Prescriptions Kept in One's Sleeve* from the Eastern Jin Dynasty. According to TCM, the etiology is attributed to emotional and dietary imbalances, as well as impairment of the Chong and Ren meridians, resulting in qi stagnation, phlegm accumulation, and the concomitant entanglement of blood stasis and toxins[20]. Professor Lu Wenping posits that the treatment of triple-negative breast cancer (TNBC) should primarily target the liver, spleen, and kidney, in addition to considering the patient's overall constitution. The therapeutic approach involves dispersing nodules and detoxification to address symptoms, while predominantly employing sweet and warm tonics to replenish deficiencies and treat the underlying causes. Following a screening process, it was observed that CPPP was utilized 88 times, representing 81.48% of the total usage. Subsequent drug association analysis identified a core prescription for TNBC[21], in which CPPP was included as one of the 13 essential TCMs. Liu Jiaxiang, a distinguished master of TCM, pioneered the theoretical system of "strengthening the body's resistance to treat cancer" after breast cancer surgery. In the early stages of mammary cancer, when the body's vital energy remains sufficient to resist pathological attacks[22], she emphasized strengthening this vital energy and frequently selected CPPP as a primary agent to eliminate pathogenic factors. Professor Li Xiurong identified two principal pathogenic mechanisms underlying breast cancer: a "deficiency syndrome" characterized by liver depression and spleen weakness, accompanied by disharmony between the Chong and Ren meridians; and an "excess syndrome" marked by phlegm turbidity, blood stasis, and toxic heat accumulation, which obstruct the circulation of qi and blood, thereby promoting nodule formation and the generation of cancer toxins. Clinical treatment consistently adheres to the principle of "unblocking the meridians"[23]. CPPP and Rhapontici Radix are representative herbal pairs employed to clear heat, detoxify, and resolve nodules. Ren[24] summarized the mechanism of action of CPPP on breast diseases and proposed a hypothesis involving a three-tiered combined prevention and treatment system of "inflammation, hyperplasia, and carcinogenesis". This hypothesis offers innovative perspectives for the research method and theoretical framework of CPPP and significantly enhances the concept to the "prevention and treatment" of breast diseases.

Zhang Ziqi *et al.*[25] showed that selenium nanoparticles of glucomannan extracted from CPPP significantly inhibited the proliferation of 4T1 breast cancer cells in *in vitro* cytotoxicity assays. In terms of anti-tumor activity in mice, these nanoparticles exhibited greater stability compared to the glucomannan solution ob-

tained from CPPP. Chen Si *et al.*[26] reported that drug serum containing compounds from CPPP inhibited the activity of SK-BR-3 breast tumor cells, thereby suppressing cell proliferation, inducing apoptosis, and delaying cell migration. Yang Xuewei *et al.*[27] reported that CPPP inhibited tumor cell proliferation in breast cancer rats. The underlying mechanism may involve the suppression of vascular endothelial growth factor (VEGF) and matrix metalloproteinase-9 (MMP-9) expression in tumor tissues. Liang Cong *et al.*[28] demonstrated that alcohol extracts of CPPP and *Typhonium giganteum* inhibited the proliferation of human TNBC cells *in vitro* in a concentration- and time-dependent manner. These extracts also promoted tumor cell apoptosis and concurrently downregulated Bcl-2 expression while upregulating the protein levels of Bax and Caspase-3, thereby further elucidating the drug's mechanism of action in TNBC treatment. Song Yinhui *et al.*[29] showed that the extract of CPPP mitigated the inflammatory response and decreased angiogenesis in rats in a dose-dependent manner, thereby inhibiting tumor progression. The underlying mechanism may involve activation of the JNK1/AP-1 signaling pathway, which enhances the expression of Bcl-2-related proteins Bax, P53, and TNF, ultimately promoting apoptosis of tumor cells. Yang Dongdong *et al.*[30] employed network pharmacology and molecular docking to predict the molecular mechanisms by which CPPP exerts resistance against TNBC. Their findings suggested that the extract regulated cancer-related biological processes, including cell proliferation and protein phosphorylation. Key targets such as MAPK1 and JUN were identified as critical in combating TNBC, with these targets predominantly enriched in the PI3K-AKT signaling pathway. Downregulation of phosphorylated PI3K (p-PI3K) and AKT (p-AKT) protein expression was shown to inhibit the proliferation of breast cancer cells.

3.3 Anti-liver cancer In ancient China, the term "liver cancer" did not exist. Traditional Chinese medical texts described conditions such as "fatty qi" and "liver accumulation", highlighting the pathological features of qi and blood stasis, as well as the interaction between toxins and heat. The therapeutic approach emphasized both enhancing the body's resistance and eliminating pathogenic factors[31]. Professor Yin Changjian assumes that liver cancer frequently arises from a deficiency in the body's vital energy, which permits the invasion of both external and internal pathogenic toxins, as well as physical exhaustion and other pathological factors. This process results in the formation of pathological conditions such as liver qi stagnation and blood stasis, leading to the accumulation of turbidity and the generation of toxins that ultimately develop into cancerous toxins. The treatment approach for liver cancer integrates both macroscopic diagnosis and therapy with microscopic medication. Specifically, guided by the principles of TCM syndrome differentiation and supplemented by contemporary biomedical research in fields such as virology, immunology, and molecular biology, treatment targets the disease while appropriately incorporating insights from modern pharmacology to enhance drug precision[32]. In clinical practices, commonly used agents such as CPPP and Arisaema Cum Bile have been shown to significantly improve therapeutic effects. Through an analysis of 492 clinical prescriptions by Professor Lin Lizhu for the treatment of liver cancer, Han Haicheng[33] identified CPPP as the primary drug utilized, appearing 350 times, thereby reflecting the significant clinical efficacy of this medicine. Zhang Qi *et al.*[34] studied the anti-cancer empirical formula proposed by Professor Zhou Zhongying, a master of TCM, and found that the combination of the anti-cancer detoxification formula and cisplatin significantly inhibited tumor growth in H22 liver cancer mice. *In vitro* experiments showed that this combination markedly suppressed the proliferation and migration of HepG2 liver cancer cells and induced their apoptosis. The mechanism of action may involve down-regulating lncRNA Srrd and inhibiting the expression of the JAK/STAT/PI3K signaling pathway, thereby affecting the proliferation, migration, and apoptosis of liver cancer cells. CPPP and Pseudostellariae Radix displayed notable anti-cancer efficacy as ministerial drugs. The research methods, which included both animal and *in vitro* experiments, verified the mechanism of action, confirming the rigor and reliability of the findings.

3.4 Anti-thyroid cancer In traditional Chinese medical texts, thyroid cancer is categorized under "fleshy goiter", "goiter tumor", and "stony goiter". The *Yifang Jiyi* (*Medical Prescription Collection · Methods for Treating Goiters and Tumors*) advises that for all goiter symptoms, it is essential to first eliminate thick and rich flavors from the diet, avoid anger and irritability, and use medications that promote qi circulation and soften hardness[35]. This suggests that treatment should combine drugs that regulate qi and disperse nodules, alongside adjustments in diet and emotional well-being[36]. Professor Yin Cuimei suggests that the development of goiter tumors is primarily due to abnormal transformation and transport functions caused by spleen deficiency. This condition subsequently affects the other four internal organs, leading to the formation of pathological products such as "phlegm turbidity and blood stasis". Therefore, regulating the spleen and stomach is essential for effective treatment[37]. In clinical practice, medications like CPPP, Sargassum, and Laminariae Thallus are commonly used to address both symptoms and underlying causes. Among the 200 prescriptions prescribed by Professor Yin Cuimei, CPPP was used 59 times, ranking tenth in frequency. Further analysis of high-frequency drug combinations revealed that the pairing of CPPP with Radix Ranunculi Ternati was the most common[38].

Wu Xifang[39] treated 62 patients with thyroid nodules using a self-formulated remedy called Zishen Xiaoying Huayu Decoction. The study revealed significant improvements in the size of thyroid nodules as well as in the patients' TSH and FT4 levels compared to their initial conditions, achieving an effective cure rate of 79.03%. CPPP, considered a ministerial drug, showed notable

therapeutic effects. Yu Zhifan *et al.*[40] discovered that a low-concentration of CPPP extract inhibited the proliferation of thyroid cancer SW579 cells and induced apoptosis. The underlying mechanism is believed to involve the suppression of Bcl-protein expression.

4 Conclusions and prospects

Based on previous research into the combined use of CPPP and other TCMs[41], researchers further explore its mechanisms of action to broaden its therapeutic effects and applications. By reviewing a large number of literatures on CPPP, the article systematically demonstrates that this traditional Chinese medicinal material not only has a wide range of pharmacological effects and clinical value but also shows significant potential in anti-tumor therapy. Studies indicate that CPPP combats tumors through multiple mechanisms. Moreover, its extracts are primarily used in clinical settings to treat various cancers, including lung, breast, liver, and thyroid cancers.

At present, most experimental research on CPPP is limited to cellular and animal studies, while clinical research primarily focuses on analyzing medication patterns from renowned doctors and their prescriptions. A complete industrial chain from extracting active ingredients to developing new drugs and applying them in clinical settings has yet to be established. Therefore, future research should explore the molecular mechanisms of CPPP through more comprehensive and systematic studies. It should also promote a collaborative approach combining TCM and Western medicine for precise anti-tumor treatments, clarify the targets and proportions involved in synergistic effects, optimize strategies to reduce toxicity and enhance efficacy, and ensure safety for long-term clinical use. This article aims to address the existing research gap by providing a systematic summary and constructing a logical framework of "basic experimental research + efficient clinical transformation". It seeks to offer a safe, scientific, and effective theoretical foundation for clinical applications. Additionally, theoretical innovations can generate new research ideas and plans through clinical transformation.

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