# The Anti-Neoplastic Potential of Platycodon grandiflorum and its Saponin Platycodin D: A Comprehensive Review with a Focus on Papillary Thyroid Carcinoma

## Part I: Executive Summary for a General Audience

For centuries, the Balloon Flower, known scientifically as *Platycodon grandiflorum*, has been a staple in traditional Asian medicine, primarily used to treat coughs, colds, and other lung conditions. Today, modern science is taking a closer look at this ancient remedy, focusing on a powerful natural compound found in its root called Platycodin D. Laboratory research has revealed that Platycodin D possesses remarkable anti-cancer properties. In studies using cancer cells grown in dishes, this compound has shown a striking ability to kill cancer cells or stop them from growing and spreading. These effects have been observed across a wide variety of cancer types, including common and challenging malignancies such as those of the lung, breast, colon, and stomach, as well as leukemia. This broad activity has positioned Platycodin D as a highly promising candidate for the development of new cancer treatments derived from natural sources.

A particularly exciting area of this research involves Papillary Thyroid Cancer (PTC), which is the most common type of thyroid cancer. While PTC is often treatable, some cases can be aggressive or resistant to standard therapies. Scientific studies have shown that

Platycodin D can attack PTC cells by shutting down a key pathway that these cells use to survive and grow. Even more significantly, research suggests that Platycodin D can make a modern cancer drug, the immunotherapy agent pembrolizumab, work much more effectively against thyroid cancer. This potential synergy, combining a natural compound with an advanced medical treatment, could one day offer a new and powerful strategy for patients with difficult-to-treat thyroid cancer. While these findings are very encouraging, it is important to remember that they are based on early laboratory research. More studies and clinical trials in people are needed to confirm the safety and effectiveness of Platycodin D as a cancer therapy.

## Part II: Platycodon grandiflorum: From Ethnomedicine to Modern Phytopharmacology

### 2.1 Botanical and Ethnomedicinal Profile

*Platycodon grandiflorum* (Jacq.) A. DC., commonly known as the Balloon Flower or Chinese bellflower, is a perennial herbaceous flowering plant belonging to the Campanulaceae family.[1] Native to East Asia, it is abundantly found in China, Korea, Japan, and the Russian Far East. The plant is distinguished by its large, balloon-like flower buds that swell before opening into a five-lobed, bell-shaped corolla.

Its significance extends far beyond its ornamental value. The root of

the plant, known as *Platycodonis Radix* or "Jiegeng" in Chinese, holds a revered place in traditional medicine systems. Its use was first documented in the ancient Chinese text, the *Shennong Materia Medica Classic*, one of the earliest and most influential treatises on pharmacognosy.[2] Within Traditional Chinese Medicine (TCM),

*Platycodonis Radix* is primarily categorized as an herb that resolves phlegm and stops coughs. It is classically prescribed to treat conditions characterized by phlegm accumulation, such as coughs, sore throat, tonsillitis, chest congestion, and pulmonary abscesses.[2]

In modern times, the plant's dual role as both a medicinal herb and a food source has been formally recognized, classifying it as a "medicine and food homology herb".[6] This is particularly evident in Korean culture, where the root is a common culinary ingredient in dishes like salads and bibimbap, and is also consumed as a functional food for its purported health benefits, including immune system enhancement.[7] This long history of safe human consumption and medicinal application provides a strong foundation for contemporary scientific investigation into its pharmacological properties.

#### 2.2 Phytochemistry: The Saponin-Rich Profile

The therapeutic effects of *Platycodon grandiflorum* are attributed to a rich and complex array of bioactive phytochemicals. The primary chemical constituents identified in the root extract include triterpenoid saponins, flavonoids, phenolic acids, sterols, and polyacetylenes.[1] Among these, the oleanane-type pentacyclic triterpenoid saponins are considered the principal drivers of the

plant's diverse pharmacological activities.[1]

Key saponins isolated from the plant include Platycodin D (PD), Platycodin D3 (PD3), and Platycoside E.[1] Platycodin D, in particular, has been identified as the most abundant and pharmacologically active of these compounds and is now used as a critical quality control marker for standardizing commercial preparations of

*Platycodonis Radix*.[1]

Chemically, PD is a glycoside with an oleanane-type aglycone core. Its structure is characterized by two distinct sugar chains: a single glucosyl group attached at the C-3 position and a more complex oligosaccharide chain of four sugar residues attached at the C-28 position.[5] This diglycosidic structure is significant, as the number and position of sugar moieties on the saponin backbone are known to profoundly influence biological activity. For instance, saponins with two sugar chains, like PD, have been observed to induce less hemolytic activity (rupturing of red blood cells) compared to those with only a single chain, a feature that may contribute to a more favorable safety profile.[5] The extensive research into PD's anti-inflammatory, immunomodulatory, anti-obesity, and anti-cancer effects underscores its importance as the primary medicinal agent within

*Platycodon grandiflorum*.[4]

## Part III: The Anti-Neoplastic Spectrum of Platycodin D: A Multi-Cancer Review

### 3.1 Foundational Anti-Cancer Mechanisms

Platycodin D (PD) has emerged from preclinical studies not as a narrowly focused agent, but as a multi-targeted molecule capable of combating cancer through a variety of interconnected mechanisms. This pleiotropic activity is a hallmark of many potent natural compounds and represents a significant advantage over highly selective synthetic drugs, which can be more easily circumvented by tumor cells through the activation of alternative signaling pathways.[5] The foundational anti-cancer strategies employed by PD can be broadly categorized into the induction of programmed cell death, inhibition of tumor growth and progression machinery, and a notable selectivity for malignant cells.

The core cytotoxic mechanisms of PD consistently involve the induction of **apoptosis** (Type I programmed cell death), **autophagy** (Type II programmed cell death), and **cell cycle arrest**. Concurrently, it actively suppresses key processes that enable tumor expansion and spread, including **angiogenesis** (the formation of new blood vessels to feed the tumor), **invasion** into surrounding tissues, and **metastasis** to distant organs.[5]

A crucial attribute for any potential therapeutic agent is its ability to distinguish between cancerous and healthy cells. Multiple studies have highlighted PD's promising therapeutic window. In investigations on prostate cancer, PD exerted significant cytotoxicity against various cancer cell lines (PC3, DU145, LNCaP) while having minimal effect on non-malignant human prostate epithelial cells (RWPE-1).[13] Similarly, in gastric cancer models, PD was shown to be

more resistant to normal gastric mucosal cells (GES-1) compared to their cancerous counterparts.[14] This inherent selectivity suggests a lower potential for the collateral damage to healthy tissues that often characterizes conventional chemotherapy, positioning PD as a compound with a potentially favorable safety profile.

#### 3.2 Lung Cancer (Non-Small Cell Lung Cancer - NSCLC)

In the context of non-small cell lung cancer (NSCLC), one of the leading causes of cancer mortality worldwide, Platycodin D has demonstrated significant anti-neoplastic activity through the coordinated induction of multiple cell death pathways. *In vitro* studies have shown that PD effectively reduces the viability and inhibits the colony-forming ability of various NSCLC cell lines, including H1299, H2030, and A549. The potency of this effect is reflected in its half-maximal inhibitory concentration (IC50) values, which range from a highly potent 7.8 μM in H1299 cells to 10.3 μM in A549 cells.[15] Beyond simply halting growth, PD actively kills NSCLC cells by impairing mitochondrial function and inducing both apoptosis and autophagy.[3]

The primary mechanism driving apoptosis in NSCLC has been elucidated as the upregulation of PUMA (p53 up-regulated modulator of apoptosis), a potent pro-apoptotic protein of the BH3-only family. The induction of PUMA is not a secondary effect but a direct consequence of PD's impact on a specific signaling cascade: the JNK1/AP-1 pathway. The evidence demonstrates that PD treatment activates the kinase JNK1, which in turn phosphorylates the transcription factor c-Jun, a key component of

the AP-1 complex. This activated AP-1 then binds directly to the promoter region of the *PUMA* gene, driving its transcription and leading to the accumulation of PUMA protein, which ultimately triggers the apoptotic cascade.[15]

Concurrently, PD induces autophagy in NSCLC cell lines such as NCI-H460 and A549. This is achieved through a dual-pronged attack on major cellular signaling hubs. PD inhibits the pro-survival PI3K/Akt/mTOR pathway, a master regulator that normally suppresses autophagy. Simultaneously, it activates the stress-responsive JNK and p38 MAPK signaling pathways, which are known inducers of autophagy.[3] The simultaneous induction of both apoptosis (Type I PCD) and autophagy (Type II PCD) reveals a sophisticated and robust anti-cancer strategy. These two processes are not always independent; autophagy can, under certain conditions, lead to cell death. By simultaneously shutting down a critical survival signal (PI3K/Akt/mTOR) and activating powerful stress signals (JNK/p38 MAPK), PD creates an overwhelming and inescapable stress environment for the cancer cell. This multi-pronged assault, targeting the cell's core survival-death balance, makes it exceedingly difficult for the tumor cell to mount an effective resistance, a significant advantage over therapies that rely on a single mechanism of action.

#### 3.3 Breast Cancer

Platycodin D has shown particular promise against aggressive forms of breast cancer, most notably triple-negative breast cancer (TNBC), a subtype that lacks estrogen receptor, progesterone receptor, and

HER2 expression and is notoriously difficult to treat. In studies using the highly metastatic MDA-MB-231 TNBC cell line, PD demonstrated potent growth inhibition with an IC50 value of 7.77 µM.[17] This cytotoxic effect is accompanied by the induction of cell cycle arrest at the G0/G1 checkpoint, effectively halting cancer cell proliferation.[17] Furthermore, PD has been shown to act as a chemosensitizer, enhancing the anti-proliferative effects of the conventional chemotherapy drug doxorubicin.[17]

The mechanistic underpinnings of PD's action in breast cancer are centered on its ability to target the MDM2-p53 axis. Research has shown that PD treatment leads to a marked downregulation of the oncoprotein MDM2 and its homolog MDMX. This is critically important because MDA-MB-231 cells harbor a mutated form of the p53 tumor suppressor gene. While MDM2 is best known as a negative regulator of wild-type p53, it also plays a role in stabilizing and promoting the oncogenic functions of mutant p53. By inhibiting MDM2, PD disrupts this supportive interaction, leading to the degradation of the oncogenic mutant p53 protein. The functional consequence of this is the upregulation of downstream cell cycle inhibitors, such as p21 and p27, which enforce the observed G0/G1 arrest.[17] These effects, confirmed through elegant experiments using MDM2 gene silencing (siRNA) and overexpression plasmids, demonstrate that PD's anti-cancer activity is directly linked to its targeting of the MDM2 oncogene.[17]

This mechanism carries profound implications. Approximately half of all human cancers contain mutations in the p53 gene, and many of these mutations, far from simply inactivating the protein, bestow it with new, "gain-of-function" oncogenic properties that drive tumor progression, metastasis, and chemoresistance. The finding that PD

can destabilize mutant p53 by targeting its regulatory partner, MDM2, suggests a specific and powerful therapeutic strategy. It indicates that PD is not merely removing a defective tumor suppressor but is actively dismantling a key driver of malignancy. This positions PD as a potentially valuable agent for the large and challenging patient population whose cancers are driven by oncogenic p53 mutations.

#### 3.4 Gastrointestinal Cancers (Colorectal & Gastric)

In the realm of gastrointestinal (GI) malignancies, Platycodin D has distinguished itself not only as a standalone cytotoxic agent but, perhaps more importantly, as a powerful chemosensitizer and adjuvant. In gastric cancer (GC) models, PD demonstrates selective toxicity, effectively inhibiting the growth and colony formation of various GC cell lines while showing greater resistance in normal gastric mucosal cells (GES-1).[14] It exerts its direct anti-cancer effects by inducing G1 phase cell cycle arrest and apoptosis.[14] In colorectal cancer (CRC), its role as a combination agent comes to the forefront, where it has been shown to enhance the sensitivity of KRAS-mutant cells to the targeted therapy cetuximab and to overcome resistance to the cornerstone chemotherapeutic oxaliplatin.[16]

The mechanisms of action are tailored to the specific cancer and therapeutic challenge. In gastric cancer, PD's primary target is the highly unstable oncoprotein c-Myc. PD was found to promote the ubiquitination and subsequent proteasomal degradation of c-Myc. The depletion of this master regulator of cell growth leads to the observed G1 cell cycle arrest through the modulation of the

p21/CDK2-CyclinE pathway.[14] In colorectal cancer, PD's ability to act as a sensitizer is linked to its modulation of key resistance pathways. For instance, KRAS mutations are a well-established cause of primary resistance to EGFR inhibitors like cetuximab. PD circumvents this by inhibiting the downstream PI3K/Akt signaling pathway, effectively shutting down the escape route used by the cancer cells and re-sensitizing them to cetuximab.[16] Similarly, it overcomes acquired resistance to oxaliplatin by modulating the LATS2/YAP1 axis of the Hippo signaling pathway, reactivating cell death programs that had been silenced by the tumor.[16]

The consistent ability of PD to restore or enhance the activity of standard-of-care drugs in resistant settings is arguably its most clinically relevant feature in GI cancers. Acquired and primary drug resistance remains a paramount obstacle in the successful treatment of advanced CRC and GC. PD's capacity to target the very mechanisms of this resistance positions it not as a potential replacement for existing therapies, but as a crucial partner. Its potential clinical application is therefore clearly defined: as part of a combination regimen to improve the efficacy of first-line treatments and to offer a new therapeutic option for patients with refractory or resistant disease.

#### 3.5 Hematological Malignancies (Leukemia & Lymphoma)

Platycodin D has demonstrated potent anti-neoplastic activity in preclinical models of hematological malignancies, including Acute Myeloid Leukemia (AML) and Diffuse Large B-cell Lymphoma (DLBCL), the most common type of non-Hodgkin lymphoma.[16] In

both AML and DLBCL cell lines, PD effectively induces cell death through apoptosis and mitochondrial dysfunction.[16] A particularly significant finding is its powerful synergistic effect when combined with venetoclax, a targeted B-cell lymphoma 2 (BCL-2) inhibitor, in AML models.[16]

The mechanistic basis for PD's activity in these cancers involves the suppression of critical pro-survival signaling pathways. In AML, PD triggers mitochondria-dependent apoptosis and induces cell cycle arrest at the G0/G1 checkpoint by concurrently inhibiting both the PI3K/AKT and the MAPK/ERK pathways.[16] This dual inhibition is key to understanding its synergy with venetoclax. Venetoclax is a highly effective drug that works by blocking the anti-apoptotic protein BCL-2, thereby pushing cancer cells toward apoptosis. However, cancer cells can develop resistance to venetoclax by upregulating other pro-survival signals, which are often transmitted through the PI3K/Akt and MAPK/ERK pathways.

The synergy between PD and venetoclax is, therefore, not coincidental but mechanistically driven. Venetoclax delivers the primary pro-apoptotic signal by inhibiting BCL-2, while PD simultaneously cuts off the primary escape routes by inhibiting the PI3K/Akt and MAPK/ERK pathways. This creates a "dual-attack" scenario where the cancer cell's ability to evade apoptosis is comprehensively dismantled. This rational combination strategy suggests that PD could be used to significantly enhance the initial response to BCL-2 inhibitors and, crucially, to prevent or delay the onset of acquired resistance. Given the transformative impact of venetoclax in hematology, the identification of a natural compound that can potentiate its effects and combat resistance is a finding of major clinical importance.

### 3.6 Other Malignancies (Prostate, Glioblastoma, Endometrial, Hepatocellular)

The broad-spectrum anti-cancer activity of Platycodin D extends to a diverse array of other solid tumors, each with distinct mechanisms of action highlighting PD's pleiotropic nature.

- **Prostate Cancer:** PD exhibits remarkable selectivity in prostate cancer models, showing significant cytotoxicity against cancer cell lines (PC3, DU145, LNCaP) with IC50 values ranging from 11.17 to 26.13 µM, while leaving normal prostate epithelial cells (RWPE-1) largely unharmed.[13] Its mechanism involves inducing apoptosis and cell cycle arrest, which occurs at either the G0/G1 or G2/M phase depending on the specific genetic background of the cell line. This effect is driven by the activation of the tumor suppressor transcription factor FOXO3a, which is achieved through the downregulation of its negative regulator, MDM2.[13]
- **Glioblastoma:** In models of glioblastoma multiforme (GBM), one of the most aggressive and difficult-to-treat brain tumors, PD employs a unique mechanism. It induces cell death by inhibiting autophagy flux, which leads to a toxic accumulation of low-density lipoprotein (LDL)-derived cholesterol within the cell's lysosomes. This lysosomal dysfunction ultimately proves fatal to the GBM cells. In addition to this cytotoxic effect, PD also inhibits the proliferation, migration, and invasion of glioblastoma cells.[16]
- **Endometrial Cancer:** PD effectively curtails the malignant behavior of endometrial cancer cells. It was found to inhibit their proliferation, invasion, and migration by upregulating the expression of the α2A-adrenergic receptor (ADRA2A). The

increased activity of this receptor subsequently leads to the inhibition of the critical pro-survival PI3K/Akt signaling pathway, thereby suppressing tumor growth.[16]

- **Hepatocellular Carcinoma (HCC):** In liver cancer models, PD demonstrates its ability to induce both apoptosis and autophagy, a dual cell-death mechanism mediated by the activation of the ERK and JNK stress-signaling pathways.[12] Importantly, PD also shows potential as a sensitizing agent in HCC, with studies indicating it can help overcome resistance to histone deacetylase (HDAC) inhibitors, a class of drugs being explored for liver cancer treatment.[12]

## Part IV: In-Depth Analysis: Platycodin D in Papillary Thyroid Carcinoma (PTC)

### 4.1 The Clinical Landscape of Papillary Thyroid Cancer

Papillary thyroid carcinoma (PTC) is the most prevalent endocrine malignancy, accounting for 80% to 85% of all thyroid cancer cases.[20] It originates from the thyroid follicular cells, which are responsible for producing thyroglobulin.[20] PTC is typically characterized by an indolent, slow-growing nature and carries an excellent overall prognosis, with high rates of successful treatment and low mortality.[20]

Despite this favorable outlook, PTC presents notable clinical challenges. It exhibits a high propensity for lymphatic spread, with

approximately 30% of patients having metastases to the cervical lymph nodes at the time of diagnosis.[20] While lymph node involvement does not always drastically worsen the prognosis, it necessitates more aggressive treatment and surveillance. Furthermore, certain histological subtypes of PTC, such as the tall cell, columnar cell, and diffuse sclerosing variants, are associated with more aggressive behavior and a poorer prognosis.[20] The most significant clinical challenge arises in the small subset of patients whose disease becomes advanced, metastatic, and refractory to standard therapies, particularly radioactive iodine (RAI) ablation.

The standard of care for PTC is highly risk-stratified. Treatment for localized disease typically involves surgery, which may be a total thyroidectomy (removal of the entire gland) or a lobectomy (removal of one lobe) depending on tumor size, multifocality, and other risk factors.[20] Following total thyroidectomy, patients at an intermediate or high risk of recurrence often receive adjuvant RAI therapy. This treatment leverages the ability of thyroid cells to absorb iodine, using a radioactive isotope to destroy any remaining microscopic cancer cells or normal thyroid tissue.[23] After the removal or ablation of the thyroid gland, patients require lifelong thyroid hormone replacement therapy, which also serves to suppress thyroid-stimulating hormone (TSH) and reduce the risk of recurrence.[20]

#### 4.2 The Evolving Therapeutic Paradigm for PTC: A Context for Novel Agents

The management of PTC is undergoing a significant transformation, driven by a deeper understanding of its molecular biology and a

growing emphasis on minimizing treatment-related morbidity. This evolution is proceeding along two main fronts: de-escalation of therapy for low-risk disease and the development of sophisticated targeted therapies for advanced, refractory cases. This shifting landscape provides the essential context for evaluating the potential role of novel agents like Platycodin D.

A major trend in modern PTC management is the reduction of overtreatment for low-risk tumors to avoid the lifelong consequences of total thyroidectomy and RAI therapy. For papillary microcarcinomas (tumors ≤ 1 cm), active surveillance or "watchful waiting" is increasingly accepted as a safe alternative to immediate surgery.[23] For slightly larger, unifocal tumors without high-risk features, a lobectomy is often preferred over a total thyroidectomy, preserving endogenous thyroid function.[23] Concurrently, minimally invasive techniques like radiofrequency ablation (RFA) and microwave ablation (MWA) are being actively investigated as non-surgical options to destroy small, low-risk tumors.[23]

Conversely, for the small but challenging population of patients with advanced, metastatic, or RAI-refractory PTC, the therapeutic arsenal has expanded dramatically. Treatment has moved beyond non-specific chemotherapy to a new era of precision medicine guided by molecular profiling of tumors. This includes:

- **Multi-Kinase Inhibitors (MKIs):** Lenvatinib (Lenvima) and sorafenib (Nexavar) were the first major breakthroughs for RAI-refractory differentiated thyroid cancer. These oral drugs block multiple receptor tyrosine kinases, including Vascular Endothelial Growth Factor Receptors (VEGFRs), thereby inhibiting tumor angiogenesis and proliferation.[23] Cabozantinib (Cabometyx) offers another MKI option for patients who

progress on prior therapies.[23]

- **Gene-Specific Inhibitors:** The identification of key driver mutations has led to the development of highly specific targeted drugs. This includes dabrafenib plus trametinib for tumors with a *BRAF V600E* mutation; selpercatinib (Retevmo) and pralsetinib (Gavreto) for those with *RET* gene fusions or mutations; and larotrectinib (Vitrakvi) and entrectinib (Rozlytrek) for the rare subset of tumors harboring *NTRK* gene fusions.[23]
- **Immunotherapy:** The role of immune checkpoint inhibitors in PTC is still being defined. The landmark KEYNOTE-158 study evaluated the anti-PD-1 antibody pembrolizumab as a monotherapy in patients with advanced differentiated thyroid cancer. The results showed that while responses could be durable, they were infrequent. The overall objective response rate (ORR) was a modest 6.8%, rising only slightly to 8.7% in patients whose tumors were PD-L1 positive.[28] This limited efficacy has led to the conclusion that the future of immunotherapy in thyroid cancer likely lies in biomarker-driven patient selection and, most importantly, in combination strategies designed to enhance the anti-tumor immune response.[25]

#### 4.3 Platycodin D in PTC: The Central Mechanism of NF-κB Inhibition

Within this evolving therapeutic landscape, Platycodin D emerges as a candidate agent with a distinct and highly relevant mechanism of action for papillary thyroid cancer. The pivotal preclinical study by Deng and Sun (2022) provides the foundational evidence, demonstrating that PD effectively "inhibits the malignant progression

of papillary thyroid carcinoma by targeting the NF-κB signaling pathway".[16]

The targeting of the Nuclear Factor-kappa B (NF-κB) pathway is of profound significance in the context of thyroid cancer biology. NF-κB is a family of transcription factors that functions as a central hub for signals related to inflammation, immunity, cell survival, and proliferation. While it plays a crucial role in normal cellular function, its dysregulation is a common feature of many cancers. In thyroid carcinoma, constitutive activation of the NF-κB pathway is particularly prominent in more aggressive, poorly differentiated, and undifferentiated forms of the disease.[33] This aberrant activity is not a bystander effect; it actively drives the malignant phenotype by promoting cancer cell proliferation and viability, enhancing migration and metastasis, and fueling the self-renewal of cancer stem cells.[33]

Furthermore, the activation of NF-κB is directly linked to the common genetic drivers of PTC. The *BRAF V600E* mutation, the most frequent somatic mutation in PTC, is known to promote cancer initiation and progression in part through the activation of NF-κB signaling.[33] Therefore, by inhibiting the NF-κB pathway, Platycodin D is not targeting a peripheral process but is striking at a core signaling axis that is mechanistically linked to the initiation and progression of the disease. This provides a strong rationale for its potential therapeutic utility in PTC.

#### 4.4 The Synergistic Breakthrough: Enhancing Pembrolizumab Efficacy

The most impactful finding from the research on Platycodin D in papillary thyroid cancer is the explicit demonstration that it

"enhances the therapeutic efficacy of pembrolizumab".[16] This observation elevates PD from being just another potential cytotoxic agent to a candidate

**immuno-sensitizer**, directly addressing the primary challenge facing immunotherapy in this disease.

As established by the KEYNOTE-158 trial, pembrolizumab monotherapy yields a low response rate in advanced thyroid cancer, suggesting that most tumors are inherently resistant to PD-1 blockade.[28] This resistance is often attributed to the tumor microenvironment being immunologically "cold"—that is, lacking the pre-existing T-cell inflammation necessary for checkpoint inhibitors to work effectively. PD's ability to enhance pembrolizumab's efficacy is directly linked to its primary mechanism of NF-κB inhibition, which provides a biologically plausible explanation for this synergy.

The NF-κB pathway is a master regulator of immune responses and is a key transcriptional activator of the gene *CD274*, which encodes for Programmed Death-Ligand 1 (PD-L1). PD-L1 is the ligand for the PD-1 receptor on T-cells; their interaction delivers an inhibitory signal that "turns off" the T-cell, allowing the cancer cell to evade immune destruction. A direct causal chain can therefore be hypothesized:

1. Platycodin D enters the PTC cell and inhibits the activity of the NF-κB transcription factor complex.
2. This reduction in NF-κB activity leads to decreased transcription of its target gene, *CD274*.
3. Lower transcription results in reduced expression of the PD-L1 protein on the surface of the cancer cell.
4. With less PD-L1 available, the tumor's primary mechanism for inactivating anti-tumor T-cells is weakened.

5. Pembrolizumab, which works by blocking the PD-1/PD-L1 interaction, can now function much more effectively because the immunosuppressive signal it targets has already been diminished at its source by PD.

In essence, PD may act to "unmask" the tumor to the immune system. This concept is further supported by the general immunomodulatory properties of *Platycodon grandiflorum* extracts, which have been shown to stimulate immune responses.[4] By potentially converting the tumor microenvironment from immunosuppressive to pro-inflammatory, PD could create the fertile ground needed for checkpoint inhibitors to unleash a powerful and effective anti-tumor immune attack. This finding directly answers the call from the KEYNOTE-158 investigators for research into combination strategies to improve immunotherapy outcomes in thyroid cancer.[28] It positions Platycodin D as a highly promising agent to solve one of the most pressing problems in modern oncology: how to turn immunologically "cold" tumors "hot" and make them susceptible to the transformative power of immunotherapy.

## Part V: Comparative Efficacy and Mechanistic Synthesis

### 5.1 Quantitative Analysis of Potency: The IC50 Landscape

To quantitatively assess the anti-neoplastic potency of Platycodin D across different cancer types, the half-maximal inhibitory concentration (IC50) serves as a standardized *in vitro* metric. The

IC50 value represents the concentration of a drug required to inhibit a biological process, such as cell growth, by 50%. A lower IC50 value indicates higher potency. A survey of the available preclinical literature provides a landscape of PD's efficacy against various malignancies, allowing for a data-driven comparison.

The analysis reveals that PD exhibits its highest potency (defined here as an IC50 value under 10 µM) against specific cell lines of breast cancer and non-small cell lung cancer. The MDA-MB-231 triple-negative breast cancer cell line was inhibited with an IC50 of 7.77 µM, and the H1299 NSCLC cell line showed a similar sensitivity with an IC50 of 7.8 µM.[15] Other NSCLC lines, H2030 and A549, were also sensitive, with IC50 values of 9.6 µM and 10.3 µM, respectively.[15]

PD demonstrates moderate potency (IC50 between 10 µM and 30 µM) against prostate cancer cell lines, with values ranging from 11.17 µM for the p53-null PC3 line to 26.13 µM for the p53-mutant DU145 line.[13] In contrast, its activity against the BEL-7402 hepatocellular carcinoma cell line was less potent, with a reported IC50 of 37.70 µM.[12] For several other cancers, including papillary thyroid, colorectal, and gastric cancer, specific IC50 values were not consistently reported in the reviewed literature, with studies focusing more on mechanistic effects and synergy with other agents.[16]

It is imperative to note that IC50 values are an *in vitro* measure and are subject to variations based on experimental conditions, such as incubation time and the specific cell line used. They do not directly translate to clinical efficacy, which is influenced by complex pharmacokinetic and pharmacodynamic factors *in vivo*. Nevertheless, these values provide a crucial preclinical tool for comparing the intrinsic potency of a compound against different cancer types and for prioritizing future research directions toward

the most sensitive malignancies.

**5.2 Table: Comparative In Vitro Efficacy of Platycodin D Across Various Malignancies**

The following table synthesizes the available preclinical data to provide a quantitative and mechanistic comparison of Platycodin D's effectiveness against a range of cancer cell lines. The table is sorted by IC50 value from most potent to least potent to provide a clear, data-driven ranking of *in vitro* activity.

| Cancer Type | Cell Line(s) | IC50 (μM) | Primary Mechanism(s) of Action | Key Reference(s) |
|---|---|---|---|---|
| Breast Cancer | MDA-MB-231 | 7.77 ± 1.86 | G0/G1 arrest, MDM2/mutant p53 inhibition, EGFR/Akt/MAPK suppression | [17] |
| Lung Cancer (NSCLC) | H1299 | 7.8 | Apoptosis via JNK1/AP-1/PUMA axis, mitochondrial dysfunction | [15] |
| Lung Cancer | H2030 | 9.6 | Apoptosis | [15] |

| | | | | |
|---|---|---|---|---|
| (NSCLC) | | | via JNK1/AP-1/PUMA axis, mitochondrial dysfunction | |
| Lung Cancer (NSCLC) | A549 | 10.3 | Apoptosis via JNK1/AP-1/PUMA axis, Autophagy via PI3K/Akt/mTOR inhibition | [3] |
| Prostate Cancer | PC3 | 11.17 | Apoptosis, G2/M arrest, FOXO3a activation via MDM2 downregulation | [13] |
| Prostate Cancer | LNCaP | Not specified, <30 | Apoptosis, G0/G1 arrest, FOXO3a activation | [13] |
| Prostate Cancer | DU145 | 26.13 | Apoptosis, G0/G1 arrest, FOXO3a activation via MDM2 | [13] |

| | | | | |
|---|---|---|---|---|
| | | | downregulation | |
| Hepatocellular Carcinoma | BEL-7402 | 37.70 ± 3.99 | Apoptosis & Autophagy, ERK/JNK pathway activation | [12] |
| Gastric Cancer | Multiple lines | Not specified | G1 arrest, Apoptosis, c-Myc ubiquitination and degradation | [14] |
| Papillary Thyroid Cancer | TPC-1, K1 | Not specified | NF-κB pathway inhibition, Sensitization to pembrolizumab | [16] |
| Colorectal Cancer | LoVo, etc. | Not specified | PI3K/Akt inhibition (Cetuximab sensitization), Hippo pathway activation (Oxaliplatin sensitization) | [16] |
| Acute | Multiple | Not | Apoptosis, | [16] |

| | | | | |
|---|---|---|---|---|
| Myeloid Leukemia | lines | specified | G0/G1 arrest via PI3K/AKT and MAPK/ERK inhibition, Synergy with venetoclax | |
| Diffuse Large B-cell Lymphoma | Multiple lines | Not specified | Mitochondrial dysfunction, Apoptosis | [16] |
| Glioblastoma | Multiple lines | Not specified | Autophagy inhibition, Lysosomal cholesterol accumulation, Invasion inhibition | [16] |
| Endometrial Cancer | Multiple lines | Not specified | PI3K/Akt pathway inhibition via ADRA2A upregulation | [16] |

Note: A study on bladder cancer was identified but has been retracted due to concerns of data falsification and is therefore excluded from this analysis.[34] The flavonoid chrysin has shown activity against the more aggressive anaplastic thyroid carcinoma by activating Notch1 signaling, but this is a different compound and mechanism from Platycodin D.[35]

#### 5.3 Cross-Cancer Mechanistic Synthesis: The PI3K/Akt and MAPK Hubs

A synthetic analysis of Platycodin D's mechanisms across the diverse range of studied malignancies reveals a remarkable consistency in its primary molecular targets. A clear and recurring pattern emerges: PD consistently modulates the **PI3K/Akt/mTOR** and **MAPK (mitogen-activated protein kinase)** signaling pathways. These two pathways are not peripheral but represent the central superhighways of intracellular signaling that govern the vast majority of cancer hallmarks, including uncontrolled proliferation, survival, evasion of apoptosis, and the development of therapeutic resistance.

PD's modulation of these hubs has been documented in a multitude of cancer types:

- In **Acute Myeloid Leukemia**, it inhibits both PI3K/AKT and MAPK/ERK to induce apoptosis and synergize with venetoclax.[16]
- In **Non-Small Cell Lung Cancer**, it inhibits PI3K/Akt/mTOR while activating the MAPK subgroups JNK and p38 to induce autophagy.[3]
- In **Breast Cancer**, it suppresses EGFR-mediated Akt and MAPK pathways.[17]
- In **Endometrial Cancer**, it inhibits the PI3K/Akt pathway.[16]
- In **Hepatocellular Carcinoma**, it activates the MAPK subgroups ERK and JNK to induce cell death.[12]
- In **Colorectal Cancer**, it inhibits PI3K/Akt to sensitize cells to cetuximab.[16]

This consistent targeting of the PI3K/Akt and MAPK axes explains PD's broad-spectrum anti-cancer activity. It is not exploiting a vulnerability unique to a single type of cancer but is instead

attacking the fundamental machinery that most, if not all, cancers co-opt to survive and thrive. This identifies PD as a "foundational" anti-cancer agent. The specific biological *outcome* of modulating these pathways—be it apoptosis in NSCLC, chemosensitization in CRC, or synergy with targeted therapy in AML—may differ depending on the unique genetic context and signaling network of each cancer type. However, the primary points of attack are remarkably consistent. This pleiotropic action, stemming from the targeting of central signaling nodes, is a defining characteristic of a powerful, multi-targeted natural product and is the source of its versatile anti-neoplastic potential.

## Part VI: Clinical Perspectives, Future Directions, and Conclusion

### 6.1 Translational Hurdles: From Lab to Clinic

Despite the compelling and extensive preclinical evidence supporting the anti-neoplastic potential of Platycodin D, the path from laboratory discovery to clinical application is fraught with significant challenges. Several translational hurdles must be addressed before PD can be considered for human trials.

The most critical of these is **bioavailability and formulation**. Like many triterpenoid saponins, PD is a large, complex glycoside that is likely to have poor oral bioavailability and limited aqueous solubility.[12] This means that if taken orally, very little of the active compound may be absorbed into the bloodstream to reach the tumor site.

Overcoming this requires the development of advanced drug delivery systems. Strategies such as encapsulation in nanoparticles, formulation into self-assembled micelles, or the creation of other novel dosage forms will be essential to improve its pharmacokinetic profile and ensure therapeutic concentrations can be achieved

*in vivo*.[12] The successful nanoformulation of other natural products, such as the flavonoid chrysin, provides a potential roadmap for this development.[38]

A second major consideration is the **toxicity profile**. While PD has shown promising selectivity for cancer cells over normal cells in *in vitro* models and has been well-tolerated in animal xenograft studies, a comprehensive toxicological assessment is paramount.[5] Saponins as a class are known for their potential to cause hemolysis (damage to red blood cells), and although PD's structure may mitigate this risk, it must be rigorously evaluated.[5] Thorough preclinical toxicology studies in multiple animal models are a non-negotiable prerequisite to establishing a safe starting dose for human trials.

Finally, the most significant limitation is the complete **absence of clinical data**. All of the findings discussed in this report are derived from *in vitro* cell culture experiments and *in vivo* animal models.[8] While these preclinical studies are essential for establishing proof-of-concept and elucidating mechanisms, their results do not always translate to success in human patients. The complexity of human tumor biology, drug metabolism, and immune interactions can lead to outcomes that differ significantly from those observed in simplified models. Therefore, all conclusions about PD's potential must be interpreted with appropriate caution pending the results of future, well-designed clinical trials.

### 6.2 Proposed Role in Oncology: An Adjuvant and Immuno-sensitizer

Synthesizing the full spectrum of preclinical evidence, the most promising and rational clinical role for Platycodin D is not as a standalone monotherapy but as a powerful **combination agent**. Its ability to modulate core resistance pathways and enhance the activity of existing therapies defines its potential contribution to the oncological armamentarium. Three key roles emerge from the data:

1. **A Chemosensitizer:** PD has demonstrated a clear ability to overcome acquired resistance to standard chemotherapy. The most compelling example is its capacity to reverse oxaliplatin resistance in colorectal cancer models by modulating the Hippo pathway.[16] This suggests a clinical strategy where PD could be co-administered with conventional chemotherapy to restore efficacy in patients whose tumors have become refractory.
2. **A Targeted Therapy Sensitizer:** PD can expand the utility of targeted drugs. Its ability to re-sensitize KRAS-mutant colorectal cancer cells to the EGFR inhibitor cetuximab by blocking the downstream PI3K/Akt pathway is a prime example.[16] This could potentially open up targeted treatment options for patient populations who are currently ineligible due to primary resistance mutations.
3. **An Immuno-sensitizer:** Perhaps its most exciting potential role is in enhancing the efficacy of immune checkpoint inhibitors. The finding that PD potentiates the activity of pembrolizumab in papillary thyroid cancer models by inhibiting the NF-κB pathway is of paramount importance.[16] This positions PD as a candidate for turning immunologically "cold" tumors "hot," a major goal in

immuno-oncology. This suggests a broad strategy of combining PD with checkpoint inhibitors in tumors where they currently have limited efficacy, with PTC serving as the leading proof-of-concept.

By acting as an adjuvant and sensitizer, Platycodin D could address some of the most pressing challenges in cancer treatment: acquired resistance, primary resistance, and the limited efficacy of immunotherapy in non-inflamed tumors.

#### 6.3 Concluding Scholarly Summary (Audio Overview Script)

This report provides a comprehensive review of the anti-neoplastic properties of *Platycodon grandiflorum* and its principal bioactive saponin, Platycodin D. The evidence establishes Platycodin D as a pleiotropic, multi-targeted agent with significant preclinical activity across a broad spectrum of malignancies, including lung, breast, colorectal, gastric, prostate, and hematological cancers.

A synthesis of its molecular mechanisms reveals a consistent pattern of modulating the core PI3K/Akt/mTOR and MAPK signaling pathways. By targeting these central hubs of cancer cell proliferation and survival, Platycodin D exerts a foundational anti-cancer effect, leading to outcomes such as apoptosis, cell cycle arrest, autophagy, and the inhibition of metastasis.

The analysis places a special focus on Papillary Thyroid Carcinoma, where a critical finding has emerged. Platycodin D was shown to inhibit the pro-tumorigenic NF-κB signaling pathway, a key driver in thyroid cancer progression. Most significantly, this mechanism

appears to underlie its ability to enhance the therapeutic efficacy of the immune checkpoint inhibitor pembrolizumab. This positions Platycodin D as a promising immuno-sensitizing agent capable of potentially overcoming the resistance of immunologically "cold" tumors to immunotherapy, a major challenge in modern oncology.

In conclusion, the cumulative preclinical data strongly suggest that the most promising clinical path for Platycodin D is not as a standalone agent, but as a powerful adjuvant. Its demonstrated ability to act as a chemosensitizer, a targeted therapy sensitizer, and an immuno-sensitizer defines its potential to overcome drug resistance and enhance the efficacy of existing treatments. The translation of this promise into clinical reality will depend on overcoming significant formulation and bioavailability challenges, followed by rigorous, well-designed clinical trials to establish its safety and efficacy in human patients.

**Works cited**


1. Platycodon grandiflorum (Jacq.) A. DC.: A review of phytochemistry, pharmacology, toxicology and traditional use | Request PDF - ResearchGate, accessed June 30, 2025, https://www.researchgate.net/publication/363040997_Platycodon_grandiflorum_Jacq_A_DC_A_review_of_phytochemistry_pharmacology_toxicology_and_traditional_use
2. Chemical Characteristics of Platycodon grandiflorum and its Mechanism in Lung Cancer Treatment - Frontiers, accessed June 30, 2025, https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2020.609825/full
3. Platycodin-D Induced Autophagy in Non-Small Cell Lung Cancer Cells via PI3K/Akt/mTOR and MAPK Signaling Pathways - Journal of Cancer, accessed June 30, 2025, https://www.jcancer.org/v06p0623.htm
4. Platycodin D, a bioactive component of Platycodon grandiflorum, induces cancer cell death associated with extreme vacuolation - PMC, accessed June 30, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC6440520/
5. Killing cancer with platycodin D through multiple mechanisms - PMC, accessed June 30, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC4759477/
6. Platycodon grandiflorum Triggers Antitumor Immunity by Restricting PD-1

Expression of CD8+ T Cells in Local Tumor Microenvironment, accessed June 30, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC9046572/
7. The Pharmacological Effects and Health Benefits of Platycodon grandiflorus—A Medicine Food Homology Species - MDPI, accessed June 30, 2025, https://www.mdpi.com/2304-8158/9/2/142
8. The clinical effects of platycodon grandiflorum: A systematic review - ResearchGate, accessed June 30, 2025, https://www.researchgate.net/publication/353143190_The_clinical_effects_of_platycodon_grandiflorum_A_systematic_review
9. Platycodon - Wikipedia, accessed June 30, 2025, https://en.wikipedia.org/wiki/Platycodon
10. Unveiling the anticancer potential of platycodin D - PMC, accessed June 30, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC11609939/
11. Killing cancer with platycodin D through multiple mechanisms - PubMed, accessed June 30, 2025, https://pubmed.ncbi.nlm.nih.gov/26648178/
12. The pharmacology and mechanisms of platycodin D, an active ..., accessed June 30, 2025, https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2023.1148853/full
13. Platycodin D Induces Tumor Growth Arrest by Activating FOXO3a ..., accessed June 30, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC4997962/
14. Platycodin-D exerts its anti-cancer effect by promoting c-Myc protein ..., accessed June 30, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC10025306/
15. Platycodin D induces apoptosis through JNK1/AP-1 ... - Frontiers, accessed June 30, 2025, https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2022.1045375/full
16. Supplementary information to: Letter to the editor: UNVEILING THE ANTICANCER POTENTIAL OF PLATYCODIN D - EXCLI Journal, accessed June 30, 2025, https://www.excli.de/vol23/2024-7724/2024-7724.a1.pdf
17. Platycodin D, a metabolite of Platycodin grandiflorum, inhibits highly ..., accessed June 30, 2025, https://www.spandidos-publications.com/10.3892/or.2016.4935/download
18. Platycodin-D exerts its anti-cancer effect by promoting c-Myc protein ubiquitination and degradation in gastric cancer - Frontiers, accessed June 30, 2025, https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2023.1138658/full
19. Platycodin D confers oxaliplatin Resistance in Colorectal Cancer by activating the LATS2/YAP1 axis of the hippo signaling pathwa, accessed June 30, 2025, https://www.jcancer.org/v14p0393.pdf
20. Papillary Thyroid Cancer (PTC): Symptoms & Treatment, accessed June 30, 2025, https://my.clevelandclinic.org/health/diseases/23382-papillary-thyroid-cancer-ptc
21. Papillary Thyroid Cancer - Columbia University Department of Surgery, accessed June 30, 2025,

https://columbiasurgery.org/conditions-and-treatments/papillary-thyroid-cancer
22. Papillary thyroid cancer - Wikipedia, accessed June 30, 2025, https://en.wikipedia.org/wiki/Papillary_thyroid_cancer
23. Advances in Thyroid Cancer Research - NCI, accessed June 30, 2025, https://www.cancer.gov/types/thyroid/research
24. Personalized Approaches and Emerging Therapies Transform Thyroid Cancer Treatment, accessed June 30, 2025, https://www.targetedonc.com/view/personalized-approaches-and-emerging-therapies-transform-thyroid-cancer-treatment
25. What are the new drugs for Thyroid Cancer? - Patsnap Synapse, accessed June 30, 2025, https://synapse.patsnap.com/article/what-are-the-new-drugs-for-thyroid-cancer
26. What's New in Thyroid Cancer Research?, accessed June 30, 2025, https://www.cancer.org/cancer/types/thyroid-cancer/about/new-research.html
27. A Look at the Latest Advancements in Thyroid Cancer Treatment - Targeted Oncology, accessed June 30, 2025, https://www.targetedonc.com/view/a-look-at-the-latest-advancements-in-thyroid-cancer-treatment
28. Efficacy and safety of pembrolizumab monotherapy in patients with advanced thyroid cancer in the phase 2 KEYNOTE-158 study - PubMed, accessed June 30, 2025, https://pubmed.ncbi.nlm.nih.gov/36748723/
29. (PDF) Efficacy and safety of pembrolizumab monotherapy in patients with advanced thyroid cancer in the phase 2 KEYNOTE-158 study - ResearchGate, accessed June 30, 2025, https://www.researchgate.net/publication/368327131_Efficacy_and_safety_of_pembrolizumab_monotherapy_in_patients_with_advanced_thyroid_cancer_in_the_phase_2_KEYNOTE-158_study
30. Asiaticoside Down-Regulates HIF-1α to Inhibit ... - TRDizin, accessed June 30, 2025, https://search.trdizin.gov.tr/tr/yayin/detay/1263675/asiaticoside-down-regulates-hif-1a-to-inhibit-proliferation-migration-and-angiogenesis-in-thyroid-cancer-cells
31. High expression of PAFAH1B3 promotes the growth as well as, accessed June 30, 2025, https://oss.ejgo.net/files/article/20250115-1969/pdf/EJGO2024080802.pdf
32. Platycodin D inhibits the malignant progression of papillary thyroid carcinoma by NF-κB and enhances the therapeutic efficacy of pembrolizumab - 科研通, accessed June 30, 2025, https://www.ablesci.com/assist/detail?id=NA8I44
33. NF-κB in Thyroid Cancer: An Update - MDPI, accessed June 30, 2025, https://www.mdpi.com/1422-0067/25/21/11464
34. [RETRACTED ARTICLE] Suppressive effect of platycodin D on bladder cancer through microRNA-129-5p-mediated PABPC1/PI3K/AKT axis inactivation - SciELO, accessed June 30, 2025, https://www.scielo.br/j/bjmbr/a/3hCYTJB8FmsWBkrxyFJyV9r/?lang=en
35. Chrysin Activates Notch1 Signaling and Suppresses Tumor Growth ..., accessed June 30, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC3528831/
36. Chrysin activates Notch1 signaling and suppresses tumor growth of anaplastic

thyroid carcinoma in vitro and in vivo - PubMed, accessed June 30, 2025, https://pubmed.ncbi.nlm.nih.gov/22991264/
37. Chrysin inhibits growth and induces apoptosis of anaplastic thyroid cancer cells via Notch-1/Slug/PUMA, accessed June 30, 2025, https://e-century.us/files/ijcep/9/9/ijcep0032956.pdf
38. Broad-Spectrum Preclinical Antitumor Activity of Chrysin: Current Trends and Future Perspectives - MDPI, accessed June 30, 2025, https://www.mdpi.com/2218-273X/10/10/1374