Review

Research Progress on Chemical Constituents and Pharmacological Activity of Pleione

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Review

Research Progress on Chemical Constituents and Pharmacological Activity of *Pleione*

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Abstract: *Pleione* is a genus of Orchidaceae and is one of the major sources of *Pseudobulbus Cremastrae seu Pleiones* (PCsP). It contains many constituents, such as phenanthrene, bibenzyl, glycoside, flavonoid and so on, which have plenty of bioactivities, including anti-tumor, anti-oxidation, anti-inflammatory, lowering glycemic levels and other pharma cological activities. In order to further utilize the edible and medicinal functions of *Pleione*, and clarify its medicinal active ingredients, this review systematically summarizes the constituents and pharmacological effects of *Pleione*, which will provide a theoretical foundation for the clinical application and new drug development.

Keywords: *Pleione*; chemical constituents; pharmacological activity

1. Introduction

Pleione genus, belonging to Orchidaceae, is an internationally renowned and ornamental plant [1]. The dried pseudobulb of the plant is one of the sources of the traditional Chinese medicine *Pseudobulbus Cremastrae seu Pleiones* (PCsP) [2]. According to the 2020 edition of the "Pharmacopoeia of the People's Republic of China", PCsP has the effect of relieving asthma, cough, inflammation, pain, and hemostasis [3]. Modern studies have shown that *Pleione* is rich in many active ingredients and has pharmacological effects such as anti-tumor, anti-oxidation, anti-inflammatory, and lowering glycemic levels [4]. In this paper, we summarized the chemical composition and pharmacological action of *Pleione*, in order to provide theoretical basis for further development and research of this plant.

2. Study on the chemical constituents of *Pleione*

In recent years, with the increasing application of *Pleione*, the chemical constituents of this plant have been studied deeply by pharmacologist. So far, researchers have isolated several types of chemical components from *Pleione*, including phenanthrene, bibenzyl, glycosides, lignans,

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anthraquinones, flavonoids, steroids [5]. These studies provide a reference for the basic research of *Pleione*, and also provide a basis for its quality control.

2.1. Phenanthrene compounds

Wang et al. (2013) made a systematic study on the chemical constituents from the bulbs of *Pleione bulbocodioides* (Franch.) Rolfe, and isolated the phenanthrene compounds, 2,7,2′ -trihydroxy-4,4,7′-trimethoxy-1,1′-dimeranthrene, etc [6] . They also purified 1-(4-Hydroxybenzyl) -2,7-dihydroxy-4-methoxy-9,10-dihydrophenanthrene,2,7,2′-trihydroxy-4,4′,7′-trimethoxy-1,1′-dimeranthrene, and 1-4-Hydroxybenzyl-2,7-dihydroxy-4-methoxy-phenanthrene from the extracts of PCsP. Li et al. (2023) isolated and identified four phenanthrene compounds from *Pleione maculata* (Lindl.) Lindl., 1,7-dihydroxy-2,5-dimethoxyphenanthrene,2,7-dihydroxy-1,5-dimethoxyphenan- threne, confusarin, 4,7-dihydroxy-2-dimethoxy-9,10-dihydrophenanthrene [7]. Dong et al. (2011) isolated three new dihydrophenanthrofurans and two known dihydrophenanthrenes from the tubers of *P. yunnanensis* [8].

2.2. Bibenzyls

Wang et al. (2013) purified Batatasin III and Gigantol (Dendrophenol) from the extract of *P. bulbocodioides* [6]. Wang et al. (2014) isolated Batatasin III from *P. yunnanensis* [9]. Zhang et al. (2013) purified 2,5,2′,5-tetrahydroxy-3-methoxy-bibenzyl, Batatasin from *P. bulbocodioides* [10]. Liu et al. (2011) isolated 3,5-dimethoxy-3-Hydroxybenzyl from *P. bulbocodioides* [11]. Wang et al. (2022) isolated shancigusin H, shancigusin H isomer, Batatasin III from *P. yunnanensis* [12].

2.3. Steroids

Few studies have been done on steroids in *P. bulbocodioides*. In the early days, steroid compounds, such as ergostere-4,6,8,22-tetraene-3-ketone and *β*-sitosterol, were isolated from the ethyl acetate fraction of *P. bulbocodioides* [6, 10].

2.4. Glycosides

Yuan et al. (2012) isolated gastrodin from *P. bulbocodioides*[13]. Wang et al. (2014) and Liu et al. (2011) purified daucosterol and *β*-daucosterol from the extract of *P. bulbocodioides* respectively[9, 11]. Han et al. (2015) isolated 10 glucosyloxybenzyl2-isobutylmalates and 1 benzyl alcohol glycoside from the dried pseudobulbs of *Pleione bulbocodioides* using macroporous adsorbent resin and HPLC techniques [14].

2.5. Flavonoids

Yuan et al. (2012) isolated a biflavone from *P. bulbocodioides* [13]. Liu et al. (2011) isolated methyl 3-(4-hydroxyphenyl) propionate and cinnamic acid [11]. Li et al. (2017) found a new chemical substance, butenyl flavone, from *P. yunnanensis* and Wang et al. (2022) used ultra-performance liquid chromatography-mass spectrometry (UHPLC-MS) to identify nobiletin [12, 15].

2.6. Other compounds

Wang et al. (2013) isolated syringaresinol from *P. bulbocodioides* [6]. Wang et al. (2014) isolated (2E)-3-(4-Hydroxy-3,5-dimethoxyphenyl)-2-propenoicAcid,(E)-Ferulic acid, triterpenoids and phenolic acids from *P. yunnanensis* [9], and Wang et al. (2022) isolated methoxybenzoic acid, dodecanedioicacid, 1-methylester, and diphenylamine from this plant [12].

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3. Pharmacological effects of *Pleione*

3.1. Antitumor effect

Pleione and its dried pseudobulb has inhibitory effect on many kinds of tumor such as colorectal cancer, breast cancer, liver cancer, thyroid cancer, gastric cancer and so on. Wang et al. (2021) observed the effects of PCsP extract on the proliferation and apoptosis of colorecta cancer cell carcinoma SW480 cells, and explored its mechanism. The experimental results show that iphigenia indica extract canobviously inhibit the proliferation and induce apoptosis of SW480 cells, its mechanism may be related to the inhibition of AEC-1 (Astrocyte elevated gene-1) protein expression, then down-regulation of Bcl-2 (B-cell lymphoma 2) protein expression and up-regulation of Bax protein expression [16]. Cheng et al. (2021) studied the effect of PCsP pharmaceutic serum on apoptosis and epithelial-mesenchymal transition of Hep G2 cells [17]. They found that PCsP could obviously inhibit the growth of Hep G2, induce apoptosis, and inhibit the epithelial-mesenchy-mal transition. To study the chemical constituents from the herbs of *P. bulbocodioides* and find theirs antitumor bioactive compounds, Zhou et al. (2023) obtained and identified twelve compouds from this plant and studied the antitumor activity of the constituents by MTT assay *in vitro* [18]. The results showed that (8R)-4,5′dihydroxy-8-hydroxymehtyl-3′ -methoxydeoxybenzoin expressed good inhibitory activity on SKOV-3 cell line. Liu et al. (2007) found that the compounds isolated from *P. bulbocodioides* have some activity to inhibit LA795 (Mouse lung adenocarcinoma cells) [19]. Shao et al. (2020) isolated eight new phenanthrenequinones, named bulbocodioidins A–D from the ethanolic extract of tubers of *P. bulbocodioides* [20]. The cytotoxic effects of the isolated phenanthrenequinones were evaluated in several human cancer cell lines, and compounds 1a and 4a exhibited marked cytotoxic activities. They also isolated two new phenanthrenequinones from the tubers of *P. bulbocodioides*, they exhibited cytotoxic activity against human breast cancer cell lines (MCF-7) with the IC_{50} value of 2.1 μM *in vitro*, so they thought that *P. bulbocodioides* has the anti-tumor property. Li et al. (2023) obtained and identified ten compounds from *P. maculata*, studied the antitumor activity of the compounds by MTT assay *in vitro*, the results showed that compound1,3′,5′,7-tetrahydroxy-4,7′ -dimethoxy-9,9′,10,10′tetrahydro-2,2′-biphenanthrene has good inhibitory activity against three tumor cell lines, A549, MCF-7/S, and SKOV-3 [7].

PCsP is rich in polysaccharides, which non-specifically inhibits the stimulation of reticulo endothelium system, improving the immune response ability of the host to the specific antigen of cancer cells to improve the immune capacity of the body and play the anticancer effect [21]. To study on the anti-tumor effect and mechanism of PCsP on mice with H22 hepatocellular carcinoma, Xu et al. (2015) established an ascitic type and solid tumor of H22. The result showed that PCsP on the life extension of H22 ascites type mice is 21.4% [22]. Ye et al. (2019) studied the inhibitory efficacy of water extract of PCsP on gastric cancer HGC-27 and its mechanism. The conclusion showed that the water extract of PCsP can inhibit the proliferation of gastric cancer HGC-27, and it has a certain dependence on drug concentration and administration time, which may be achieved by inhibiting Akt activity in PI3K/Akt pathway [23].

3.2. Anti-inflammatory effect

Wang et al. (2012) studied acute toxicity and anti-inflammatory, and antibechic test of *P. yunnanensis* [4]. Adopt maximal dosages of the suspension of *P. yunnanensis* extractum, it was more than 8.0 g/kg (equal to 14.16 g/kg of raw pharmacognosy and 106 times of people in common use). The result indicate that *P. yunnanensis* is no toxic effect. By experiment of anti-inflammatory, antibechic test, *P. yunnanensis* is proved that able to show out anti-inflammatory and antibechic effect under some fixed dosage. Hou et al. (2006) induced and sampled mouse peritoneal macrophages to determine the inhibitory rate of chemical components in *P. yunnanensis* on cell growth [24]. The results show that the compound Shanciol D has obvious anti-inflammatory effect at the concentration of 10^{-5} M.

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3.3. Anti-dementia effect

Han et al. (2014) proved that the extract benzyl bisaccharide glycosides, which isolated from *P. bulbocodioides*, have a significant improvement effect on the symptoms of learning and memory disorders induced by scopolamine in mice, so it is believed that *P. bulbocodioides* has certain anti-dementia effect [25].

3.4. Affecting hematopoietic function

With the development of industry, the discovery rate of secondary aplastic anemia caused by exposure to various chemicals, drugs or rays is increasing year by year. *P. bulbocodioides* can significantly reduce the toxicity of cyclophosphamide and toluene to bone marrow, and it can also stimulate bone marrow hematopoietic cells and make myeloid cell lines proliferate, which is conducive to the recovery of injured body functions. Hao et al. (2018) investigated the effects of ethyl acetate (EtOAc) extract of *P. bulbocodioides* on proliferation and apoptosis of human leukemia K562 and HL-60 cells and the possible apoptosis path way [26]. The result showed that EtOAc extract of *P. bulbocodioides* significantly inhibits cell proliferation and induces cell apoptosis in human leukemia cell lines HL-60 and K562 through intrinsic mitochondrial apoptosis pathway. Huang et al. (2002) observed the pharmacodynamic effects of PCsP compound on mice of aplastic anemia [27]. The result showed that PCsP compound group has obvious function of increasing periphery hematocytes and strengthening the function of hematopolesis of bone marrow. Yang et al. (2009) proved that Qingduyin, a compound Chinese medicine of PCsP, can reduce the number of leukemia cells in liver, spleen, bone marrow and peripheral blood of L7212 mice, prolong the survival period of the model mice, regulate immune function, and improve the activity of interleukin 2, interleukin 6 and tumor necrosis factor A and their mRNA expression [28]. Li et al. (2000) observed interleukin-2(-2) activity and lL-2 RNA expression in L7212 leukemia mice and the influence of the recipe of Qingduyin on them, and they confirmed that the recipe of Qingduyin can treat leukemia in clinic as biological response modulatlor [29].

3.5. Antioxygenation

Cremastra appendiculata polysaccharide (CAP) is the active ingredient of PCsP. Meng et al. (2015) studied on antioxygenation of CAP. The results showed that compared with the blank control group, CAP in each dose group can significantly increased in serum, liver and kidney of GSH-Px, SOD, CAT activity ($p < 0.01$) and T-AOC, decreased significantly in serum, liver and kidney MDA levels ($p < 0.01$) [30]. Han et al. (2019) found that four compounds which isolated from *P. bulbocodioides*, exhibited moderate antioxidant activity with increasing viability at 10 μM of 36.1%, 45.0%, 25.5% and 20.7% [31]. Fang et al. (2017) found that CAP could have antioxidative effects by scavenging superoxide anion radicals, DPPH free radicals and hydroxyl free radicals [32]. These results showed that, *P. bulbocodioides* has a significant antioxidant effect.

3.6. Hypolipidemic effect

Zhang et al. (2007) found that the extract of PCsP has a good inhibitory effect on α-glucosidase, and inhibiting α-glucosidase can reduce the postprandial blood sugar peak, adjust blood sugar level and improve insulin sensitivity [33]. These studies indicated that PCsP play an important role in the improvement of diabetes and lipid reduction. Meng et al. (2015) studied on hypolipidemic effects of CAP [30]. The result showed that compared with the model group, mountain arrowhead polysaccharide with different dose group can significantly reduce the serum TG, TC and LDL-C levels ($p < 0.01$), significantly increased the content of HDL-C ($p < 0.01$), so they think that *P. bulbocodioides* has significant lipid-lowering effect.

3. Prospects

Rich in chemical components is an important pharmacological basis for clinical application of *Pleione* [3]. With the development of science and technology, people have taken a deep dive into the

pharmacological effects of *Pleione* in many aspects, and found that this plant has the functions of anti-tumor , anti-oxidation, anti-inflammatory , regulating blood sugar, reducing blood lipid, and stimulating the activity of tyrosinase.

As a small genus with only about 30 species, the genus *Pleione* has great ornamental and medicinal market demands , and has great potential for development [34]. However, the following problems still exist in the development and application of *Pleione*.

3.1. Wild resources are seriously damaged and need to be sustainably preserved

The *Pleione* genus is extremely popular among gardeners due to its beautiful flowers. The demand for wild resources by breeders and hobbyists is increasing every year, and a large number of wild resources are being mined for private sale every year. At the same time, according to incomplete statistics, about 15×10^3 kg of *Pleione* species balls are dug up and used in medicine, resulting in the reduction of wild resources year by year, and its sustainable living condition is worrying. Wild resources are important resources for breeding and industrialized development and application, so there is an urgent need to carry out technical research on key conservation and sustainable development and utilization of *Pleione*. Moreover, people are also lack of in-depth exploration of the current situation of the resources of *Pleione*. Therefore, it is necessary to collect and protect germplasm resources of *Pleione*.

3.2. Urgent need for the establishment of efficient asexual propagation technology and cultivation technology system.

The tiny seeds of the *Pleione* plant make it difficult to germinate seedlings independently in the natural state, so it is necessary to establish a rapid and modern technique of propagation of *Pleione*. At present, there are few studies on the rapid propagation technology of *Pleione*, and the researchers mostly use the traditional split method to cultivate *Pleione*, which has the risk of variety degradation due to the accumulation of viruses. Therefore, although the basic cultivation technology of *Pleione* has been mastered, there is an urgent need to establish an artificial pollution-free and large-scale cultivation technology system, so as to meet the demand of the pharmaceutical market and realize the increase of added value.

3.3. Discovery of more active compounds and study on their pharmacological activities.

Phenanthrene and bibenzyl compounds are the main components of *Pleione*, further detailed and in-depth researches on its chemical constituent and pharmacological activity are expected to find more active compounds, which will provide scientific basis for its clinical rational use and lay a material foundation for the medicinal use of *Pleione* as a traditional Chinese medicine with anticancer activity.

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