Review Article

Paris Polyphylla Sm.: Phytochemistry, Pharmacological Activities, Molecular Mechanisms, Traditional Uses And Emerging Therapeutic Applications—A Comprehensive Review

Nazli Shahin[1]*, Swamita Arora[2], Robin Singh[2], Sanjar Alam[2]

[1]Pharmacy Consultant, Dubai
[2]R.V. Northland Institute, G.B. Nagar, Dadri, Greater Noida. U.P, India
Corresponding Author: Nazli Shahin nazli5leo@gmail.com

Abstract

Background: Paris polyphylla Smith.(chonglou) is an important traditional Chinese medicinal herb which has been used widely in the treatment of infectious and inflammatory diseases and cancer in China for thousands of years. The IUCN red list has designated it as "vulnerable" due to depletion of wild population by deforestation, habitat degradation and uncontrolled harvesting for local medicine. The rhizome of Paris polyphylla has historically been used to treat various diseases. including skin allergies, tumors, pain, fungal illnesses, bleeding, and snake bites. Paris saponins or steroidal saponins are the main bioactive chemical constituents from this plant which have demonstrated significant pharmacological effects in various diseases.

Objective: The current review investigates how P. polyphylla functions to treat various disease conditions, while current scientific studies continue to expand its medicinal applications. The review further explores recent research findings in the medicinal properties of P. polyphylla and its integration into present healthcare systems.

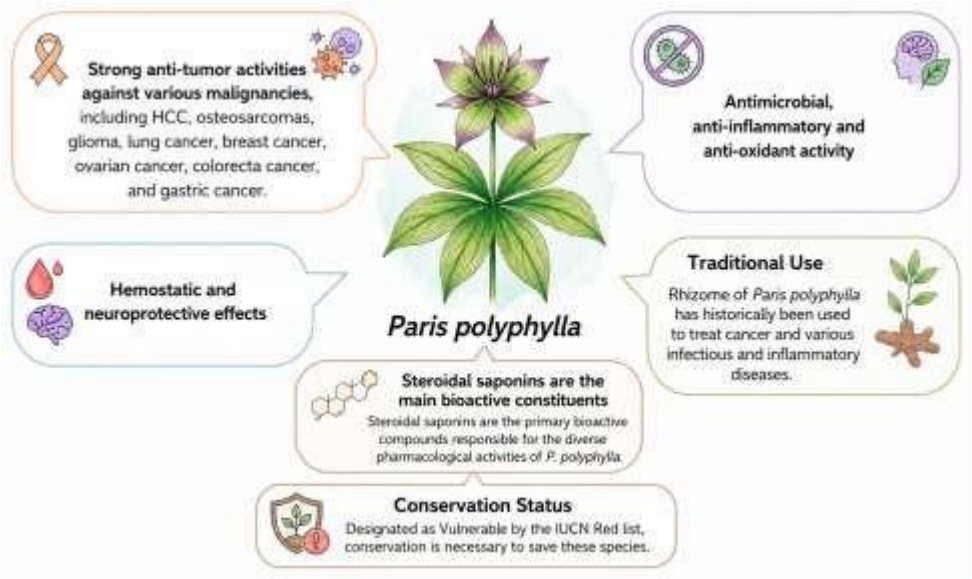
Method: This detailed review presents recent findings on P. polyphylla and explains how its numerous health benefits operate through various biological pathways. The study presents both traditional uses and current scientific research on its pharmacological properties. It also examines both the challenges and opportunities in P. polyphylla research, aiming to bridge traditional knowledge with modern scientific approaches in integrated medicine.

Results: Polyphyllins I, II, VI, VII, and Polyphyllin H have demonstrated strong anti-tumor activities against various malignancies, including hepatocellular carcinoma, osteosarcomas, glioma**,** lung cancer**,** breast cancer**,** Chronic myelogenous leukaemia **,** ovarian cancer, colorecta cancer, and gastric cancer. Anti-inflammatory, antioxidant, antimicrobial, anti-gynecological disease, hemostatic, and neuroprotective effects have also been exhibited by the medicinal plant.

Conclusion: This review summarizes the bioactive compounds from the P. polyphylla which will be of great value in the development of Polyphyllin products.

Keywords: Paris polyphylla**,** chonglou, traditional chinese medicine, anticancer, bioactive compounds, rhizoma paridis, paris saponins, pharmacological properties, integrative medicine.

Figure 1: Graphical abstract



1. Introduction

Natural products derived from plants have been used as traditional medicines to treat various pathological conditions since ancient times. These herbal medicines were given initially in the form of infusions, pastes, powders, tinctures, teas, and other herbal formulations. Drug discovery from medicinal plants led to the isolation of drugs such as morphine, codeine, digitoxin, and quinine. Use of drugs from natural sources has evolved from the formulation of crude drugs to the isolation of active constituents in the field of drug discovery.

The global utilization of herbal medicine is increasing in modern societies due to rising health consciousness and increasing preference for plant-based remedies. According to the WHO Global Report on Traditional and Complementary Medicine, traditional medicine functions as the primary mode of healthcare, especially in the management of chronic diseases. In addition, around 40% of modern pharmaceutical products are derived from natural sources and traditional knowledge. [1] In developed countries, approximately 10–50% of individuals regularly use herbal medicines, mainly due to their believed immune-boosting benefits. In contrast, in regions such as China, India, Vietnam, and South Africa, herbal medicines serve as the most affordable and accessible options for treating common conditions such as cold and joint pain. [2]

One notable example of herbal medicine is Paris polyphylla Smith, a perennial herb that exemplifies the rich traditional knowledge and cultural significance associated with medicinal herbs around the globe. Paris polyphylla Smith belongs to the family Melanthiaceae, which was previously classified under Liliaceae or Trilliaceae. It is known as 'Chonglou' in Chinese and 'Satuwa' in the Himalayas. This has been used as an important natural medicinal plant to treat infection, inflammation, and cancer for over 2000 years. The IUCN red list of threatened species 2020 has designated it as a "vulnerable" species due to a decline in wild population by habitat destruction, overexploitation and illegal collection for trade and traditional use.[3] Conservation of this plant is highly important as it is on the verge of extinction.

The Plants of the World Online (POWO) listed 29 Paris species. [4] The World Flora Online (WFO) included 27 species of Paris and one variety of Paris polyphylla Smith., namely Paris polyphylla var. polyphylla. [5]

The plants of genus Paris, containing about 33 species and 15 varieties, are mainly distributed in Southwest China. Paris polyphylla var. chinensis (Franch.) Hara, and P. polyphylla Smith. Var. yunnanensis (Franch.) were traditionally used to treat trauma.[6]

This herb has been widely found in Asia temperate regions such as China (China North-Central, China South-Central, Qinghai, Tibet) and Asia-tropical Indian subcontinent (Assam, Bangladesh, East Himalaya, West Himalaya. Nepal, Indo-China Myanmar).[4] In Indian Himalayan region, the Paris polyphylla is found distributed in Arunachal Pradesh, Assam, Jammu and Kashmir, Himachal Pradesh, Uttarakhand, Manipur, Meghalaya, Mizoram, Nagaland and Sikkim. All species of Paris are native to Asian regions while P. quadrifolia L. is the only one that is native to Europe.

The rhizome is the economic part which is used for its various medicinal properties. Steroidal compounds are the main chemical constituents found in the plant. The rhizomes are used in traditional medicine known as 'Rhizoma Paridis' in Chinese Pharmacopoeia.[7]

The main raw material for 'Yunnan Baiyao' and 'Gong Xue Ning (GXN) capsule' is a rhizome of this plant. Back discomfort, bleeding, shattered bones, wound healing, pain, fungal illnesses, poisonous snakes or bugs bites, skin allergy, tumours, and a variety of disease conditions are treated with the 'Yunnan Baiyao'. It is also a source for "Jidesheng Sheyaopian" a Chinese patent medicine. [10,11]

The study of traditional medicine together with modern pharmacological research has focused on this plant because it contains multiple bioactive compounds including steroidal saponins, C-21 steroids, phytosterols, insect hormones, pentacyclic triterpenes, flavonoids, and other compounds. Polyphyllin D, diosgenin, paris saponins I, II, VI, VII, and H are steroidal saponins having anticancer activity. Additionally, the extracts and pure compounds from the plant have shown antioxidant, anti-leishmaniasis, antibacterial, antifungal, anthelmintic, antityrosinase and antiviral in vivo and in vitro experiments. [10]

In traditional medicine, the crude herb has been used to manage parotitis, mastitis, sore throat, snakebite, convulsion, fractures, abscess and various malignant tumors for thousands of years.[11]

Paris polyphylla has extensive applicational prospects and developmental potential as an adjuvant drug for the treatment of digestive tract cancers. [12]. Numerous studies have shown that Steroidal saponins extracted from Rhizoma Paridis have strong activity against hepatocellular carcinoma (HCC), lung cancer, colon cancer, and glioma. Rhizoma Paridis Saponins has been widely reported as a potential anticancer drug with the main mechanism of inhibiting cell proliferation, inducing apoptosis, autopha gy, and cell cycle arrest, as well as enhancing the sensitivity of chemotherapeutic drugs.[13]

Its diverse pharmacological activities, due to its various bioactive components, makes it valuable in both traditional and modern medicine. With further research, greater understanding of this herb and its role in integrated medicine will be achieved.

2. Botanical Description

2.1 Plant characteristics

P. polyphylla is a perennial, rhizomatous, herbaceous plant with green and unbranched aerial parts which grow upto 50–100 cm. The plants have horizontal and creeping rhizomes, 1-2 cm thick, with transverse rings/bud scale scars on it. The leaves are oblong to lanceolate in shape and have parallel reticulate venation. The flowers are borne above the leaves whorl and are yellow green in colour. The Inflorescence is solitary. They start blooming around March-April. The ovary is round with usually 5 stigmatic lobes that are wet in nature. The stigma turns deep purple when the flower is ready for pollination. The anthers are arranged in two whorls. The outer whorl has two more filaments than the inner whorl. The tepals may be 3, 4 or 5. It contains 6–11 Androceum and the stamens are free. [14,15]

Figure 2: **Botanical Illustration of Paris polyphylla**

Table 1. Morphological Identification of P. polyphylla Plant

Character	**Description**
Rhizome	1-2 cm thick, horizontal and creeping
Leaves	Oblong to lanceolate having parallel reticulate venation
Flower	Solitary and terminal, inner tepal yellowish green and filiform
Fruit	Globular capsule
Seeds	Reddish orange colour

2.2 Habitat and Distribution

Genus Paris, comprises of rhizomatous geophyte that grows primarily in the temperate biome. Paris plants typically grow deep inside forests where they receive lots of shade. They prefer shaded areas with more than 80% canopy cover. They are found at altitudes of 1300 and 2500 meters above sea level in subtropical and temperate regions. These plants love moist, well-drained humus soil and usually grow on north-facing slopes with soil covered in dry, decayed organic material. Paris herbs are erect herbs and can reach up to a meter in height. Excess water or waterlogging can be deadly for them [15].

2.3. Taxonomical Classification

Table 2: Taxonomy

Kingdom	Plantae
Phylum	Streptophyta
Class	Equisetopsida
Sub Class	Magnoliidae

Order	Liliales
Family	Melanthiaceae
Genus	Paris
Species	polyphylla

3. Traditional Uses

3.1 Historical Background

Paris polyphylla Sm. is an important medicinal plant used to treat many diseases through traditional medicine systems such as Ayurveda, Tibetan traditional medicines and Chinese traditional medicines. In the "Chinensis Pharmacopoeia", it was listed for the first time in 1985. P.polyphylla saponins I, II, VI, and VII have been recognized as the quality standard components in the Chinensis Pharmacopoeia. It is used as a component of topical medicaments indicated for treatment of boils, carbuncles, sore throat, venomous snake bite, and traumatic pain according to Chinese Pharmacopoeia.[9]

3.2 Preparations

Paris polyphylla J.E. Smith is extensively used in traditional systems of Indian and Chinese medicines mainly for its anticancerous property.The rhizome and other parts of P. polyphylla in the form of infusions, juices, powders and pastes have been used in the traditional medicine to treat cuts, wounds, blisters, scabies, rashes or itching, burns, sprain, headache, fever, anthelmintic, vermifuge, expectorant, antispasmodic. digestive, gastritis, diarrhoea, dysentery, menstruation pain, tonic, antidote of poison (aconite poisoning), antidote of poisonous insects and snake, antiseptic.jaundice, vasoconstriction in the kidney, vasodilation in spleen and limbs.[10]

3.3 Traditional indications and treatments

With a history of thousands of years in clinical practice, Traditional Chinese Medicine (TCM) has demonstrated its rationale and efficacy in managing complex diseases. P. polyphylla is widely used in traditional Chinese medicine (TCM) for the treatment of boils, venomous snake bites, carbuncles, sore throat, and traumatic discomfort. [6] Diosgenin rich fresh extracts of Paris polyphylla rhizome from Indian Himalaya is traditionally used as wound healing, anti-bleeding, anti-inflammatory and anti-cancer agent by the folk healers. [16]

The dried rhizomes of P.polyphylla, P. polyphylla var. chinensis, and P. polyphylla var. yunnanensis were used to treat wound, bleeding, and stomachache, etc. in folk medicine. Rhizome Paridis, in traditional uses, is made into a decoction compatible with other herbs. Their formulations has been found in 79 Chinese patent medicines and this proves the outstanding efficacy of Rhizome Paridis. [6] According to TCM theory, 'blood stasis and stagnation' is the primary cause of adenomyosis and frequently contributes to menorrhagia and dysmenorrhea. As per Chinese Pharmacopoeia (Committee, 2020), Gong Xue Ning capsules consist of only Paris polyphylla ethanol extract (PPE) and can effectively cure a variety of gynecologic conditions, including Adenomyosis [17].

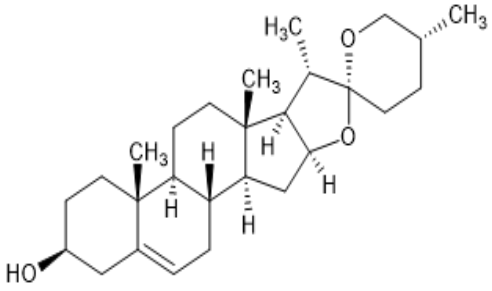
4. Phytochemistry

4.1 Key Bioactive Compounds

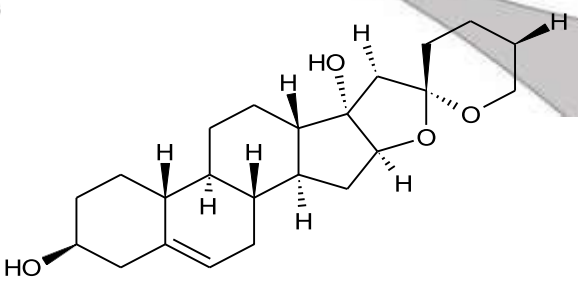
Paris polyphylla contains an abundance of secondary metabolites, which are responsible for its varied medicinal properties. The chemical components of P.Polyphylla include steroid saponins, C21 steroidal compounds, flavonoids, phytosterols, polysaccharides, phytoecdysones, alkaloids, terpenoids, phenolic acids, lipids and amino acids.The essential chemical components of the plant are steroidal compounds, known for their significant pharmacological activities. [18,19,20,21,22]

Structures of some of the main compounds are represented in Figure 3.

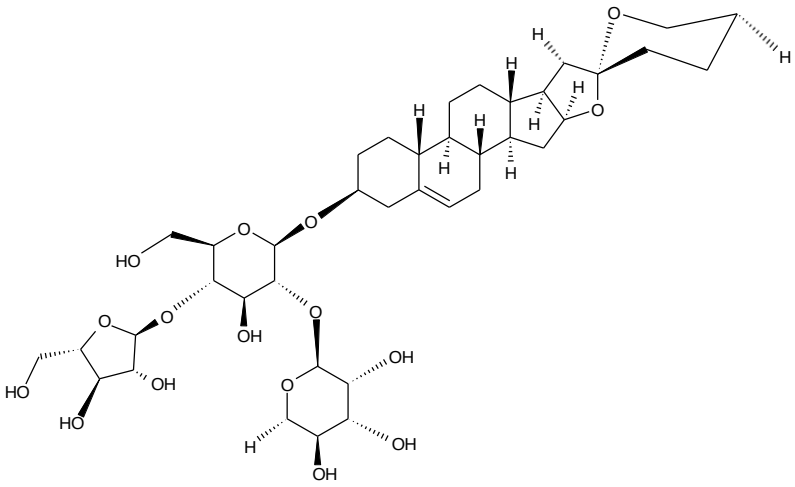
Figure 3: Structure of Steroidal saponins



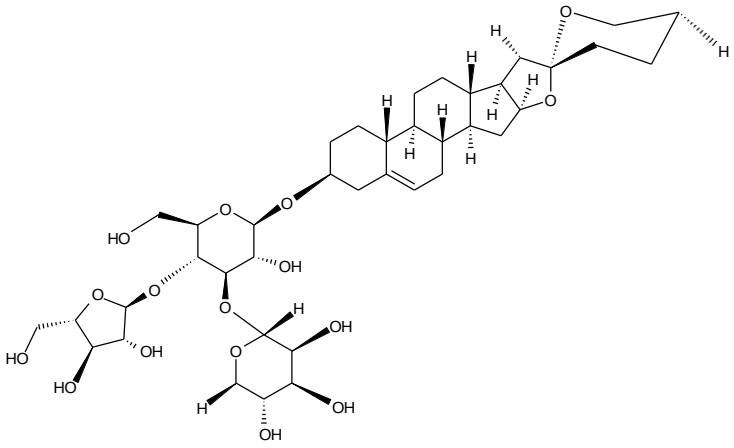
Diosgenin



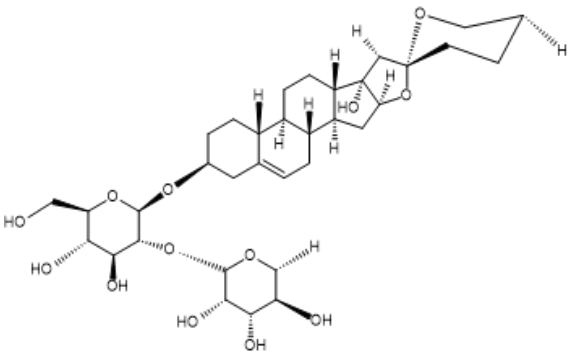
Pennogenin



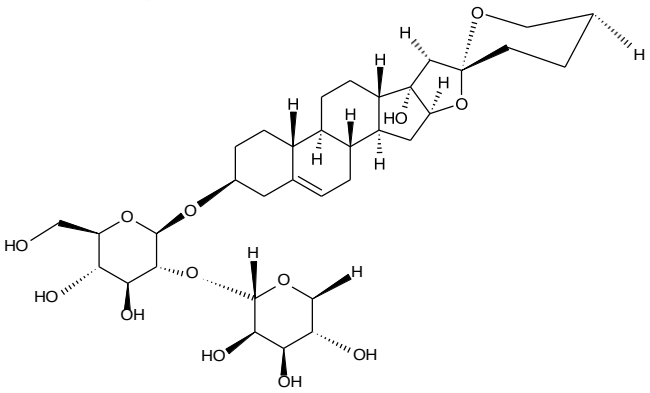
Polyphyllin I



Polyphyllin II



Polyphyllin VI



Polyphyllin VII

4.1.1 Steroids

Steroidal compounds represent the main active constituents of P. polyphylla, accounting for over 52% of the total secondary metabolites.[6]. Saponins are a type of glycoside consisting of aglycones (water-insoluble) such as steroids or triterpenoids attached via C-3, as well as one or more sugar chains (water-soluble) such as glucose, galactose, pentose, or methyl pentose. Based on aglycone molecular skeleton, they are classed as triterpenoid saponins or steroidal saponins. [21] [23]

4.1.2. Flavonoids

Flavonoids constitute 19.49% out of total metabolites present in Paris polyphylla sm. The diversity and abundance of flavonoids in leaves are the highest, followed by stems and roots. Leaves are the main site for the biosynthesis of flavonoids in Paris polyphylla Sm. Among them, kaempferol-3-O-glucoside, quercetin 3-β-D-glucoside, rutin, and other flavonoids are present in higher contents in leaves. [19, 24, 25] Rutin is one of the important flavonoids with rich pharmacological activity. Rutin reduces psoriasis inflammation by down-regulating the AGE-RAGE signaling pathway [26] and improves inflammatory pain by inhibiting mast cell P2 X 7 receptors [27].

4.1.3. Polysacharides

The polysaccharides were mainly composed of glucose, mannose, galactose, rhamnose, and arabinose, with glucose and mannose being the main components. The biological activities of P. polyphylla polysaccharides include immune regulation, reducing blood lipid, anti-oxidant and anti-aging, liver protection, enhanced learning and memory, regulating muscle movement, anti-fatigue, and plant growth regulation. [28]

Several studies have shown that the bioactive compounds obtained from P. polyphylla have a wide range of pharmacological activities. These diverse chemical compounds demonstrate its ability to function as an important medicinal herb for both traditional and modern medical practices. Ongoing studies will focus on analyzing these compounds in conjunction with traditional plant practices, helping to enhance their role in modern healthcare.

4.2. Types of Steroids

Steroid saponins are classified into the following four types according to the configuration of C-25 and the cyclized state of F ring in the spirostanane structure: isospirostanols, spirostanols, furostanols, and pseudo-spirostanols.

4.2.1. Isospirostanols

Most of the glycosides are derived from diosgenin and pennogenin, having a double bond at the 5(6) position and hydroxyl groups at the 3β, 7β, 23β, 24β, and 27β positions. The sugars are attached to these hydroxyl groups to form saponins. The sugar components primarily include D-glucose, L-rhamnose, and L-arabinose, D-xylose and L-fructose. The bioactive compounds belonging to the isospirostanol type include diosgenin, pennogenin, Polyphyllin I, Polyphyllin II, Polyphyllin III, Polyphyl lin V, Polyphyllin VII, and pariposides A-D.

4.2.2. Spirostanol Type

The spirostanol type is a class of steroidal saponins characterized by a C25 S-configuration. It is an epimer of the isospironstanol type. Spirostanols isolated and extracted from P. polyphylla, include dianchonglouoside A, dianchonglouoside B, disoseptemloside H, and parisverticoside A.

4..2.3 Furostanol Type

Furostanol-type steroid saponins are often considered precursors of the spirostanol-type steroidal saponins. The hydroxyl groups are located at the 3, 7, 17, and 26 positions, leading to the formation of steroidal saponins. In addition, some saponins are linked to sugar groups at the 3-OH position, with glucose attached at the 26-OH position, forming a double sugar chain. Saponins that belong to this type include polyphyllin G and polyphyllin H.

4. 2.4 Pseudospirostanol Type

The pseudospirostanol type contains a five-membered tetrahydrofuran ring. The bioactive compounds include chonglouside SL-9–chonglouside SL-15 and abutiloside L.

4.3. Biosynthesis of steroidal saponins

Steroidal saponins are biosynthesized through a sequence of steps on the squalene molecular backbone, involving oxidation, hydroxylation, and glycosylation.The biosynthesis of steroidal saponins can be categorized into three sequential stages: first, the formation of 2,3-oxidosqualene through the mevalonate (MVA) pathway and the 2-C-methyl-D-erythritol-4-phosphate (MEP) pathway; second, the conversion of 2,3-oxidosqualene into cholesterol or β-sitosterol via a series of catalytic reactions; and third, the formation of steroidal saponins through hydroxylation, oxidation, and glycosylation processes on cholesterol or β-sitosterol, at side chains such as the C-16, C-22, and C-26 positions.[29]

4.3.1 Biosynthesis of 2,3-Oxysqualene

Isopentenyl diphosphate (IPP), the precursor of 2,3-oxidosqualene, is synthesized via two pathways: mevalonate kinase (MVA) pathway, found in the cytoplasm and mitochondria, involving enzymes like acetyl Co-A acetyltransferase (ACAT), 3-hydroxy-3-methylglutarylCoA synthase (HMGS), mevalonate kinase (MVA), phosphomevalonate kinase (PMK), and mevalonate-5-diphosphate decarboxylase (MVD). The methylerythritol phosphate (MEP) pathway is found in plastids involving 1-deoxy-D-xylulose 5-phosphate synthase (DXS), 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DXR), 2-C-methyl-D-erythritol 4-phosphate cytidylyltransferase (MCT), 4-diphosphocytidyl2-C-methyl-D-erythritol kinase (CMK), 2-C-methyl-D-erythritol 2,4-cyclodiphosphate synthase (MDS), 4-hydroxy-3-methylbut-2-enyl pyrophosphate (HMBPP) synthase (HDS), and 4-hydroxy-3-methylbut-2-enyl pyrophosphate (HMBPP) reductase (HDR). These pathways produce IPP (isopentenyl -5-diphosphate), which is converted into farnesyl pyrophosphate (FPP) through the actions of isopentenyl diphosphate isomerase (IDI), geranyl pyrophosphate synthase (GPPS), and farnesyl pyrophosphate synthase FPPS; FPP is then converted by squalene synthase (SQS) into squalene, which is epoxidized by squalene epoxidase (SQE) into 2,3-oxidosqualene.[30]

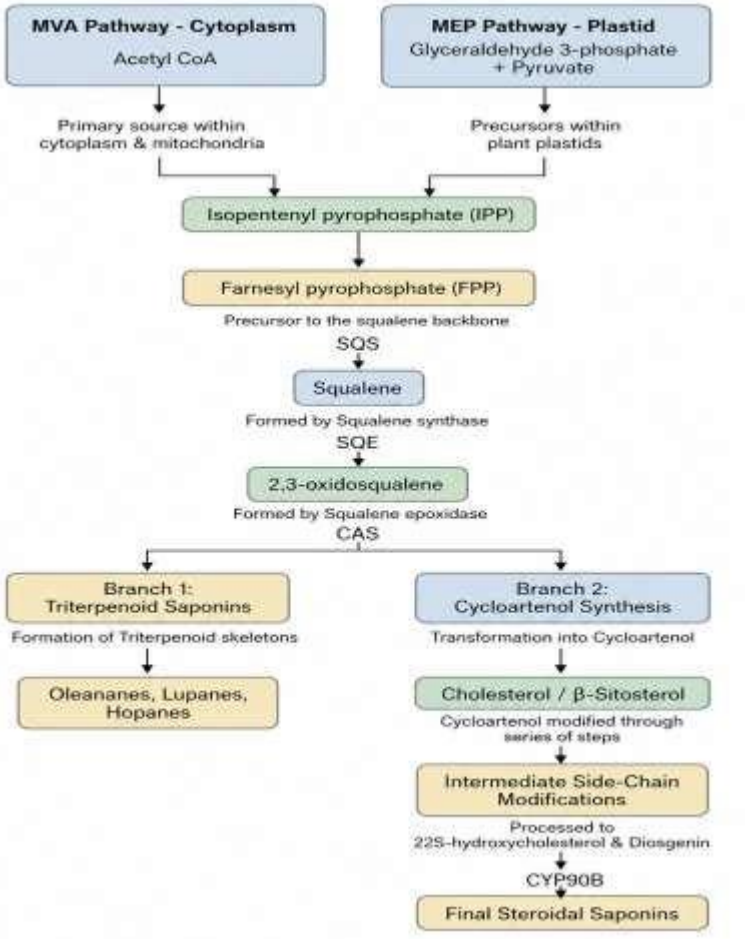
4.3.2 Biosynthesis of Cholesterol/β-Sitosterol

2,3-oxidosqualene is cyclized by oxidosqualene cyclases, primarily cycloartenol synthase (CAS), to produce cycloartenol, the plant sterol precursor. From cycloartenol, enzymes such as sterol side-chain reductase 1/2 (SSR1/2), sterol C-24 methyltransferase (SMT), C-4 sterol methyl oxidase (SMO), cyclopropylsterol isomerase (CPI), sterol C-14 demethylase (CYP51), sterol C-14 reductase (C14-R), sterol 8,7 isomerase (8,7 SI), sterol 5(6) desaturase (C5-SD), and 7-dehydrocholesterol reductase (7-DR) facilitate a series of modifications that lead to the synthesis of cholesterol/β-sitosterol.[31]

4.3.3. Modification of Cholesterol or Sitosterol Side Chain to Form Steroidal Saponins

Steroidal saponins are generated by a series of complex catalytic reactions, such as the oxidation, hydroxylation, and glycosylation of cholesterol or the β-sitosterol molecular skeleton. 22S-hydroxycholesterol was formed by catalytic side chains of cholesterol. The generated 22S-hydroxycholesterol was then catalyzed by CYPs and other enzymes to finally synthesize steroidal saponins.
Diosgenin is generated from cholesterol through the catalysis of cholesterol C16/C22-monohydroxylase (CYP90B/CYP94), cholesterol 26-hydroxylase (CYP72A), and other enzymes. The first step of the biosynthesis of steroidal saponins from diosgenin is the glycosylation of 3-O-sterol glycosyltransferase (S3GT belongs to the UGT80 family), which transfers the glycosyl group to the 3-OH site of the diosgenin.[31]

Figure 3. Biosynthesis Pathway of Steroidal Saponins



4.4 Extraction of Steroidal Saponins

The methods for extracting saponins have advanced from traditional methods like maceration and reflux extraction to innovative, more environmentally friendly techniques such as ultrasound-assisted extraction, microwave-assisted extraction, supercritical fluid extraction, and deep eutectic solvent extraction. Additionally, fermentation-based methods are increasingly being recognized as sustainable alternatives [32].
Maceration, Soxhlet extraction, and reflux extraction are conventional methods used to extract saponins. These techniques are generally simple to perform and do not require complex apparatus. Saponins can be extracted from plants using various solvents such as water, methanol, ethanol, acetone, ethyl acetate, n-butanol, dichloromethane, or their combinations. Among these, ethanol and n-butanol are the most used solvents. [33]
Traditional extraction methods are often time-consuming, solvent-intensive, and can cause degradation of heat-sensitive saponins. Innovative green extraction technologies have emerged as promising alternatives to address these issues. These new technologies seek to improve extraction efficiency, reduce environmental impact, and preserve the bioactivity of saponins. The techniques such as ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), supercritical fluid extraction (SFE), deep eutectic solvent extraction (DES), and fermentation increase yield as well as support environmental sustainability. [34]

5. Pharmacological Activities

Phytochemical components of P. polyphylla have anticancer, antioxidant, antibacterial, antifungal, anti-gynecological disease, and antiviral properties.

Table 3: Phytoconstituents and their Bioactivities

Compound name	Biological activity	Reference
Polyphyllin VI	**HCC**: In vitro: inhibits the proliferation, invasion, and metastasis of HCC cells by inducing ferroptosis. It inhibited the STAT3/GPX4 axis and triggered ferroptotic cell death. In vivo: polyphyllin VI suppressed the growth of subcutaneously transplanted tumors. **Prostate cancer with bone metastasis:** In vitro: PPVI suppressed osteoclast differentiation, inhibited tumor cell proliferation, migration, and invasion, and induced apoptosis and cell cycle arrest at G2/M phase. In vivo: inhibited the growth of metastatic tumors as well as mitigating the resulting bone destruction. **Breast cancer:** In vitro and in vivo: PP-VI at sub-cytotoxic doses suppressed the migration and invasion of mouse mammary carcinoma and human breast cancer cells. It reduced the metastatic potential by targeting a microRNA-mediated pathway. By suppressing miR-18a, PPVI increases the expression of its direct target, Rell2 (Receptor expressed in lymphoid tissue- RELT-like 2), which possesses anti-metastatic functions. **Osteosarcoma**: Polyphyllin VI promotes apoptosis and autophagy in human osteosarcoma cells by modulating ROS/JNK pathway activation. **Neuroprotective**: In vitro: PPVI enhanced cell viability and morphology in an in vitro Parkinson's disease PD model, reducing rotenone (ROT) induced oxidative stress and preserving mitochondrial function.	Huang et al. 2023 **[35]** Feng et al. 2025 **[36]** Wang et al. 2019 **[37]** Yuan et al 2019 **[38]** Li et al. 2024 [39**]**
Polyphyllin I	**Hepatocellular carcinoma**: In vitro: suppressed the proliferation, invasion, and metastasis of HCC cells by promoting mitochondrial disruption and inducing ferroptosis through the Nrf2/HO-1/GPX4 pathway. **Gastric cancer:** In vitro: PPI inhibits the growth of gastric cancer cells by inducing ferroptosis through NRF2/FTH1 pathway. **Colorectal cancer:** In vitro: inhibited CRC patient-derived organoids. PPI promoted cell apoptosis in CRC cells leading to cell cycle arrest at G2 phase by partially inhibiting the Notch signaling pathway in colorectal cancer. **Castration-resistant prostate cancer**: induced ferroptosis in CRPC cells via regulation of the ERK/DNMT1/ACSL4 axis. **Acute myeloid leukemia (AML)**: In vitro: showed cytotoxic effects on AML cells MOLM-13 with an IC50 value of 0.44 ± 0.09 μM. PPI-induced rapid ferroptosis is due to the simultaneous targeting PI3K/SREBP-1/SCD1 axis and triggering lipid peroxidation In vivo: PPI effectively inhibited tumor progression and extended survival in mice at a dose of 4 mg/kg,	Yang et al.2024 **[40]** Zheng et al. 2023 **[41]** Wang et al. 2024[**42]** Zou et al. 2023**[43]** Zhou et al. **[44]**

	Lung adenocarcinoma (LUAD): In vitro: suppressed cell survival, growth, and migration/invasion in gefitinib-resistant (PC9/GR) LUAD cells (IC_{50} at 2.0 μM) by modulating the VEGF/VEGFR2/p38 pathway. PPI serves as potential therapeutic agent in Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) resistance, in LUAD. In vivo: using cell-derived xenograft experiments have shown that combination of PPI and gefitinib overcame gefitinib resistance.	Zhang et al. 2024 **[45]**
	Temozolomide resistant glioma: suppressed temozolomide-resistant glioma tumor cells and induced reactive oxygen species (ROS)-dependent apoptosis and autophagy through the regulation of mitogen-activated protein kinase (MAPK)-signaling (p38-JNK) pathway.	
	Glioblastoma: In vitro: suppressed GBM growth and spread by promoting ferroptosis. PPI binds directly to SIRT1, decreasing its levels, and subsequently promoting oxidative cell death through the SIRT1/Nrf2/GPX4/HO-1 signaling pathway, thus inhibiting glioblastoma.	Feng et al. 2024 **[46]**
	In vivo, animal model experiment demonstrated PPI's ability to suppress tumor growth, by ferroptosis within GBM cells.	Fu et al. 2026 **[47]**
	Non-small-cell lung cancer (NSCLC) : In vitro: PPI enhanced autophagy and apoptosis in non-small-cell lung cancer (NSCLC) cells by activating AMP-activated protein kinase (AMPK) and subsequently inhibiting mTOR signaling in cultured human NSCLC cell lines. In vivo: inhibited the tumor growth and elevated the levels of LC3-II and phosphorylated AMPK in tumors derived from a mouse xenograft model of NSCLC.	Wu et al 2020 **[48]**
	NSCLC: In vitro: induced ferroptosis in NSCLC cells by promoting NCOA4-mediated autophagy, and degradation of ferritin protein, with reduction of EZH2. In vivo: enhanced antitumor immunity by promoting the infiltration of CD8+ T cells.	
	Cervical cancer metastasis: In vitro: showed marked inhibitory effect on the growth and metastasis of cervical cancer (CC) cells by modulating the Wnt/β-catenin signaling pathway, as well as promoting the β-catenin degradation via autophagy.In vivo: PPI effectively suppressed peritoneal metastasis in a luciferase-labeled HO-8910PM xenograft mouse model.	Xu et al. 2025 **[49]**
	Melanoma: In vitro: increased melanoma cell autophagy and apoptosis, as well as blocked melanoma cell cycle by suppressing PI3K/Akt/mTOR signal pathway. In vivo: suppressed xenograft tumor growth, enhanced apoptotic index, and reduced Ki67 level in tumor tissues in xenograft model.	[Chai et al.] 2025 **[50]**
	Ovarian cancer: In vitro: suppressed ovarian cancer cell growth by cell cycle arrest at G0/G1, and inhibited c-Myc protein levels and c-Myc signaling pathway.	
	Bladder cancer (BCa): In vitro: PPI promoted BCa cell apoptosis, cell cycle arrest, as well as suppress cell proliferation via the activation of FOXO3 signaling pathway. In vivo: suppressed the growth of BCa in the xenograft mice model.	Long J, Pi X., 2020 **[51]**

	Coronary artery disease (CAD): In vitro: PPI alleviated lipid metabolism disorder in Hypoxia/reoxygenation (H/R)-treated H9c2 cells model. In vivo: PI attenuated myocardial dysfunction in CAD rats by improving left ventricular systolic pressure, maximum rate of change of left ventricular pressure (±dp/dtmax), and arterial blood flow (CF). The effect of PPI on myocardial damage in CAD was mediated through the regulation of MEK/ERK pathway. **Adenomyosis:** Polyphyllin I (PPI) inhibited the epithelial–mesenchymal transition (EMT) progression through the TGFβ1/Smad2/3 pathway in adenomyosis-derived cells.	Tang et al.2025 **[52]** Li et al 2020 **[53]** Yang et al. 2022 **[54]** \ Shi et al. 2024 **[55]**
Polyphyllin II	**Mycobacterium tuberculosis induced bronchial infection**: In vitro: inhibited Mycobacterium tuberculosis (Mtb) infection in bronchial epithelial cells, by suppressing Mtb-induced inflammatory reactions and activation of NLPR3 inflammasome. **Colorectal cancer**: In vitro: promoted cytoprotective autophagy in CRC cells by the inhibition of PI3K/AKT/mTOR and STAT3 signaling. In vivo: suppressed cell proliferation and induced cell apoptosis in mouse model. **Non-small cell lung cancer (NSCLC)** PPII facilitated the autophagosome formation, elevated the expression of LC3-II/LC3-I ($p < 0.05$), while decreasing levels of p62 and p-mTOR ($p < 0.05$) **Breast cancer**: PPII stimulated apoptosis and suppressed invasion and migration. The findings demonstrated that PPII reduced aerobic glycolysis in breast cancer cells via the PI3K/Akt signaling pathway, leading to inhibition of breast cancer progression. **Ovarian cancer: polyphyllin** II inhibited ovarian cancer cell angiogenesis by modulating the NF-κB signaling pathway, thereby suppressing ovarian cancer cell growth.	Chen et al. 2024 **[56]** Li et al., 2022 **[57]** Jiao et al. 2022 [**58]** Miao et al. 2024 **[59]** Yang et al 2015 **[60]**
Polyphyllin H	**Hepatocellular carcinoma**: reduced cell viability, migration, and invasion, and promoted apoptosis in HCC cell lines by downregulating β-catenin and inhibiting Wnt/β-catenin signaling.	Chen et al. 2019 [61]
Polyphyllin VII	**Human ovarian cancer:** Polyphyllin VII affected cell viability, triggered apoptosis, and induced mitochondrial dysfunction by modulating the PP2A/AKT/DRP1 signaling axis. **Hepatoblastoma cancer:** triggered an autophagic cell death in HepG2 cells by inhibiting the PI3K/AKT/mTOR pathway, and activating JNK pathway. This promoted phosphorylation of Bcl-2 and dissociation of Beclin-1 from Beclin-1/Bcl-2 complex, leading to initiation of autophagy.	Zhao et al. 2020 **[62]** Zhang et al 2016 **[63]**

	Osteosarcoma : promoted apoptosis and suppressed cell proliferation by upregulating the expression of LC3II, Atg5, Atg7 and the Atg12-Atg5 complex. **Glioma**: Both apoptotic and autophagic processes were involved in the cytotoxic effect; PP7 activated the Bcl2/Bax pathway. **Lung cancer**: Polyphyllin VII was able to induce apoptotic cell death in A549 human lung cancer cells via inhibition of the PI3K/Akt and NF-κB pathways.	Li et al 2021 **[64]** Pang et al 2019 **[65]** He et al. 2020 **[66]**
Polysaccharides	**Anti-tumor:** Polysaccharides from Paris polyphylla (PPP). having molecular weight10 692 Da and consist of 10.29% mannose, 76.96% glucose, 7.26% galactose, and 5.49% arabinose, suppressed tumor growth in S180 tumor bearing mice by promoting a balanced Th1/Th2 immune response and remodeling the tumor immune microenvironment.	Song et al 2025 **[67]**
Pennogenin 3-O-beta chacotrioside and Polyphyllin VI	**Colorectal cancer:** suppressed the growth of CRC cell lines. Polyphyllin VI and pennogenin 3-O-beta-chacotrioside isolated from P. Polyphylla fruits, inhibited the growth of gut microbe Fusobacterium Nucleatum, which is strongly correlated with the development of CRC. Furthermore, these compounds reversed the mitochondrial fusion and cell migration in CRC cells triggered by F. Nucleatum-derived extracellular vesicles (EVs).	Lin et al. 2021 [68]
Pennogenin tetraglycoside)	**Abnormal Uterine bleeding**: Pennogenin tetraglycoside), extracted from the rhizome of Paris polyphylla Sm. var. Yunnanensis reduced abnormal uterine bleeding. Tg-induced rat myometrial contractions are mediated by activation of the phospholipase C (PLC)-inositol triphosphate (IP3) signaling pathway.[41]	Wang et al. 2012 [69]
Polyphyllin PPI, PPII and PPVII,	**Neurodegenerative Disease (NDs)**: PP-II interrupted with the KEAP1-NRF2 interaction, upregulated antioxidant gene expression. PP-I induced mitophagy by the PINK1-Parkin pathway, while PP-VII modulated neuroinflammation by activating the cGAS-STING axis. These actions collectively are responsible for the protection of neurons, preservation of mitochondrial function, and reducing pathological cascades that are linked with NDs.	Hussain et al. 2025 **[70]**

5.1 Anticancer activity

Cancer is a disease that results when there are an uncontrolled growth and division of cells in the body. Some types of cancer cause rapid cell growth, while others can grow and divide at a slower rate. The abnormal cells grow and form a mass that is called a tumor. Cancer remains the second leading cause of death globally, after cardiovascular disease with an estimated 20.6 million new cases and close to 10 million deaths annually. According to the latest global cancer data released by the World Health Organization and International Agency for Research on Cancer (IARC), without urgent action, annual cancer cases are projected to rise to nearly 35 million by 2050. [71]

Lung cancer remains the leading cause of cancer death globally. Lung, prostate and colorectal cancers are among the most common cancers in men, while breast, lung and colorectal cancers account for a substantial share of the burden among women. Surgery is the primary treatment for cancer, but the prognosis remains poor due to rapid disease progression and early metastasis at diagnosis. Although chemotherapy and radiotherapy serve as key complementary therapies for cancer treatment, resistance may result in treatment failure or even cancer recurrence. [72]

With advancements in antitumor research, numerous natural drugs have been increasingly incorporated into basic clinical studies due to their low toxicity, minimal adverse reactions, and their important synergistic role in multidisciplinary approaches to cancer treatment. Their mechanisms of action and therapeutic effects have gradually improved through a large number of basic experiments and clinical studies. They have become potential therapeutic options in the field of antitumor therapy because

natural drugs have multiple advantages as they are widely available, rich in natural resources, comparatively affordable, have good clinical effects, and have great potential for the development of more promising antitumor drugs. TCM, as natural substances, has long been considered to have the advantages of multi-pathway and multi-targets in tumor treatment and exerts multifaceted pharmacological active effects through comprehensive regulation, showing potential value in alleviating adverse effects, reversing drug resistance, inhibiting metastasis, regulating tumor immunity and improving therapeutic efficacy. [73], [74]
One of the most notable properties of Paris polyphylla is its antitumor effects largely due to the presence of steroidal saponins such as Polyphyllin I, Polyphyllin II, Polyphyllin VI, Polyphyllin VII. These active ingredients of Paris polyphylla have demonstrated strong anti tumor activities against various malignancies, including hepatocellular carcinoma.[75], osteosarcomas [38], glioma [76], lung cancer [77], breast cancer.[78], Chronic myelogenous leukaemia [79], ovarian cancer [80, 60], colorecta cancer [68], and gastric cancer [41].
Steroidal saponins have demonstrated anticancer effects across diverse cell lines by induction of apoptosis, autophagy, cell-cycle arrest, Iron-dependent cell death (ferroptosis), inhibition of cell migration and invasion as well as enhancing the sensitivity of chemotherapeutic drugs. [Fig: 5, 6, 7, 8]

Figure 5: Molecular mechanism of Polyphyllin I

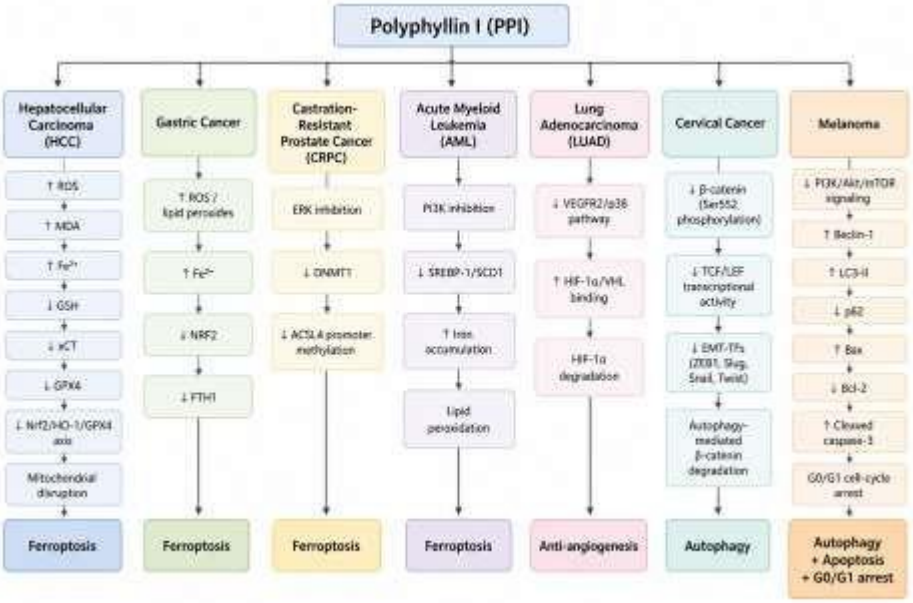


Figure 6: Molecular mechanism of Polyphyllin II

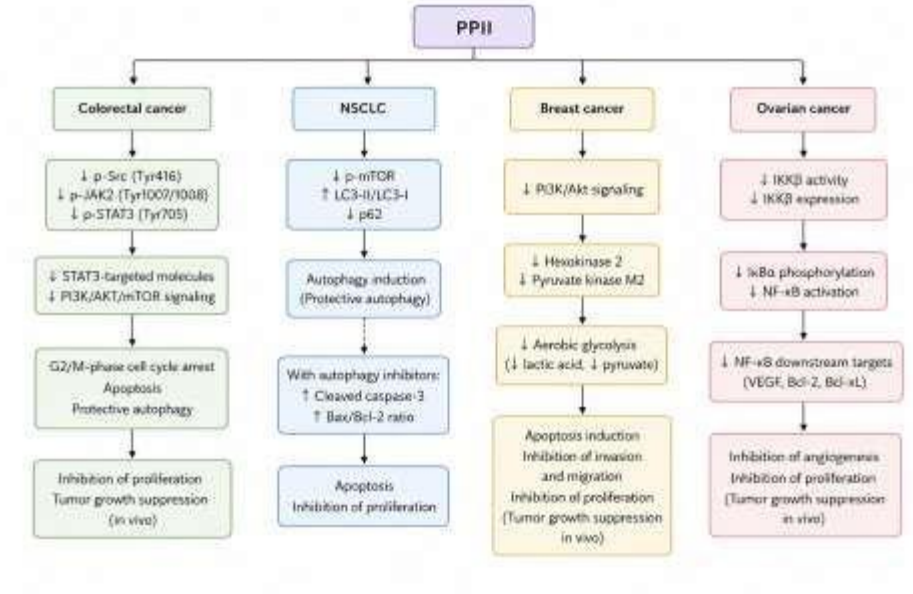


Figure 7: Molecular mechanism of Polyphyllin VI

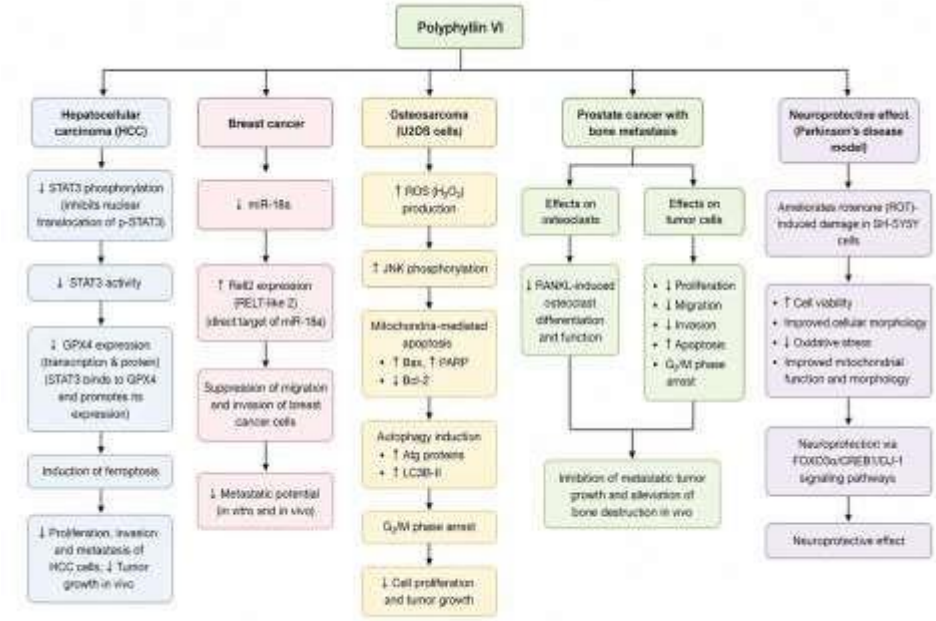
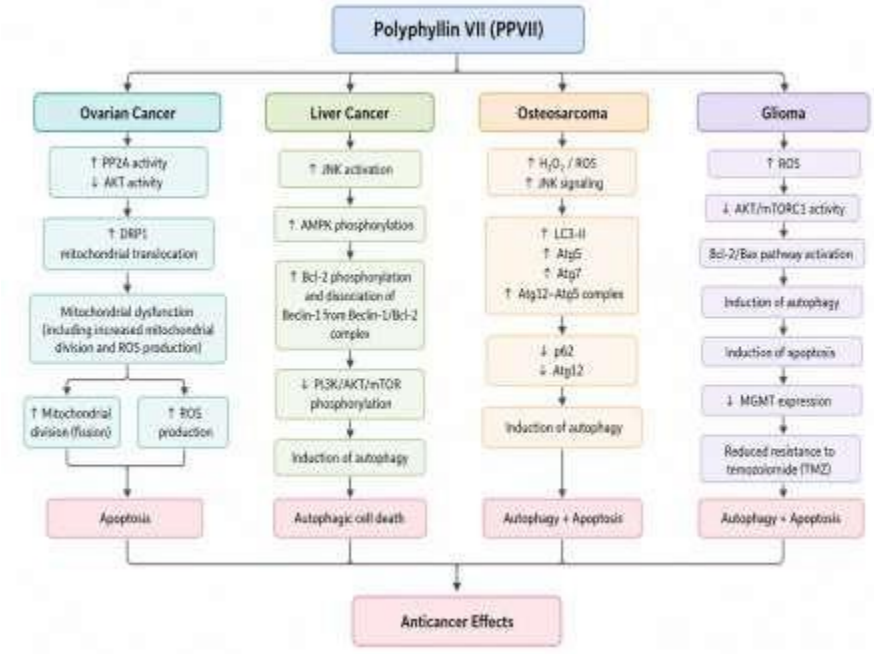


Figure 8: Molecular Mechanism of Polyphyllin VII



Polyphyllin I exerts anticancer effects including induction of apoptosis, autophagy, cycle arrest, Iron-dependent cell death (ferroptosis), and inhibition of cell migration and invasion. In recent studies, PPI's most prominent mechanism across multiple cancers such as liver, gastric, prostate, glioblastoma and lung cancers, is by induction of ferroptosis. PPI inhibited the proliferation, invasion, and metastasis of HCC cells by enhancing mitochondrial disruption and inducing ferroptosis via the Nrf2/HO-1/GPX4 axis [40]. PPI triggered an accumulation of iron (Fe2+) and reactive oxygen species (ROS) /lipid peroxides in gastric cancer cells. Induced cancer cell ferroptosis via regulating NRF2/FTH1 pathway[. [41]. In NSCLC, it induced ferroptos by enhancing NCOA4-mediated autophagy, and degradation of ferritin protein, with downregulation of EZH2 [49]. In addition, PPI suppressed growth and spread of glioblastoma cells by inducing ferroptosis. It targets SIRT1 protein, reducing its levels, and promotes oxidative cell death via the SIRT1/Nrf2/GPX4/HO-1 signaling pathway [47].

Polyphyllins inhibit cancer growth through targetting distinct pathways, including inhibiting the STAT3/GPX4 axis.[35], cell arrest at G2/M-phase [33] 36], suppress PI3K/AKT/mTOR pathway,[57] [59], [63], regulation of Receptor expressed in lymphoid tissue (RELT)-like 2 (Rell2) by microRNA, miR-18a [37], modulation of ROS/JNK pathway [38], Cell cycle arrest at G2 phase [42], modulating the VEGF/VEGFR2/p38 pathway [45], mitogen-activated protein kinase (MAPK)-signaling (p38-JNK) pathway [46], AMPK/mTOR signaling transduction pathway [48], modulation of the Wnt/β-catenin signaling pathway [50], [61], suppressing PI3K/Akt/mTOR signal pathway [51], Cell cycle arrest at G0/G1 phase [52], activating FOXO3 signaling pathway [53], increased the expression of LC3-II/LC3-I [58], suppress pathological angiogenesis [60], regulating the PP2A/AKT/DRP1 signaling axis [62], LC3II, Atg5, Atg7 and the Atg12-Atg5 complex [64], suppress nuclear factor-κB (NF-κB) pathway [66].

5.2 Anti-Inflammatory activity

Traditional Chinese Medicine has used Paris polyphylla since ancient times as potential anti-inflammatory agent while modern scientific studies confirm its ability to suppress the release of inflammatory cytokines. In one study. PPI significantly suppressed the tumor necrosis factor (TNF-α), interleukin (IL)-6, IL-8, and the expression of Toll-like receptor 2 (TLR2) [81]. PP VII, an isospirostanol saponin inhibited angiogenesis, lymph angiogenesis, adhesion, inflammation, and invasiveness. PP7 reduced the production of nitric oxide (NO) and prostaglandin E2 (PGE_2) and the protein and mRNA expressions of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) by suppressing the NF-κB and MAPKs pathways. [82, 83]

5.3 Gynaecological problems

Abnormal uterine bleeding (AUB) Abnormal uterine bleeding could be caused by structural issues, benign and malignant tumours as well as pregnancy-related diseases and endocrine disorders. Tg (pennogenin tetraglycoside), one of the active ingredients in total steroidal saponins (TSSPs) extracted from the rhizome of Paris polyphylla Sm. var. Yunnanensis reduced abnormal uterine bleeding in in-vitro experiment. Tg-induced rat myometrial contractions are mediated by activation of the phospholipase C (PLC)-inositol triphosphate (IP3) signaling pathway.[68]

Adenomyosis

Adenomyosis is a benign condition characterized by the presence of ectopic endometrial glands within the underlying myometrium. The most common signs and symptoms are abnormal uterine bleeding, chronic pelvic pain, and infertility. [84]
Recent research study has concluded that the P. polyphylla ethanol extract (PPE) and polyphyllin I (PPI) inhibited the epithelial–mesenchymal transition (EMT) progression through the TGFβ1/Smad2/3 pathway in adenomyosis-derived cells (AMDCs) isolated from human adenomyosis (AM) ectopic endometrial tissues. Additionally, this research has confirmed the safety of PPE (3 mg/kg) and PPI (3 mg/kg) in relation to the liver, kidney, and spleen tissues of ICR mice. [55].

5.4 Neuroprotective Effect

Recent studies have supported that polyphyllins (PPI, PPII, PPVII) have neuroprotective efficacy in the neurodegenerative diseases (NDs), where inflammation, oxidative stress, and dysregulated cell death are the causes of disease progression.
PP-II interrupts the KEAP1-NRF2 interaction, activating antioxidant gene expression, while PP-I induces mitophagy via the PINK1-Parkin pathway. PP-VII modulates neuroinflammation through activation of the cGAS-STING axis. These actions collectively protect neurons, preserve mitochondrial function, and reduce pathological cascades associated with NDs.
Advances in nanomedicine, including lipid nanoparticles and carbon dots; have improved polyphyllin delivery to the central nervous system surpassing barriers like poor solubility and limited blood-brain barrier permeability. [70]

5.5 Other Pharmacological Actions

In addition to its anticancer, anti-inflammatory and neuroprotective properties, Paris polyphylla has various other pharmacological activities. Steroidal saponins have been shown to have antimicrobial activity against a wide range of bacteria and fungi, which could be helpful in the treatment of infections. [85]. Spirostanol saponins (paris saponins I, II, VI, and VII) extracted from the rhizomes and leaves of P. Polyphylla var. yunnanensis have been shown to exhibit antimicrobial effects.[86]. Past studies have demonstrated that Paris saponin H, polyphyllin I, polyphyllin II, Polyphyllin VI and polyphyllin VII could serve as favorable hemostatic agents. [86] [87]
Additionally, P. polyphylla has been investigated for antioxidant property. Some of its constituents, mainly steroidal saponins derived from the rhizome showed antioxidant activity. [85, 88] Rhizome Paridis saponin mainly exerts antioxidant effects through scavenging free radicals, activating antioxidant enzyme activities, and regulating apoptotic protein signaling pathways. [89] Paris saponins have an immunomodulatory effect. [90] Recent study found that PP I could inhibit P. acnes-induced secretion of IL-8 from HaCaT cells mediated by the CD36/NOX1/ROS/NLRP3/IL-1β pathway. PP I, PPII, PPVII and diosgenin show anti-inflammatory effects and play a crucial part in acne treatment. [90] This implies a novel potential treatment for Acne vulgaris.

6. Conclusion

Paris polyphylla have shown great potential in the treatment of neurological, antitumor, hemostatic, antimicrobial (against fungi, bacteria, and parasites), anti-inflammatory, and antioxidant related diseases due to the existence of useful secondary metabolites. The rhizome is the most extensively used plant part, and it has more activity against various diorders.

P. polyphylla promotes the therapeutic effects of radiotherapy, chemotherapy, and targeted therapy, and greatly reduces the toxic side effects and adverse reactions associated with antitumor therapy. The experimental results proved that Polyphyllin had potential development and utilization prospects, which is of great value to the development of Polyphyllin products.

Since this species is designated as 'vulnerable' due to a decrease in its population, and the demand is increasing across the globe, conservation of this herb is necessary to save these herbs from extinction. Domestication of this plant, cultivation in large scale in those areas similar to natural habitat and propagation by tissue culture are some of the solutions to save this vulnerable species.

7. Future Perspective

As an anticancer for TCM, Rhizoma Paridis has shown good results in clinical applications for many years. Paris polyphylla is one of the ingredients of the Gan-Fu-Le capsules, Bo-Er-Ning capsules, Lou-Lian capsules and other Chinese patented anticancer medicines.[91] In the last few decades, there has been an increase in the use of traditional Chinese medicine for the treatment and prevention of cancer. TCM has its advantages such as prevention of tumorigenesis; reducing toxicity and increasing the treatment effect and decreasing tumor recurrence and metastasis.[92]

Meta-analyses of clinical trials show that integrating TCM with targeted therapies provides a synergistic method to reduce toxicity in primary liver cancer (PLC). This can increase treatment efficacy and overall quality of life in patients. These findings not only provide a functional basis for the synergistic effects of TCM and conventional treatments but also highlight its potential as a valuable adjunct in cancer therapy. [93]

The Steroidal saponins possess anticancer and neuroprotective properties, making them suitable candidates for the treatment of various cancers and neurological disorders.

Future investigations should prioritize optimized drug formulations and validation in human models to bridge preclinical evidence with therapeutic applications.

Bibliography

1. World Health Organization. WHO Global Report on traditional and complementary medicine 2019. Geneva: WHO; 2019. ISBN 978-92-4-151543-6.
2. Fortune Business Insights. Herbal medicine market size, share & industry analysis, 2024 [Internet]. 2024. Available from: https://www.fortunebusinessinsights.com/herbal-medicine-market-106320
3. IUCN 2026. The IUCN Red List of Threatened Species. Version 2025-2. https://www.iucnredlist.org/species/175617476/176257430
4. POWO (2026). Paris polyphylla Smith. In: Plants of the World Online [Internet]. Royal Botanic Gardens, Kew; 2026. https://powo.science.kew.org/taxon/urn:lsid:ipni.org:names:24614-1 [Retrieved 20 July 2026].
5. WFO (2026). Paris polyphylla Smith. In: World Flora Online [Internet]. https://www.worldfloraonline.org/taxon/wfo-0000715243, [Accessed on: 20 July 2026]
6. Ding Y-G, Zhao Y-L, Zhang J, Zuo Z-T, Zhang Q-Z, Wang Y-Z. The traditional uses, phytochemistry, and pharmacological properties of Paris L. (Liliaceae): A review. J Ethnopharmacol. 2021;278:114293. https://doi.org/10.1016/j.jep.2021.114293
7. N.P. Committee, Pharmacopoeia of the People's Republic of China, China Medical Science Technology Press, Beijing (2020)
8. Cunningham A, Brinckmann J, Bi YF, Pei SJ, Schippmann U, Luo P. Paris in the spring: A review of the trade, conservation and opportunities in the shift from wild harvest to cultivation of Paris polyphylla (Trilliaceae). J Ethnopharmacol. 2018;222:208-216.
9. Long CL, Li H, Ouyang Z, Yang X, Li Q, Trangmar B. Strategies for agrobiodiversity conservation and promotion: a case from Yunnan, China. Biodivers Conserv. 2003;12(6):1145–1156.
10. Thapa CB, Paudel MR, Bhattarai HD, Pant KK, Devkota HP, Adhikari YP, et al. Bioactive secondary metabolites in Paris polyphylla Sm. and their biological activities: A review. Heliyon. 2022 Feb 17;8(2):e08982. doi: 10.1016/j.heliyon.2022.e08982
11. Tian Y, Gong G-Y, Ma L-L, Wang Z-Q, Song D, Fang M-Y. Anti-cancer effects of Polyphyllin I: An update in 5 years. Chem Biol Interact. 2020 Jan 25;316:108936. Doi.org/10.1016/j.cbi.2019.108936
12. Wang J, Ni B-Y, Wang J, Han L, Ni X, Wang X-m, Cao L-c, Sun Q-h, Han X-p, Cui H-j. Research progress of Paris polyphylla in the treatment of digestive tract cancers. Discover Oncol. 2024;15:31.

13. Li J, Jia J, Zhu W, Chen J, Zheng Q, Li D. Therapeutic effects on cancer of the active ingredients in Rhizoma Paridis. Front Pharmacol. 2023;14:1095786. doi: 10.3389/fphar.2023.1095786
14. Phurailatpam A, Choudhury A. Paris polyphylla: An important endangered medicinal plant of Himalayan foothills. Med Plants. 2022 May 5. DOI: 10.5772/intechopen.102920
15. Deb CR, Jamir SL, Jamir NS. Studies on vegetative and reproductive ecology of Paris polyphylla Smith: a vulnerable medicinal plant. Am J Plant Sci. 2015;6(16). DOI: 10.4236/ajps.2015.616258
16. Das Gupta D, Mishra S, Verma SS, Shekher A, Rai V, Awasthee N, et al. Evaluation of antioxidant, anti-inflammatory and anticancer activities of diosgenin enriched Paris polyphylla rhizome extract of Indian Himalayan landraces. J Ethnopharmacol. 2021 Apr 24;270:113842. DOI: 10.1016/j.jep.2021.113842
17. Wang Y, Wei S. Diagnostic application of proprietary Chinese medicines in the treatment of endometriosis and adenomyosis of the uterus. Chin J Fam Plan Gynecol. 2015;7:13-15.
18. Yue J, Li Z, Zuo Z, Zhao Y, Zhang J, Wang Y. Study on the identification and evaluation of growth years for Paris polyphylla var. yunnanensis using deep learning combined with 2DCOS. Spectrochim Acta Part A Mol Biomol Spectrosc. 2021;261:120033.
19. Su F, Ye L, Zhou Z, et al. Study of chemical compositions and anticancer effects of Paris polyphylla var. chinensis leaves. Molecules. 2022;27(9):2724.
20. Zhao B, Wang Z, Han J, Wei G, Yi B, Li Z. Rhizoma Paridis total saponins alleviate H2O2-induced oxidative stress injury by upregulating the Nrf2 pathway. Mol Med Rep. 2019;21:220-228.
21. Liu F, Li L, Tian X, Zhang D, Sun W, Jiang S. Chemical constituents and pharmacological activities of steroid saponins isolated from Rhizoma Paridis. J Chem. 2021;2021:1442906.
22. Yan T, Hu G, Wang A, Sun X, Yu X, Jia J. Paris saponin VII induces cell cycle arrest and apoptosis by regulating Akt/MAPK pathway and inhibition of P-glycoprotein in K562/ADR cells. Phytother Res. 2018;32(5):898–907.
23. Hua X, Kou C, Wang F, Zhang J, Yuan J, Xue Z. Steroidal compounds in Paris polyphylla: structure, biological activities, and biosynthesis. Curr Opin Plant Biol. 2025 Apr;84:102695. DOI: 10.1016/j.pbi.2025.102695
24. Wang Y, Li Z, Lin J, Ke C, Liu H, Ren F, Huang H, Wang P, Wu L, Ming T, Liu J, Li P. Integrated metabolomic and transcriptomic profiling reveals leaf-specific flavonoid biosynthesis in Paris polyphylla Sm. BMC Plant Biol. 2025 Oct 7;25(1):1327. doi: 10.1186/s12870-025-07350-8
25. Zhang X, Chen J, Xu P, Zhang X, Yang S, Zhang J, Wan X, Gao Y, Zheng G. Transcriptomics and metabolomics profiling of Paris polyphylla var. yunnanensis with different growth years. Sci Data. 2025 May 26;12(1):866. doi:10.1038/s41597-025-05242-y.
26. Wang M, Ma X, Gao C, Luo Y, Fei X, Zheng Q, Ma X, Kuai L, Li B, Wang R, Song J. Rutin attenuates inflammation by downregulating AGE-RAGE signaling pathway in psoriasis: network pharmacology analysis and experimental evidence. Int Immunopharmacol. 2023 Dec;125(Part A):111033. https://doi.org/10.1016/j.intimp.2023.111033
27. Ye F, Lv J, Shen X, Zhang J, Zong Y, Zhu C, Yang Y, Jia K, Jiang Y, Tang Z. Rutin ameliorates inflammatory pain by inhibiting P2X7 receptor in mast cells. J Physiol Biochem. 2022 Dec 13;79(2):287-295. https://doi.org/10.1007/s13105-022-00938-w
28. Sha A, Li Y. Preparation, structural characterization, bioactivities, and potential clinical applications of the polysaccharides from Paris polyphylla: a review. Front Pharmacol. 2025 Feb 25;16. https://doi.org/10.3389/fphar.2025.1539237
29. Upadhyay S, Jeena GS, Shikha, Shukla RK. Recent advances in steroidal saponins biosynthesis and in vitro production. Planta. 2018;248(3):519-544.
30. Li Y, Yang H, Li Z, Li S, Li J. Advances in the biosynthesis and molecular evolution of steroidal saponins in plants. Int J Mol Sci. 2023;24(3):2620. doi:10.3390/ijms24032620
31. Kavya NM, Adil L, Senthilkumar P. A review on saponin biosynthesis and its transcriptomic resources in medicinal plants. Plant Mol Biol Rep. 2021;39(5):833–840. doi: 10.1007/s11105-021-01293-8
32. Fordos S, Amin S, Abid N, Pasha I, Iqbal MK, Amin A, Gulzar M, Subtain M, Abdi G. Saponins: advances in extraction techniques, functional properties, and industrial applications. Appl Food Res. 2025;5(2):101146. doi: 10.1016/j.afres.2025.101146
33. Timilsena YP, Phosanam A, Stockmann R. Perspectives on saponins: food functionality and applications. Int J Mol Sci. 2023;24(17):13538. doi: 10.3390/ijms241713538
34. Krakowska-Sieprawska A, Rafińska K, Walczak-Skierska J, Kiełbasa A, Buszewski BJM. Promising green technology in obtaining functional plant preparations: combined enzyme-assisted supercritical fluid extraction of flavonoids isolation from Medicago sativa leaves. Materials. 2021;14(11):2724. doi: 10.3390/ma14112724
35. Huang Q, Li J, Ma M, Lv M, Hu R, Sun J, Zhong X, Sun X, Feng W, Ma W, Zhang W, Zhan B, Han Z, Zhou X. High-throughput screening identification of a small-molecule compound that induces ferroptosis and attenuates the invasion and migration of hepatocellular carcinoma cells by targeting the STAT3/GPX4 axis. Int J Oncol. 2023;62(1):42. doi: 10.3892/ijo.2023.5490
36. Feng Y, Mo Y, Zhang Y, Teng Y, Xi D, Zhou J, et al. Polyphyllin VI: A promising treatment for prostate cancer bone metastasis. Int Immunopharmacol. 2025;144:113684. doi:10.1016/j.intimp.2024.113684
37. Wang P, Yang Q, Du X, Chen Y, Zhang T. Targeted regulation of Rell2 by microRNA-18a is implicated in the anti-metastatic effect of polyphyllin VI in breast cancer cells. Eur J Pharmacol. 2019;851:161-173.

38. Yuan YL, Jiang N, Li ZY, Song ZZ, Yang ZH, Xue WH, Zhang XJ, Du Y. Polyphyllin VI induces apoptosis and autophagy in human osteosarcoma cells by modulation of ROS/JNK activation. Drug Des Devel Ther. 2019; 13:3091–3103. doi: 10.2147/DDDT.S194961
39. Li L, Chen Z, Hao C. Neuroprotective effects of polyphyllin VI against rotenone-induced toxicity in SH-SY5Y cells. Brain Res. 2024;1830:148824. doi:10.1016/j.brainres.2024.148824
40. Yang R, Gao W, Wang Z, Jian H, Peng L, Yu X, et al. Polyphyllin I induced ferroptosis to suppress the progression of hepatocellular carcinoma through activation of the mitochondrial dysfunction via Nrf2/HO-1/GPX4 axis. Phytomedicine. 2024 Jan;122:155135. doi: 10.1016/j.phymed.2023.155135.
41. Zheng F, Wang Y, Zhang Q, Chen Q, Liang C-L, Liu H, Qiu F, Chen Y, Lu W, Dai Z. Polyphyllin I suppresses gastric cancer growth by promoting cancer cell ferroptosis. Front Pharmacol. 2023;14:1145407. doi: 10.3389/fphar.2023.1145407
42. Wang Y, Ge H, Zhang Y, Wang P, Zhao H, Wang L, Fan Z. Antitumor effect of polyphyllin I (PPI) on colorectal cancer: Evidence from patient-derived organoids and Notch signaling suppression. Heliyon. 2024;10(18):e37226. doi: 10.1016/j.heliyon.2024.e37226
43. Zou P, Chen Z, He Q, Zhuo Y. Polyphyllin I induces ferroptosis in castration-resistant prostate cancer cells through the ERK/DNMT1/ACSL4 axis. The Prostate. 2023;84(1):64–73.
44. Zhou X, Zhang D, Lei J, Ren J, Yang B, Cao Z, Guo C, Li Y. Polyphyllin I induces rapid ferroptosis in acute myeloid leukemia through simultaneous targeting PI3K/SREBP-1/SCD1 axis and triggering of lipid peroxidation. J Nat Med. 2024; 78:618–632.
45. Zhang D, Tian X, Wang Y, Liu F, Zhang J, Wang H, Zhang N, Yan T, Lin C, Shi Z, Liu R, Jiang S. Polyphyllin I ameliorates gefitinib resistance and inhibits the VEGF/VEGFR2/p38 pathway by targeting HIF-1a in lung adenocarcinoma. Phytomedicine. 2024; 129:155690.
46. Feng P, Sun C, Wang X, Zhang H, Cheng P. Polyphyllin I induces apoptosis and autophagy in temozolomide-resistant glioma via modulation of NRF2 and MAPK-signaling activation. Biotechnology and Genetic Engineering Reviews. 2024;40(3):2409-2428. https://doi.org/10.1080/02648725.2023.2199553
47. Fu A, Feng H, Sun M, Luo X, Li Z, Tang H, Qiao F. Polyphyllin I inhibits glioblastoma progression by initiating ferroptosis via the Sirt1/Nrf2/HO-1/GPX4 signaling cascade. Mol Basis Dis. 2026;187(1):168028. doi: 10.1016/j.bbadis.2025.168028
48. Wu Y, Si Y, Xiang Y, Zhou T, Liu X, Wu M, Li W, Zhang T, Xiang K, Zhang L, Zhao H. Polyphyllin I activates AMPK to suppress the growth of non-small-cell lung cancer via induction of autophagy. Arch Biochem Biophys. 2020;687:108285.
49. Xu M, Yu X, Jia L, Ye M, Zhao Y, Wang R, Tang Q, Zhu G, Chen J, Zhou Q, Deng S, Wang S. Polyphyllin I induces ferritinophagy-dependent ferroptosis through EZH2 and promotes anti-tumor immunity. Biomed Pharmacother. 2025;187:118165. doi: 10.1016/j.biopha.2025.118165
50. Chai Y, Yu S, Lin G, Luo C, Wang X, Zhang R, Peng J, Zhu Y, Zhang J. Polyphyllin I inhibits the metastasis of cervical cancer through the regulation of the β-catenin signaling pathway. Int J Mol Sci. 2025;26(19):4630.
51. Long J, Pi X. Polyphyllin I promoted melanoma cells autophagy and apoptosis via PI3K/Akt/mTOR signaling pathway. Biomed Res Int; 2020:5149417. https://doi.org/10.1155/2020/5149417
52. Tang Q, Huang K, Li M, Zhao Z, Deng Y, Zuo Y, Wang N, Zhu Y. Polyphyllin I inhibits ovarian cancer growth by inducing G0/G1 phase arrest and inhibiting the c-Myc signaling pathway. J Blood Med. 2025;42:254. doi: 10.1007/s12032-025-02824-z
53. Li J, Ma W, Cheng X, Zhang X, Xie Y, Ji Z, Wu S. Activation of FOXO3 pathway is involved in polyphyllin I-induced apoptosis and cell cycle arrest in human bladder cancer cells. Arch Biochem Biophys. 2020;687:108363. doi: 10.1016/j.abb.2020.108363
54. Yang Z, Yang X, An M. Polyphyllin I improves myocardial damage in coronary artery disease via modulating lipid metabolism and myocardial apoptosis. J Biochem Mol Toxicol. 2022 Dec;36(12):e23219. doi: 10.1002/jbt.23219.
55. Shi Y-X, Xu L, Wang X, Zhang K-K, Zhang C-Y, Liu H-Y, et al. Paris polyphylla ethanol extract and polyphyllin I ameliorate adenomyosis by inhibiting epithelial-mesenchymal transition. Phytomedicine. 2024 May;127:155461. doi: 10.1016/j.phymed.2024.155461.
56. Cheng G, Ye G, Ma Y, Wang Y. Polyphyllin II inhibits NLPR3 inflammasome activation and inflammatory response of Mycobacterium tuberculosis-infected human bronchial epithelial cells. Allergol Immunopathol (Madr). 2024;52(1):16-23.
57. Li JK, Sun HT, Jiang XL, Chen YF, Zhang Z, Wang Y, et al. Polyphyllin II induces protective autophagy and apoptosis via inhibiting PI3K/AKT/mTOR and STAT3 signaling in colorectal cancer cells. Int J Mol Sci. 2022;23(19):11890. doi:10.3390/ijms231911890
58. Jiao Y, Xin M, Xu J, Xiang X, Li X, Jiang J, et al. Polyphyllin II induced apoptosis of NSCLC cells by inhibiting autophagy through the mTOR pathway. Pharm Biol. 2022;60(1):1781-1789. doi:10.1080/13880209.2022.2120021
59. Miao W, Wang Z, Gao J, Ohno Y. Polyphyllin II inhibits breast cancer cell proliferation via the PI3K/Akt signaling pathway. Mol Med Rep. 2024 Dec;30(6):224. doi: 10.3892/mmr.2024.13348.
60. .Yang M., Zou J., Zhu H., Liu S., Wang H., Bai P., et al. (2015). Paris saponin II inhibits human ovarian cancer cell-induced angiogenesis by modulating NF-κB signaling. Oncol. Rep. 33 (5), 2190–2198. 10.3892/or.2015.3836
61. Chen T, Lin J, Tang D, Zhang M, Wen F, Xue D, et al. Paris saponin H suppresses human hepatocellular carcinoma (HCC) by inactivation of Wnt/β-catenin pathway in vitro and in vivo. Int J Clin Exp Pathol. 2019 Aug 1;12(8):2875-86.

62. Zhao L, Liu Z, Deng X, Wang J, Sun L, Fan L, Zhang Y. Polyphyllin VII induces mitochondrial apoptosis by regulating the PP2A/AKT/DRP1 signaling axis in human ovarian cancer. Oncol Rep. 2020 Dec 2;45(2):513-522. doi: 10.3892/or.2020.7879.
63. Zhang C., Jia X., Wang K., Bao J., Li P., Chen M., et al. (2016). Polyphyllin VII induces an autophagic cell death by activation of the JNK pathway and inhibition of PI3K/AKT/mTOR pathway in HepG2 cells. PLoS One 11 (1), e0147405. 10.1371/journal.pone.0147405
64. Li X., Liu Y., Liao S., Lin C., Moro A., Liu J., et al. (2021). Polyphyllin VII induces apoptosis and autophagy via mediating H2O2 levels and the JNK pathway in human osteosarcoma U2OS cells. Oncol. Rep. 45 (1), 180–190. 10.3892/or.2020.7866
65. Pang, D. Li, C.Yang, C. Polyphyllin VII promotes apoptosis and autophagic cell death via ROS-inhibited AKT activity and sensitizes glioma cells to temozolomide,Oxid. Med. Cell. Longev. 2019; 19
66. He H, Xu C, Zheng L, Wang K, Jin M, Sun Y, et al. Polyphyllin VII induces apoptotic cell death via inhibition of the PI3K/Akt and NF-κB pathways in A549 human lung cancer cells. Mol Med Rep. 2020 Feb;21(2):597-606. doi: 10.3892/mmr.2019.10879.
67. Song H, Sun C, Li N, Zhao Q, He Y. Anti-tumor and immunomodulation activity of polysaccharide from Paris polyphylla Smith var. chinensis in S180 tumor-bearing mice. J Sci Food Agric. 2025 Oct;105(13):7169-7182. doi: 10.1002/jsfa.14415.
68. .Lin LT, Shi YC, Choong CY, Tai CJ. The fruits of Paris polyphylla Inhibit colorectal cancer cell migration Induced by Fusobacterium nucleatum-Derived Extracellular Vesicles, Molecules. 2021 Jul 4;26(13):4081. https://doi.org/10.3390/molecules26134081
69. Wang L, Jia C, Yu Z, Liu X, Kang L, Cong Y, et al. Pennogenin Tetraglycoside Induces Rat Myometrial Contraction and MLC20 Phosphorylation via PLC-IP_3 and RhoA/Rho Kinase Signaling Pathways. PLoS One. 2012 Dec 12;7(12):e51536. doi: 10.1371/journal.pone.0051536.
70. Hussain MS, Rana AJ, Maqbool M, Sulthana N, Sultana A, Ashique S, et al. Unveiling polyphyllin's role in neuroprotection: a pharmacological perspective. Pharmacological Research - Modern Chinese Medicine. 2025 Sep;16:100641. https://doi.org/10.1016/j.prmcm.2025.100641
71. Global status report on cancer 2026: WHO
72. https://www.who.int/news/item/08-07-2026-who-calls-for-urgent-action-as-new-cancer-cases-are-projected-to-nearly-double-by-2050
73. Liu Y-P, Zheng C-C, Huang Y-N, He M-L, Xu W W, Li B. Molecular mechanisms of chemo- and radiotherapy resistance and the potential implications for cancer treatment. MedComm. 2021;2(3):315-340. doi:10.1002/mco2.55
74. Li YC, Zhang HX. Overview of mechanism of TCM prevention and treatment of liver cancer. J Pract Tradit Chin Intern Med. 2024;38:43–7. doi:10.13729/j.issn.1671-7813.Z20231723
75. Wang S, Long S, Deng Z, Wu W. Positive role of Chinese herbal medicine in cancer immune regulation. Am J Chin Med. 2020;48:1577–92. doi:10.1142/S0192415X20500780
76. Liu Y, Dong X, Wang W, You L, Yin X, Yang C, Sai N, Leng X, Ni J. Molecular mechanisms of apoptosis in HepaRG cell line induced by polyphyllin VI via the Fas death pathway and mitochondrial-dependent pathway. Toxins (Basel). 2018 May 15;10(5):201. doi:10.3390/toxins10050201.
77. Liu W, Chai Y, Hu L, Wang J, Pan X, Yuan HY, Zhao ZT, Song YM, Zhang Y. Polyphyllin VI induces apoptosis and autophagy via reactive oxygen species mediated JNK and P38 activation in glioma. Onco Targets Ther. 2020 Mar 13;13:2275–2288. doi: 10.2147/OTT.S243953
78. Lin Z, Liu Y, Li F, Wu J, Zhang G, Wang Y, Lu L, Liu Z. Anti-lung cancer effects of Polyphyllin VI and VII potentially correlate with apoptosis in vitro and in vivo. Phytother Res. 2015 Oct;29(10):1568-76. doi: 10.1002/ptr.5430.
79. Emami A, Ghafouri H, Sariri R. Polyphyllin D-loaded solid lipid nanoparticles for breast cancer: synthesis, characterization, in vitro, and in vivo studies. Int J Pharm. 2023 May 25;639:122976. doi: 10.1016/j.ijpharm.2023.122976.
80. Yang C, Cai H, Meng X. Polyphyllin D induces apoptosis and differentiation in K562 human leukemia cells. Int Immunopharmacol. 2016 Jul;36:17-22. https://doi.org/10.1016/j.intimp.2016.04.011
81. Gu L, Feng J, Zheng Z, Xu H, Yu W. Polyphyllin I inhibits the growth of ovarian cancer cells in nude mice. Oncol Lett. 2016 Dec;12(6):4969-74. doi: 10.3892/ol.2016.5348.
82. Zhu T, Wu W, Yang S, Li D, Sun D, He L. Polyphyllin I inhibits Propionibacterium acnes-induced inflammation in vitro. Inflammation. 2019 Feb;42(1):35-44. doi: 10.1007/s10753-018-0870-z.
83. Yang S, Jiang Y, Yu X, Zhu L, Wang L, Mao J, Wang M, Zhou N, Yang Z, Liu Y, Zhu T. Polyphyllin I inhibits Propionibacterium acnes-induced IL-8 secretion in HaCaT cells by downregulating the CD36/NOX1/ROS/NLRP3/IL-1β pathway. Evidence-Based Complementary and Alternative Medicine. 2021 Sep 21;2021:1821220. doi: 10.1155/2021/1821220.
84. Zhang C, Li C, Jia X, Wang K, Tu Y, Wang R, Liu K, Lu T, He C. In Vitro and In Vivo Anti-Inflammatory Effects of Polyphyllin VII through Downregulating MAPK and NF-κB Pathways. Molecules. 2019 Mar 1;24(5):875. doi: 10.3390/molecules24050875.
85. Moawad G, Fruscalzo A, Youssef Y, Kheil M, Tawil T, Nehme J, et al. Adenomyosis: An Updated Review on Diagnosis and Classification. J Clin Med. 2023 Jul 21;12(14):4828. doi: 10.3390/jcm12144828.

86. Mayirnao HS, Bhat A. Evaluation of Antioxidant and Antimicrobial Activity of Paris Polyphylla Sm. Asian J Pharm Clin Res. 2017 Nov;10(11):315. DOI: 10.22159/ajpcr.2017.v10i11.20984
87. Qin XJ, Ni W, Chen CX, Liu HY. Seeing the light: shifting from wild rhizomes to extraction of active ingredients from above-ground parts of Paris polyphylla var. yunnanensis. J Ethnopharmacol. 2018 Oct 5;224:134-139.
88. Wen F, Chen T, Yin H, Lin J, Zhang H. In vitro effects on thrombin of Paris saponins and in vivo hemostatic activity evaluation of Paris fargesii var. brevipetala. Molecules. 2019;24(7):1420. doi:10.3390/molecules24071420
89. Lepcha DL, Chhetri A, Chhetri DR. Antioxidant and Cytotoxic Attributes of Paris polyphylla Smith from Sikkim Himalaya. Pharmacogn J. 2019;11(4):705-711. DOI:10.5530/pj.2019.11.112
90. Wang XF, Li P, Yang Y, Xu X, Lin J, Yang HJ, Li CY. Research progress on antioxidant, anti-inflammatory, and anti-tumor mechanisms of rhizome paridis saponins. Drug Eval Res. 2023;46(12):2699-2708.
91. Li L, Zhang J, Cheng W, Di F, Wang C, An Q. Saponins of Paris polyphylla for the improvement of acne: anti-inflammatory, antibacterial, antioxidant and immunomodulatory effects. Molecules. 2024 Apr 15;29(8):1793. doi: 10.3390/molecules29081793
92. Wang Y-H, Shi M, Niu H-M, Yang J, Xia M-Y, Luo J-F, Chen Y-J, Zhou Y-P, Li H. Substituting one Paris for another? In vitro cytotoxic and in vivo antitumor activities of Paris forrestii, a substitute of Paris polyphylla var. yunnanensis. J Ethnopharmacol. 2018 May 23;218:45-50. doi: 10.1016/j.jep.2018.02.022
93. Ling CQ, Yue XQ, Ling C. Three advantages of using traditional Chinese medicine to prevent and treat tumor. J Integr Med. 2014;12(4):331-5. doi: 10.1016/S2095-4964(14)60038-8.
94. Yan H, Li Y, Guo B, Yang B, Tang D. The effect of traditional Chinese medicine on patients undergoing targeted therapy for primary liver cancer: a systematic review and meta-analysis. Front Oncol. 2025 Oct 24;15:1674965. doi: 10.3389/fonc.2025.1674965.