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A Review on*Paris Polyphylla* Smith: As an Effective andAlternative Treatment of Cancer

Arcadius Puwein*[1], Shiny C. Thomas[2], Laishram Indira Singha[3]
[*1] *Department of Biotechnology,Assam Don Bosco University, Guwahati, India,*
[2]*Department of Biochemistry, Assam Don Bosco University, Guwahati, India*
[3] *Department of Biotechnology, St. Anthony's College Shillong, Meghalaya, India*
Corresponding AuthorArcadius Puwein

ABSTRACT:*Cancer is one of the leading causes of mortality in the world. There are many synthetic drugs available for cancer treatment, but not without side effects. Medicinal plants such as ParisPolyphylla Smith presents an alternative therapeutic drug which iscomparatively less toxic. This review aims to critically analyze the various types of cancer that use the bioactive compounds of the herb for potential treatment. It investigates the types of mechanism, that thesebioactive compoundsinhibit cancer cell lines or nude mice.The article could offer a significant scope for future researchers to dedicate more studiesformany known and unknown compounds of the herb. These unknown compounds could be effective to treat other types of cancer that have not been assessed. The data from the review provide evidence that steroidal saponins such as polyphyllin VI, polyphyllin VII, polyphyllin D, Rhizoma paridis saponins (RPS) as the main bioactive compounds that exhibits cytotoxicity and arrest cell cycle either in S or G2/M phase or both. They trigger apoptosis mainly via mitochondrial-mediated pathway (intrinsic pathway) and death receptor-mediated pathway (extrinsic pathway).*
KEYWORDS:*Paris polyphylla, apoptosis, cytotoxicity, cell cycle arrest,steroidal saponins.*

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I. INTRODUCTION

Cancer is one of the leading causes of death in the world. The International Agency for Research on Cancer reported that cancer is the second leading cause of death globally, and was responsible for 8.8 million deaths in 2015 [1].About one in five-peopledied of cancer. The development of a cancer is governed by multiple factors such as the genetic constitution of the individual, his or her environment (including the food intake), and way of life [2].There are many methods of treatment to combat various types of cancer. But due to serious side effects of major clinical treatments, such as chemotherapy and radiation therapy, many cancer patients seek alternative medicines for treatment. Many such alternative medicines are derived from plants. Traditional herbs have become the novel path for discovery and development of drugs which are comparatively less toxic [3].

Paris polyphylla Smith is a traditional herb, recently found to be an effective alternative treatment for cancer.It is an erect and herbaceous plant. *Paris polyphylla* Smith and other of its variety grow in humus-rich soil with full or partial shade. The herb has been traditionally used to relieve various ailments [4].The main chemical constituents of the herb are extracted from the rhizomes. Paris saponins account for more than 80% of the totalcompounds, play a vital role in many treatments.It has a potential anti-cancerous property [5]. The anticancer activity of paris saponins is mostly assayed for its cytotoxicity, morphological changes (cytopathology, histopathology) and apoptosis as indicated in fig 1.This review attempts to analyze the active chemical constituents of *P.polyphylla* to treat cancer as a potential alternative drug. By elucidating and comparing the mechanism of inhibitionsof the bioactive compound (Fig.1), the review could offer as a tool guide for further studies and deeper understanding of the mechanism of the herb.

II. ANTICANCER ACTIVITY

The rhizomes extract of *P. polyphylla* Smith and other variety attenuate various types of cancer. The *P. polyphylla* var. *yunnanensis* has been extensively researched in China and found to be a powerful drug for cancer. Recent studies of the aqueous, ethanolic and methanolic extracts of *P. polyphylla* showed their anticancer activity on several types of cancer cell lines. Phytochemical and pharmacological studies identified steroid saponins as the main antitumor active components [6,7]. Different steroid saponins have been studied (indicated in Table I) and found to be effective in many cancer cell lines as we shall discuss.

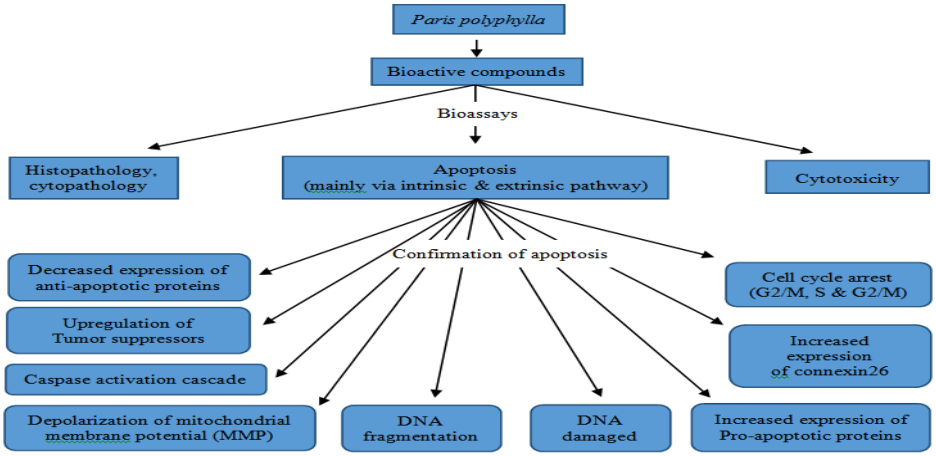

Figure 1: Schematic diagram showing the anticancer activity of bioactive compounds of *P. polyphylla*. The bioactive compounds were assayed mainly for morphological changes (Histopathology, cytopathology), cytotoxicity and apoptosis. The main mechanism of inhibition of *P. polyphylla* against various types of cancer is via apoptosis which is confirmed by different markers as shown above

2.1. Human Liver Cancer

P. polyphylla induces anticancer activity in human liver cancer HepG2 cells by triggering apoptosis and necrosis via signalling pathways (caspase cascade, mitogen protein kinase-MAPK) and tumor suppressor proteins (p53 and phosphatise and tensin homology- PTEN) [8].

Polyphyllin VII (PVII), one of the steroidal saponins of the herb is the active compound in combating human liver cancer. When PVII was examined for its cytotoxicity on five human cancercell lines (MCF7, Caco2, SKOV3, A549 and HepG2), at different concentrations for 24h, significant inhibition was observed in the growth of all cell lines, after being assayed with Methyl thiazolyl tetrazolium(MTT). We will describe the mechanism of apoptosis of HepG2 since it shows the highest sensitivity to PVII, albeit its cellular and molecular mechanism is poorly understood [9].

The induction of apoptosis was examined by exposing HepG2 cells for 24h with different concentrations of PVII. The apoptotic cells were evaluated using Annexin-V- fluorescein isothiocyanate (FITC). When PVII was treated with HepG2 cells with 0.88, 1.32 and 1.98 µM for 24h, the percentage of apoptosis was found to be 13.3, 19.2 and 40.0 %, respectively. PVII was also observed to induce apoptosis via intracellular reactive oxygen species (ROS) generation in cells. It caused oxidative stress in HepG2 cells. This ROS production leads to the depolarization of mitochondrial membrane potential, DNA damaged and eventually apoptosis [9].

The involvement of PVII in the (caspases cascade& MAPK) signalling pathway isnotified by the level of proteins expression. The proteins expression of the control and treated HepG2 cells were analyzed by Western blotting technique. When HepG2 cells were treated with 1.98 µM of PVII for 24h, the expression of cleaved caspases -3, -8, -9, andpolyADP-ribose polymerase (PARP) increased by 34%, 129%, 65% and 241%. The pro-apoptotic proteins Bax, cytochrome cexpression increased while those of anti-apoptotic protein Bcl-2 and phosphorylated Bcl-2, BAD were suppressed by PVII. The expression of proteins (JNK, ERK, p38) in the MAPK signalling pathway was observed to increase in treated HepG2 cells. These results demonstrated PVII as a potential inhibitor of liver cancer [9].

The anticancer activity of *P.polyphylla* was also found to produce a promising result in mice that were artificially induced with diethylnitrosamine (DEN). When mice were injected with DEN (70mg/kg body weight), it induced hepatocarcinogenesis which was similar to those of human hepatocellular carcinoma (HCC). After two months, the injected mice developed liver inflammation and cirrhosis [10,11].When rhizoma paridis saponins (RPS) of *Paris polyphylla* var. *yunnanensis* was treated to the DEN-induced mice, effective result was observed.After 20 weeks, the DEN-induced mice were sacrificed and histopathological examination showed decreased body weight, pseudo and disrupted hepatic lobule, large vacuolated lobule in DEN-induced mice, but no abnormal findings in normal mice. Biochemical analyses in DEN-induced mice showed increased levels of Gamma-glutamyltranspeptidase (gamma-GGT), alkaline phosphatase (ALP), albumin (ALB), cholinesterase (CHE), and total bilirubin (TBIL) in serum. The levels of malondialdehyde (MDA), nitric oxide (NO), catalase (CAT), 8-hydroxy-2'-deoxyguanosine (8-OHdG) were elevated in DEN-treated mice. However, RPS decreased

the levels of the above-mentioned proteins, thereby attenuated liver injury, and inhibited the development of liver cancer [12].

2.2Lung Cancer

Radiotherapy is one of the popular treatments for lung cancer, especially for those who are sensitive to surgery and had chemotherapy failure. In recent studies, PVI and PVII of *P. polyphylla*showed to be an effective alternative treatment for lung cancer. They were found to be associated mostly with cell cycle arrest at the G2/M phase and apoptosis by enhanced caspase 3, Bax and p21waf1/cip1 and reduced Bcl-2 production [13].

The two steroidal saponins (PVI and PVII) exhibit inhibitory effects on the proliferation of lung cancer, observed in A549 and NCI-H1299 cell lines. The MTT assay of these two cell lines showed decreased viability after being treated for 48h with PVI and PVII. These two compounds were also found to induce G2/M cell cycle arrest and trigger apoptosis. This was indicated by the fact that the number of A549 and NCI-H1299 cells increased significantly after treating with 1, 2, 4 μM for24h with both PVI and PVII,as compared to the untreated cells. Therefore, there is a lucid sign of apoptosis [14].

PVI and PVII were also observed to up-regulate the tumor suppressor protein p53 and down-regulate cyclin B1. These compounds regulate the expression of proteins related to the apoptotic pathway in A549 triggering apoptosis. When A549 cells were treated with PVI and PVII for 48h, the proteins expression level of p21 Wafi1/Cip 1 and cyclin B1 were reduced, whereas p53, Fas, DR3, and DR5 expression were upregulated [14].The MTT assay and proliferation analysis of LA795 cancer cells lines also produce similar pattern results [15].

2.3 Human Chondrosarcoma

The rhizomes extract of the herb has a potential drug for soft tissues and bones cancer. Cytotoxicity and apoptosis were conducted on *P. polyphylla* var. *chinensis* in human chondrosarcoma cell line SW1353 and found to produce a promising outcomein anticancer activity. When various concentrations of dichloromethane crude extract (900, 800, 700, 600, 500, 400, 300, 200, 100, 50, and 10 μg/ml) of the herb was treated with SW1353 cells for 24h, and MTT assay was performed, it was found that the extracthas high cytotoxicity against this human chondrosarcoma cell line. However, the bioactivity of *P. polyphylla* needs more attention so as to understand the exact mechanism [16].

2.4 Ovarian Cancer

Chia-Woei Wang et al. demonstrated the aqueous extract of *Paris polyphylla* (AEPP) as the potential suppressor of ovarian carcinoma cell line (OVCAR – 3 cells). The viability of the OVCAR – 3 cells which were treated with AEPP for 24h was found to be <50% as compared to the control. This study showed that AEPPreduced the viability of OVCAR – 3 cells through the induction of apoptosis. This induction of apoptosis was confirmed by the annexin-V-FITC and propidium iodide (PI) double staining method and flow cytometry.The researchers inducedepithelial-mesenchymal transition (EMT) on OVCAR-3 ovarian carcinoma cells using high glucose (HG) content. EMT is the main mechanism for cancer metastasis. The AEPP effectively inhibits the proliferation of the cancer cell lines through the suppression of peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1alpha [17].

2.5. Cervical Cancer

Cervical cancer was responsible for the deaths of 275,000 women in 2008, and thus required to develop new alternative drugs with a more specific effect [18].The compound derived from *Paris polyphylla* called *Paris* saponin VII (PS VII) has antitumor properties on cervical cancer which was observed in Hela cell lines. When Hela cells were exposed to different concentrations (1-100 μM) of the compound and assayed with MTT and5-ethynyl-2′-deoxyuridine(EdU), cells proliferation were inhibited. The value of inhibitory concentration (IC_{50}) showed that the Hela cells were subjected to undergo apoptosis. The number of apoptotic cells wasevaluated using flow cytometric analysis. The level of proteins expressed was measured by Western blot analysis. The increased expression of caspase-3, caspase-9, Bax and decreased expression of Bcl-2 proteins after being treated with PS VII was observed. This demonstrates that PS VII is a candidate inducer of apoptosis on cervical cancer [19].

2.6 Human Chronic Myelogenous Leukemia (CML)

CML is also known as chronic granulocytic leukemia and affects the blood and bone marrow. Chunhui Yang et al. demonstrated that polyphyllin D (PD) exhibited a growth inhibitory effect in the humanerythroleukemia cell line K562by inducing apoptosis and differentiation. After K562 cells were treated with PD for 24h, there were drastic morphological changes, which were observed inthe fluorescent microscope. The cells shrank, showedvacuolar degeneration and cytoskeleton collapsed. The number of viable cells decreased as compared to control [20].

To assess the mechanism of apoptosis, the treated K562 cells were stained with Annexin V-FITC and PI. The compound induces apoptosis in the cells in a time-dependent manner. Since depolarization of the mitochondrial

membrane potential (MMP) is an indication of early apoptosis, the MMP of K562 cells, exposed to PD with different concentrations along with the control were stained with Rhodamine 123 and examined with flow cytometry. The result shows that PD mediates apoptosis of the treated cells. In order to deepen the understanding of the mechanism, mitochondrial apoptosis regulatory proteins expression level was evaluated. The pro-apoptotic proteins of the cells were exposed to various concentrations of PD for 24h and examined. The expression of Bcl-2 was down-regulated and simultaneously the up-regulation of Bax, caspase-3 and the released of cytochrome c from the mitochondria to the cytosol was seen. This is an indication that PD induces apoptosis in K562 cells through the mitochondrial apoptosis pathway. This is furthered augmented by the fact that PD down-regulate p210-Bcr/Abl protein levels in K562 cells.These data suggest that PD has the potent therapeutic agent for treating human CML [20].

2.7 Human Glioma

The brain tumor is called glioma because it arises from the glial cells. A study was conducted to evaluate apoptotic induction of PD in U87 human glioma cells and explored its underlying pathway. U87 glioma cells were cultured and exposedto varying concentrations (10^{-8}- 10^{-4} M) of PD for 24h.When assessed by MTT assay, the cell proliferation of U87 glioma cells was inhibited by PD. The data of inhibition on U87 glioma cells displayed by the compound were observed to be in a dose-dependent manner. In order to analyze the effect of PD on the apoptotic proteins, western blot was used. It was observed that PD induced apoptosis by increasing the expression of the proteins of Bax, caspase-3, t-JNK1 (c-Jun N-terminal kinases), and p-JNK1 while simultaneously decreasing Bcl-2 expression. By using the specific JNK inhibitor SP600125,the blockage pattern of JNK junction to the above-mentioned proteins was assessed. From the obtained results, the researchers opinedthat PD induced apoptosis of U87 human glioma cells via JNK pathway [21].

2.8 Esophageal Cancer

The anticancer effect of *Paris polyphylla* Smith and its inducement of tumor cell apoptosis were not well understood. So, the researchers explored the effect of *Paris polyphylla* Smith extract (PPSE) onConnexin26 and the growth control in human esophageal cancer ECA109 cells. It has been observed that most of the cancer cells expressed a low level of connexin26. But when this protein is restored back, the tumor growth and proliferation is inhibited. So, there must be a connection between connexin26 and growth of the tumor. The researchers, therefore, increased the connexin26 by exposing with various concentrations of PPSE. After exposing the cells with PPSE for 24h, and assayed with Western blot, RT-PCR, and immunofluorescence, there were an increased in the expression of connexin26, resulting in the formation of functional gap junction (GJ). But at higher concentration (100μg/ml) of PPSE, there was no induction of increased level of connexin26.To augment the above findings, the compound was furthered treated with esophageal cancer ECA109. The expression of the pro-apoptotic proteins was analyzed by Western blot. The PPSE decreased the level of Bcl-2 and increased the level of Bad. This confirmed that PPSE inhibits cell proliferation and induces cell apoptosis of esophageal cancer ECA109 [22].

2.9 Human Breast Cancer

To ascertain the mechanism of apoptosis in human breast cancer, both the *invivo* and *in vitro*evaluations were carried out on two human breast cancer cell lines -MCH-7, MDA-MB-231 and nude mice bearing MCH-7. The steroidal saponin PD of *Paris polyphylla* was examined for the viability and apoptosis. The various concentrations of PD were exposed to MCH-7 and MDA-MB-231 for 48h, and MTT was assayed. The cytotoxicity was seen in both cell lines, however, PD is more sensitive to MDA-MB-231 [23].

The induction of apoptosis on the two cell lines was carried out by the researchers on three aspects -the formation of the nucleosome, the occurrence of hypodiploid peaks in the cell cycle analysis and the externalization of phosphatidylserine (PS). When PD was exposed to the two human breast cancer cell lines for 24h, the formation of the nucleosome in MCH-7 was observed. The formation of the hypodiploid peak in the MDA-MB-231 was observed after staining with propidium iodide (PI) and analysis with flow cytometry. Both these results showed prominent result at the concentration of 2.5 μM and 5 μM. These two results indicate that PD induced DNA fragmentation. Similarly, loss of membrane integrity and PS externalization were seen after treating with PD. These results suggest that the two human breast cancer cell lines undergo apoptosis. It was also found that PD disintegrated the mitochondrial membrane potential, increased the pro-apoptotic Bax expression, activated caspase-9 and decreased of anti-apoptotic Bcl-2 expression. These findings suggest thatPD induces apoptosis through mitochondria dysfunction [23].

The cytotoxicity agent that is active *in vitro* does not necessarily active *in vivo* condition,due to low bioavailability, failure in deliverance or fast removal rate [24].To rectify this issue, the female nude mice were injected with MCF-7 subcutaneously to induce tumor growth. After tumor formation, the nude mice bearing MCF-7 were treated with PD of 2.05 mg/kg and 2.73 mg/kg body for ten days. The mice were sacrificed and analyzed. It was found that PD reduced tumor growth by ~40% at the 2.05 mg/kg dose and ~50% at the 2.73 mg/kg. Moreover, no disruption of the heart and liver tissue were found in the treated mice when compared to the control. Therefore, PD is not toxic to the mice [23].

Similarly,a study was done on the induction of MCF-7 human breast cancer cellapoptosis by Rhizoma Paridis saponins (RPS). RPS refers to the rhizomes of*Paris polyphylla* var. *yunnanensis*. This work showed RPS as a potential agent for cell viability which was measured by MTT assay. The induction of apoptosis by RPS was confirmed by the action of the caspase cascade, cleaved of PARP, released of cytochrome c and increased of Bax/Bcl-2 ratio [25].

3.1 Gastric Cancer

Gastric cancer was reported to be the most common cause of death from cancer in China [26].As such, many studies were carried out, one of these is the effect of *Paris chinensis* dioscin(PCD)onhumangastric cancer SGC-7901 cells. In this study, the cells treated with different concentrations of PCD were incubated for 24h and their cellular morphology was observed under a phase contrast microscope. The treated cells exhibited cytoplasmic shrinkage, floated in the medium, became distorted, blurred when observed under a microscope and detached from each other.The PCB was found to exhibitan effect on SGC-7901 cells at the G2/M phase rather than S phase. This was actualized by measuring the DNA content using PI stain after the cells were exposed to PCB for 24h. The researchers came to this conclusion after evaluating the expression of cyclins B and CKD1 using Western blot assay, which is closely related to G2/M cell cycle progression [27].

The SGC-7901 cells were found to undergo apoptosis after being treated with PCB. The fact of apoptosis was examined by staining the cells with Annexin V-FITC/PI and analyzed with flow cytometry. The process of apoptosis takes place via a mitochondrial-dependent caspase pathway. This was rectified by the released of cytochrome c to the cytosol. The level of cytochrome c and caspase-3 were measured in the cytosol, and found to had been increased significantly after being treated with PCB [28].

3.2 Human Tongue Squamous Cell Carcinoma

Tongue squamous cell carcinoma (TSCC) is one of the most devastating malignancies among oral and maxillofacial tumors. Chemotherapy of oral squamous cell carcinoma has poor clinical efficacy and high toxicity. Jun-Yu Ke et al. showsthat a compound of*Paris polyphylla*, named as PP-22 could be the novel alternative treatment of TSCC. PP-22 is a monomer ethanolic extracts of the *Paris polyphylla* var. *yunannensis* [28].

The PP-22 was tested for its proliferation effect on human tongue squamous carcinoma SCC-15 cells and were analyzed using a modified MTT assay (WST-8 method). The SCC-15 cells were treated with various concentrations of PP-22 at different time (24h, 48h,72h). The assay showed that the treated cells decreased in cell proliferation in time-and concentration-dependent manner. The cell proliferation of SCC-15 was observed to be arrested in the S and G2/M phase. This was seen when the SCC-15 cells were stained with propidium iodide. This was also confirmed by the increased of cyclin A, cyclin E2, cyclin B1 levels, and up-regulation of Myt1, p-Wee1, p-cdc2 (Tyr15), and p53, when assayed by Western blotting. The PP-22 induced cell apoptosis by activating the p38/p53 and caspase 8/caspase 3 signal pathway. Therefore, PP-22 triggers apoptosis via the extrinsic apoptotic pathway [29].

Types of Cancer	Compound Used	Cell Lines/ Animal Model	Plant Species & Variety	Solvents Used	Mechanism of Inhibition	Country	Reference
Liver Cancer	Polyphyllin VII	HepG2	*P. polyphylla* var. *yunnanensis*	-	Induces apoptosis via intrinsic & extrinsic pathway	China	[8,9]
	Rhizomaparidis saponins (RPS)	Mice	*P. polyphylla* var. *yunnanensis*	70% Ethanol	Induces reactive oxygen species (ROS) and oxidative damage of DNA	China	[10,11,12]
Lung Cancer	Polyphyllin VI Polyphyllin VII	A549 NCI-H1299	*P. polyphylla*	-	Induces G2/M cell cycle arrest and triggers apoptosis.	China	[14]
	Rhizoma paridis saponins (RPS)	LA795 Mice	*P. polyphylla* var. *yunnanensis*	70% Ethanol	Inhibits the migration of the tumor cells	China	[14,15]
Human Chondro-sarcoma	Crude extract	SW1353	*P. polyphylla* var. *chinensis*	Methanol and dichloromethane	Cytotoxicity and apoptosis	Thailand	[16]
Ovarian Cancer	Aqueous extract of *P. polyphylla*	OVCAR -3	*P. polyphylla*	Water (100ml/10g)	Apoptosis via suppression of peroxisome PGC – 1alpha	Taiwan	[17]
Cervical Cancer	*Paris* saponin VII	Hela Cell	*P. polyphylla*	-	Apoptosis through intrinsic apoptotic pathway	China	[18,19]
Human Chronic Myelogenous Leukemia	Polyphyllin D	K562	*P. polyphylla*	-	Induces apoptosis via mitochondrial apoptotic pathway	China	[20]
Human Glioma	Polyphyllin D	U87 human glioma cell	*P. polyphylla*	-	Apoptosis via JNK pathway	China	[21]
Esophageal Cancer	*P.polyphylla* Smith extract (PPSE)	ECA109	*P. polyphylla* Smith	95% ethyl alcohol	Apoptosis and increased expression of Connexin26 and formation of gap junction (GJ)	China	[22].
Breast Cancer	*Rhizoma Paridis* saponins (RPS)	MCF-7	*P.polyphylla* var. *yunnanensis*	70% ethanol	Induces apoptosis via mitochondrial apoptotic pathway	China	[25]
	Polyphyllin D	MDA-MB 231 MCF-7	*P. polyphylla*	-	Elicits apoptosis through mitochondria dysfunction.	China	[23,24]
Gastric Cancer	*Paris chinensis* dioscin (PCD)	SGC-7901	*P.polyphylla* var. *chinensis*	-	Elicits G2/M phase arrest and apoptosis via mitochondrial pathway	China	[27]
Tongue squamous cell carcinoma	*P. polyphylla* (PP-22)	SCC-15	*P. polyphylla* var. *yunnanensis*	70 % ethanol	Elicits S and G2/M phases arrest and apoptosis via extrinsic apoptotic pathway	China	[29]

Table I: Anticancer Activity of *Paris polyphylla*

III. CONCLUSION

From the aforementioned research elucidated, the review presents*P. polyphylla* as a potential therapeutic drug for cancer.*P. polyphylla* exhibits significant inhibition todifferent types of cancer by cytotoxicity and apoptosis. The bioactive compounds trigger apoptosis mainly via mitochondrial-mediated pathway (intrinsic pathway) and death receptor-mediated pathway (extrinsic pathway). However, most of these mechanism pathwaysare not well understood. This review indicates that more studies need to be carried out to augment the pre-clinical treatments of the herb against cancer to predict clinical drugs response in the future.

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