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1,2,3,4,6-Penta-O-galloyl-β-D-glucopyranose: A Comprehensive Review of Its Biological Actions and Anti-Cancer Effects

Chenchen He[1], Minxuan Hou[2], Jiang Zhao[2], Xiangwei Wang[2], and Benyi Li[3]*

[1]Department of Radiation Oncology, The First Affiliated Hospital, Xi'An Jiaotong University, Xi'An 710061, China; [2]Department of Urology, The Affiliated Hospital, Guangdong Medical University, Zhanjiang 524001, China; [3]Department of Urology, The University of Kansas Medical Center, Kansas City, KS 66160, USA

* Corresponding author: Benyi Li, MD/PhD, KUMC Urology, 3901 Rainbow Blvd, Kansas City, KS 66160. Email: bli@kumc.edu.

ABSTRACT

The natural compound 1,2,3,4,6-Penta-O-galloyl-β-D-glucopyranose (PGG) is a hydrolyzable gallotannin abundantly found in numerous medicinal plants and widely recognized for its diverse pharmacological properties. This comprehensive review examines the biological actions of PGG with particular emphasis on its anti-cancer mechanisms. PGG exerts its anti-neoplastic effects through multiple molecular pathways, including direct protein targeting, modulation of key signaling cascades such as PI3K/AKT and MAPK, induction of apoptosis, and cell cycle arrest. Recent evidence has identified HER2 as a direct molecular target of PGG in colorectal cancer, while other studies have demonstrated its efficacy against gastric cancer, multiple myeloma, and various other malignancies. Beyond its anti-cancer properties, PGG exhibits significant anti-inflammatory, antioxidant, antimicrobial, and anti-diabetic activities. Despite its therapeutic promise, the clinical translation of PGG is hampered by poor oral bioavailability due to chemical instability under alkaline conditions, enzymatic degradation, and limited intestinal permeability. This review synthesizes current knowledge regarding PGG's mechanisms of action, pharmacokinetic limitations, and therapeutic potential, while identifying critical areas for future research to facilitate its development as a clinical candidate.

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1. Introduction

The pursuit of bioactive natural products as sources of novel therapeutic agents has remained a cornerstone of drug discovery for centuries. Among the vast array of phytochemicals with medicinal potential, hydrolyzable tannins represent a class of polyphenolic compounds that have garnered increasing scientific attention due to their diverse biological activities and structural complexity. 1,2,3,4,6-Penta-O-galloyl-β-D-glucopyranose (PGG) stands out as one of the most biologically potent members of this family [1].

PGG is a hydrolyzable tannin belonging to the gallotannin group, characterized structurally by a central β-D-glucose core esterified with five galloyl moieties at positions 1, 2, 3, 4, and 6 (Fig 1A). This unique structure, with the molecular formula $C_{41}H_{32}O_{26}$ and molecular weight of 940.68 g/mol, confers remarkable biological activity that exceeds that of its constituent gallic acid units [2]. The compound exists in two anomeric forms, with the β-anomer being far more prevalent in nature, while the α-anomer is relatively rare but has been synthesized chemically for structure-activity relationship studies [3].

PGG is widely distributed across the plant kingdom, having been identified in numerous medicinal plants traditionally used in various healing systems worldwide [2, 4]. Significant sources include species from the families: *Anacardiaceae* (including mango, *Mangifera indica*), *Paeoniaceae* (particularly *Paeonia suffruticosa* and *Paeonia lactiflora*), *Myrtaceae*, *Fabaceae*, and *Combretaceae* [2]. Plants such as *Rhus chinensis*, *Galla rhois*, *Phyllanthus emblica*, and *Schinus terebinthifolius* represent particularly rich sources [2, 4]. The historical use of these plants in traditional Chinese medicine, Ayurveda, and other ethnomedical systems for treating inflammatory conditions, infections, and potentially cancer provides a rich ethnopharmacological context for investigating PGG's therapeutic properties [2, 4].

The scientific interest in PGG has intensified over the past two decades, driven by accumulating

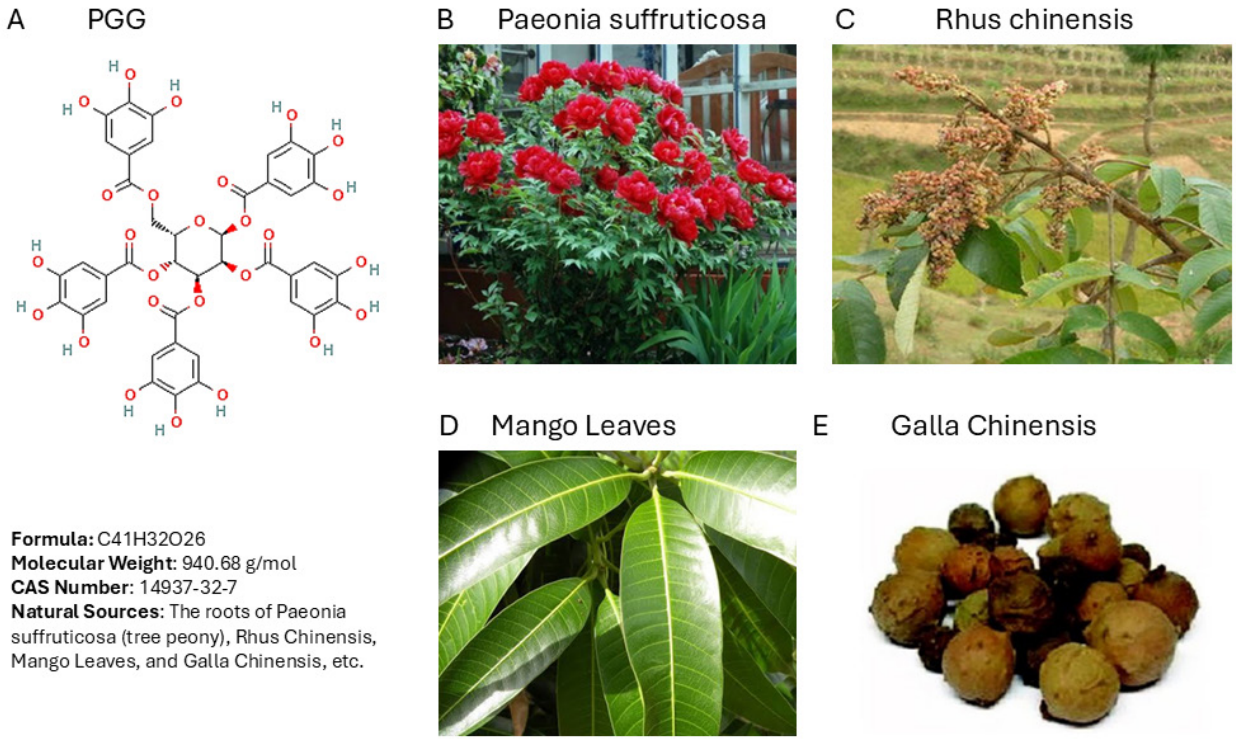

Figure 1. (A) Chemical structure of 1,2,3,4,6-Penta-O-galloyl-beta-D-glucose (PGG). The molecule comprises a central β-D-glucose (shown in pyranose form) esterified with gallic acid units at the 1, 2, 3, 4, and 6 positions. (Structure adapted from PubChem CID: 65238).
(B-E). Major natural sources of PGG extracts.

evidence of its broad-spectrum pharmacological activities [2-5]. Early studies established PGG as one of the most potent natural antioxidants, with radical-scavenging activity superior to many synthetic antioxidants, including butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) [6]. Subsequently, researchers have documented anti-inflammatory, antimicrobial, antiviral, anti-diabetic, and anti-cancer properties across multiple experimental models [2-5].

This review aimed to provide a comprehensive synthesis of current knowledge regarding PGG's biological actions, with particular emphasis on its anti-cancer mechanisms. We examined the molecular targets and signaling pathways modulated by PGG, discussed their effects in various cancer models, explored its broader pharmacological profile, and addressed the critical challenge of poor oral bioavailability that currently limits its clinical translation. By integrating findings from recent studies, this review identified both the therapeutic promise of PGG and the key obstacles that must be overcome to realize its clinical potential.

2. Chemical Properties and Sources

2.1 Structural Characteristics

The chemical structure of PGG is defined by a glucose core in the β-D-pyranose form, with all five hydroxyl groups esterified by gallic acid (3,4,5-trihydroxybenzoic acid) moieties (Fig 1). The International Union of Pure and Applied Chemistry (IUPAC) name [(2R,3R,4S,5R,6S)-3,4,5,6-tetrakis[(3,4,5-trihydroxybenzoyl)oxy]oxan-2-yl]methyl 3,4,5-trihydroxybenzoate reflects this complex architecture [2, 4]. This pentagalloylated structure creates a molecule with twenty phenolic hydroxyl groups, which are primarily responsible for its potent antioxidant activity through hydrogen donation and radical stabilization.

PGG exhibits high molecular weight and numerous hydrogen bond donors and acceptors, resulting in four violations of Lipinski's "Rule of Five," which typically predicts poor oral absorption for such molecules [7]. Nevertheless, computational models predicted high human intestinal absorption (0.997) and a 100% probability of achieving 20% oral bioavailability (Table 1). This apparent paradox may reflect active transport mechanisms or compound instability in the

Table 1. Physicochemical and pharmacokinetic properties of PGG

Property Category	Parameter	Value
Basic Information	Molecular Formula	$C_{41}H_{32}O_{26}$
	Molecular Weight	940.12–940.7 g/mol
	CAS Number	14937-32-7
Structural Features	Hydrogen Bond Donors	15
	Hydrogen Bond Acceptors	26
	Rotatable Bonds	16
	Topological Polar Surface Area	444.18 Å²
Lipophilicity	Log P (octanol-water)	2.246
	Log D (pH 7.4)	1.17
Drug-likeness	Lipinski's Rule Violations	4 (Rejected)
	Synthetic Accessibility	4.753
Absorption	Human Intestinal Absorption	0.997 (High probability)
	Caco-2 Permeability	-7.265 (Low)
	Oral Bioavailability (F20%)	1 (Positive prediction)
Distribution	Plasma Protein Binding	83.35%
	Volume of Distribution	0.289 L/kg
	Blood-Brain Barrier Penetration	0.002 (Low)
Metabolism	CYP450 Inhibition	Minimal (all isoforms <0.7)
	CYP450 Substrate	Minimal (all isoforms <0.05)
Excretion	Half-life	0.983 (arbitrary units)
	Clearance	15.905 (arbitrary units)

gastrointestinal tract, leading to absorption of degradation products. Indeed, gallotannins like PGG are known to undergo hydrolysis in the gut, potentially releasing bioavailable gallic acid moieties [8].

The compound's log P (octanol-water partition coefficient) of 2.246 indicates moderate lipophilicity, balancing aqueous solubility with membrane partitioning capacity. Plasma protein binding is approximately 83%, suggesting a substantial free fraction available for tissue distribution. The low predicted blood-brain barrier penetration (0.002) is favorable for non-brain tumor therapy, as it minimizes the potential for central nervous system toxicity (Table 1).

Metabolic profiling predicts minimal interaction with cytochrome P450 enzymes, both as substrate and inhibitor, suggesting low potential for drug-drug interactions. This is particularly relevant for combination therapy with chemotherapeutic agents that are CYP450 substrates. Toxicological predictions indicate low carcinogenic potential and acceptable safety margins, although comprehensive experimental toxicology studies remain necessary. A recent study in HCT116 colon cancer cells confirmed cellular uptake of PGG using ultra-performance liquid chromatography-mass spectrometry (UPLC-MS) [9]. Following treatment with 40 μM PGG for 12 hours, intracellular accumulation reached 204.5 ± 19.1 ng, providing direct evidence that the compound can enter cancer cells to engage intracellular targets.

The structure-activity relationship (SAR) of PGG has been partially elucidated through comparative studies with related compounds [4]. The presence of multiple galloyl groups is critical for biological activity, as compounds with fewer galloyl substitutions generally demonstrate diminished potency. The specific spatial arrangement of these galloyl groups around the glucose core enables simultaneous interactions with multiple binding sites on target proteins, explaining PGG's ability to modulate diverse molecular targets [2, 3].

2.2 Natural Sources and Biosynthesis

PGG occurs naturally in a wide array of medicinal plants, often as a key bioactive constituent. Comprehensive phytochemical surveys have identified PGG in over 50 plant species across more than 15 families. Particularly notable sources include the root bark of *Paeonia suffruticosa* (Moutan Cortex), a classic Chinese herbal medicine used for inflammatory conditions; the galls of *Rhus chinensis*, which produce some of the highest concentrations of gallotannins; and the seed kernels of *Mangifera indica* (mango),

which represent an abundant and sustainable source from agro-industrial by-products [4, 10].

The biosynthesis of PGG in plants proceeds through sequential galloylation of glucose, starting with β-glucogallin (1-O-galloyl-β-D-glucose) as the key intermediate. Specific galloyltransferases catalyze the position-specific addition of galloyl groups, ultimately yielding the fully substituted PGG molecule [10]. This compound serves not only as an end-product but also as a metabolic precursor for more complex ellagitannins through oxidative coupling of adjacent galloyl groups [2, 4].

2.3 Production Methods

Beyond natural extraction, PGG can be obtained through chemical synthesis and biotechnological approaches [2]. Chemical synthesis typically involves Steglich esterification of glucose with protected gallic acid derivatives, followed by deprotection steps. While feasible, these methods often suffer from low yields (typically 3-15%) and require multiple purification steps [4].

Biotechnological production using microbial or enzymatic systems offers an attractive alternative. Several microorganisms, including fungi such as *Aspergillus niger* and *Penicillium* species, as well as bacteria from the *genera Klebsiella* and *Lactobacillus*, can hydrolyze complex tannins to release PGG. Tannase enzymes specifically cleave galloyl esters and can be harnessed for controlled production of PGG from abundant tannic acid sources [4].

The utilization of agro-industrial by-products, particularly mango seed kernels, represents an economically and environmentally sustainable approach [10]. Mango processing generates vast quantities of seed waste that can be valorized through the extraction of PGG and related phenolics, simultaneously addressing waste management challenges and providing a cost-effective source of bioactive compounds [4, 10].

3. Pharmacokinetics and Bioavailability

3.1 Stability and Degradation

Despite its potent *in vitro* activities, the clinical development of PGG faces significant challenges related to its pharmacokinetic properties [2]. The stability of PGG is highly pH-dependent, with the compound demonstrating good stability under acidic conditions (pH 5-6) but rapid degradation under alkaline conditions (pH 7-8) [10]. This pH sensitivity has important implications for oral administration, as the compound must transit from the acidic stomach environment (where it remains stable) to the near-neutral small intestine, where degradation can occur [2]. In simulated intestinal fluid at pH 7.0, PGG undergoes progressive decomposition, yielding smaller phenolic fragments. This degradation likely involves hydrolysis of the ester bonds linking galloyl groups to the glucose core, though the exact degradation products and their biological activities require further characterization [4].

3.2 Intestinal Metabolism and Permeability

The intestinal epithelium presents multiple barriers to PGG absorption. Studies using CACO-2 cell monolayers, a well-established model of intestinal absorption, have revealed that PGG exhibits low absorptive permeability, with apparent permeability coefficients significantly lower than those of related compounds such as gallic acid and methyl gallate [10]. This poor permeability likely reflects the compound's high molecular weight (940 Da), extensive hydrogen bonding capacity, and hydrophilic character, all of which limit passive transcellular diffusion [10].

Furthermore, PGG undergoes extensive metabolism by intestinal enzymes. Incubation with CACO-2 cell lysates resulted in significant degradation of PGG, with evidence suggesting both enzymatic hydrolysis and non-specific protein binding contribute to the reduced recovery [4, 10]. The compound also interacts with gut microflora, as demonstrated by its degradation in rat fecal lysates, where microbial enzymes likely hydrolyze the galloyl esters to produce lower molecular weight metabolites [4, 10].

3.3 In Vivo Pharmacokinetic Studies

Currently, a few i*n vivo* pharmacokinetic studies have confirmed the predictions from *in vitro* models. When administered orally to rodents at doses as high as 80 mg/kg, plasma PGG concentrations remained below detectable limits, indicating extremely poor oral bioavailability [10]. This contrasts with intraperitoneal administration, which achieves micromolar plasma concentrations, demonstrating that the compound can achieve systemic exposure when parenteral routes are employed [10]. In contrast, the maximally tolerated dose was up to 200 mg/kg/day PGG, indicating an orally safe compound in mice [11].

The discrepancy between *in vitro* potency and *in vivo* oral efficacy observed in some studies suggests that either the administered PGG exerts local effects

within the gastrointestinal tract or that active metabolites contribute to the pharmacological effects [11]. Alternatively, the co-administration of PGG within complex botanical extracts may modify its pharmacokinetic behavior, as components within mango seed kernel extract appeared to influence the stability and recovery of PGG in experimental systems [10].

3.4 Implications for Drug Development

The poor oral bioavailability of PGG represents a critical barrier to its development as a conventional oral therapeutic. However, several strategies could potentially overcome this limitation. Formulation approaches, including the use of absorption enhancers, nanoparticle encapsulation, or prodrug strategies, may improve intestinal permeation. Alternatively, administration *via* non-oral routes (parenteral, transdermal, or inhalation) could bypass the gastrointestinal barriers. The development of synthetic analogs with improved pharmaceutical properties while retaining biological activity represents another promising direction [3, 4].

4. Anti-Cancer Effects and Molecular Mechanisms

4.1 Direct Molecular Targets

A major advance in understanding PGG's anti-cancer mechanism came with the recent identification of human epidermal growth factor receptor 2 (HER2) as a direct molecular target in colorectal cancer [9]. Using a combination of computational prediction and experimental validation, it was demonstrated that PGG directly binds to HER2, protecting the protein from pronase-induced degradation and enhancing its thermal stability in drug affinity responsive target stability (DARTS) and thermal shift assays [9].

HER2 (ErbB2) is a member of the epidermal growth factor receptor family that drives aberrant cell proliferation and survival when overexpressed or amplified [12]. While HER2 overexpression occurs in only 2-3% of colorectal cancer patients, it can function as a compensatory mechanism conferring resistance to EGFR-targeted therapies [9, 13]. The identification of PGG as a HER2-binding compound with subsequent suppression of HER2 expression and inhibition of the downstream PI3K-AKT-mTOR pathway provides a mechanistic rationale for its anti-proliferative effects in HER2-expressing cancers [9].

Computational docking studies suggested that PGG interacts with the ATP-binding pocket of HER2, potentially competing with ATP binding. Functional rescue experiments using the HER2 inhibitor lapatinib provided further support for HER2 as a relevant target, as combination treatment failed to produce additive effects, consistent with both compounds acting through the same pathway [9].

Beyond HER2, PGG likely interacts with multiple protein targets. Early studies identified inhibition of mammalian DNA polymerases as a potential mechanism, with PGG demonstrating nanomolar inhibitory activity against select polymerases [3]. The polyphenolic structure of PGG enables multifarious interactions with proteins through hydrogen bonding and hydrophobic contacts, potentially explaining its ability to modulate diverse signaling pathways [2-4].

4.2 Effects on Colorectal Cancer

PGG exhibits multiple anti-cancer activities in CRC models. Earlier studies demonstrated anti-proliferative effects through modulation of apoptosis-associated proteins, including caspase-3, cyclin E, Bcl-2, and CDK2 [14]. More recent work from the same group revealed anti-metastatic effects mediated through modulation of cathepsin B-driven extracellular matrix remodeling and epithelial-mesenchymal transition [15].

The identification of HER2 as a PGG target has relevance for CRC therapy [9]. Although HER2 amplification is infrequent in CRC, its presence predicts resistance to EGFR inhibitors, and HER2-targeted therapy (e.g., tucatinib) has received FDA approval for CRC treatment [13]. PGG's ability to bind HER2 and suppress downstream signaling positions it as a potential HER2-targeted therapeutic, though direct comparisons with approved HER2 inhibitors regarding potency and selectivity require further investigation [9].

5-Fluorouracil (5-FU) has been the backbone of CRC chemotherapy for decades, yet resistance develops in the majority of patients with advanced disease [16]. In a recent study, using 5-FU-resistant CRC cell lines, three-dimensional spheroid cultures, subcutaneous xenografts, and metastatic mouse models, the authors demonstrated that PGG exhibits potent activity against chemo-resistant disease [17]. Briefly, PGG treatment effectively eliminated cancer stem cells, as evidenced by reduced expression of cancer stem cell (CSC) markers (CD133 and CD44) and diminished spheroid-forming capacity. Concurrently, PGG suppressed EMT-driven invasion and metastasis, downregulating mesenchymal markers N-cadherin and vimentin while upregulating epi-

thelial markers. These phenotypic changes were accompanied by induction of apoptosis, demonstrated by cleavage of poly(ADP-ribose) polymerase (PARP) and caspase-3, and downregulation of the anti-apoptotic protein Bcl-2 [17]. Transcriptomic analysis coupled with mechanistic studies revealed that PGG selectively inhibits the JAK1/JAK3-STAT3 signaling pathway [17]. The compound substantially reduced STAT3 phosphorylation at tyrosine 705, the activating phosphorylation site required for dimerization, nuclear translocation, and transcriptional activity. This inhibition was specific to JAK1 and JAK3, with minimal effects on other STAT family members or upstream kinases [17]. Pharmacological inhibition of JAK-STAT signaling phenocopied PGG effects, while STAT3 overexpression partially rescued cells from PGG-induced cytotoxicity, confirming pathway specificity [17].

The convergence of PGG's effects on CSCs and EMT through JAK-STAT3 inhibition is particularly significant. STAT3 directly regulates the transcription of genes involved in stem cell maintenance (NANOG, OCT4, SOX2) and EMT (SNAIL, TWIST, ZEB1) [18]. By intercepting this signaling node, PGG simultaneously addresses two interconnected drivers of chemo-resistance and metastatic progression. These findings position PGG as a promising agent for salvage therapy in patients with 5-FU-resistant colorectal cancers, a population with limited treatment options [16].

4.3 Effects on Gastric Cancer

Recent studies have extended the anti-cancer profile of PGG to gastric cancer, the fifth most common cancer worldwide [2]. Using network pharmacology approaches, researchers predicted that PGG might inhibit gastric cancer through modulation of PI3K/AKT and MAPK signaling pathways, predictions subsequently validated through *in vitro* and *in vivo* experiments [19].

In mouse forestomach carcinoma (MFC) cells, PGG treatment inhibited proliferation, reduced colony formation, and induced apoptosis in a dose-dependent manner. Mechanistic investigations revealed that PGG treatment reduced mitochondrial membrane potential and increased reactive oxygen species (ROS) generation, consistent with induction of mitochondrial-mediated apoptosis [20].

In vivo, PGG significantly inhibited the growth of subcutaneous MFC xenografts in mice without obvious toxicity to the animals. Analysis of tumor tissues confirmed induction of apoptosis (increased TUNEL staining) and modulation of apoptosis-related gene expression. Specifically, PGG treatment upregulated expression of pro-apoptotic BAX and caspase-3 while downregulating anti-apoptotic Bcl-2 at both mRNA and protein levels. These effects were accompanied by inhibition of AKT phosphorylation and modulation of MAPK-P38 signaling, confirming the pathway predictions from network pharmacology [20].

4.4 Effects on Multiple Myeloma

Multiple myeloma (MM), an incurable malignancy of plasma cells, represents another cancer type susceptible to PGG's anti-proliferative effects [21]. Studies on MM cell lines demonstrated dose- and time-dependent growth inhibition accompanied by G_1 phase cell cycle arrest and induction of apoptosis, as evidenced by increased Annexin V staining, enhanced caspase-3/7 activity, and accumulation of cleaved caspase-3 [21].

A particularly significant finding in MM was the suppression of MYC expression by PGG at both mRNA and protein levels. MYC is frequently hyperactivated in MM and represents an attractive therapeutic target, as MYC inhibition leads to MM cell death [22]. PGG treatment also reversed the expression of MYC target genes, including p21, p27, and cyclin D2, consistent with functional inhibition of MYC transcriptional activity [21]. Interestingly, combination studies revealed context-dependent interactions with proteasome inhibitors. PGG antagonized the cytotoxic effects of bortezomib, a first-line proteasome inhibitor used in MM therapy [23], while sensitizing cells to the investigational proteasome inhibitor MG132. These findings raise important considerations for potential clinical combinations and highlight the need for careful evaluation of drug interactions [21].

4.5 Effects on Other Cancer Types

The anti-cancer activity of PGG extends to numerous other malignancies [2]. Comprehensive reviews have documented effects against prostate cancer, lung cancer, breast cancer, liver cancer, leukemia, and melanoma [2-4]. In prostate cancer cells, PGG induced both S-phase and G1-phase cell cycle arrests through targeting DNA replication and cyclin D1 expression [3, 24]. PGG also induced p53 expression but inhibited STAT3 signaling in prostate cancer cells *in vitro* and suppressed prostate xenograft tumor growth *in vivo* [25]. Interestingly, a PGG-rich *Trapa*

bispinosa Roxb. pericarp extract (TBE) showed concentration-dependent inhibitory effects in the 5α-reductase activity assay, leading to suppressed prostate cell proliferation, and expressions of prostate-specific antigens and transmembrane protease serine 2 in a castrated benign prostatic hyperplasia mouse model [26].

In breast cancer models, PGG exerts anti-estrogen receptor signaling, a pathway frequently dysregulated in hormone-responsive cancers [27]. PGG was also reported to induce G1/S phase arrest in human breast cancer cells and was orally active against triple-negative xenograft growth [28].

In pancreatic cancer models, PGG was shown to inhibit a critical E2 enzyme in the ubiquitin-proteasome system UBE2T (Ubiquitin-conjugating enzyme E2 T), resulting in p53 degradation and glycolysis alteration [29], potentiating gemcitabine efficacy [30], and overcoming Kras/G12D inhibitor MRTX1133-resistance [31].

In posterior fossa type A ependymoma, CXorf67 gene upregulation was found to sensitize tumor cells to PARP inhibitors by suppressing the PALB2-BRCA2 interaction [32], and treatment with PGG was found to disrupt the PALB2-BRCA2 interaction and potentiate tumor sensitivity to PARP inhibitors and radiotherapy *in vitro* and *in vivo* [33].

The breadth of PGG's anti-cancer activity across diverse tumor types suggests that it acts through fundamental cellular processes rather than a single tumor-specific target [2]. This multi-targeted mechanism may offer advantages in terms of preventing or overcoming resistance, though it also raises concerns about potential off-target effects [2].

4.6 Apoptosis Induction and Cell Cycle Regulation

Across multiple cancer models, PGG consistently induces apoptosis through both intrinsic and extrinsic pathways. Mitochondrial involvement is evidenced by loss of mitochondrial membrane potential, increased ROS generation, and modulation of Bcl-2 family proteins (downregulation of anti-apoptotic Bcl-2, upregulation of pro-apoptotic Bax) [20]. Activation of executioner caspases, particularly caspase-3, represents a common downstream event.

Cell cycle analysis reveals context-dependent effects on cell cycle progression. In multiple myeloma cells, PGG induced G1 phase arrest [21]. In prostate cancer cells, both S-phase and G1-phase arrests were observed, associated with downregulation of cyclin D1 and inhibition of DNA replication [28]. These effects likely result from modulation of multiple cell cycle regulatory proteins, including cyclins, cyclin-dependent kinases, and CDK inhibitors [2].

4.7 Signaling Pathway Modulation

PGG modulates several major signaling pathways implicated in cancer pathogenesis. The PI3K/AKT pathway, a central regulator of cell survival and metabolism, is inhibited by PGG across multiple cancer types [3]. This inhibition occurs downstream of receptor tyrosine kinases, including HER2, with reduced AKT phosphorylation leading to decreased phosphorylation of downstream effectors such as mTOR [13].

The MAPK pathway, particularly the p38 MAPK branch, is also modulated by PGG. In gastric cancer cells, PGG activated p38 signaling while inhibiting AKT, suggesting complex pathway crosstalk [19, 20]. The net effect on cell fate likely depends on the relative contribution of these pathways in specific cellular contexts.

NF-κB signaling, a master regulator of inflammation and cell survival, represents another PGG-sensitive pathway [34]. In UVB-irradiated human dermal fibroblasts and mouse skin, PGG inhibited NF-κB activation and MAPK signaling, contributing to its photoprotective and anti-inflammatory effects [34, 35]. This NF-κB inhibition may also contribute to anti-cancer activity, given the role of constitutive NF-κB activation in many malignancies [35].

5. Other Biological Activities

5.1 Anti-Inflammatory Effects

PGG exhibits potent anti-inflammatory activity through multiple mechanisms. In human neutrophils, PGG significantly down-regulated L-selectin expression, resulting in reduced neutrophil-endothelial attachment [35]. This effect may explain the anti-inflammatory activity of PGG-rich plant extracts and suggests potential applications in inflammatory diseases characterized by excessive neutrophil recruitment [34].

The compound also inhibits key inflammatory enzymes, including inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), reducing production of nitric oxide and prostaglandins [36]. These effects, combined with inhibition of NF-κB signaling, position PGG as a multi-target anti-inflammatory agent [2-4].

In models of UVB-induced skin damage, PGG protected against inflammatory responses by tar-

geting both NF-κB and MAPK signaling pathways, demonstrating potential for preventing environmental stimuli-induced inflammatory skin damage [37].

5.2 Antioxidant Activity

PGG is recognized as one of the most potent antioxidant tannins, with radical-scavenging activity exceeding that of many standard antioxidants [35, 38]. The IC_{50} for radical scavenging is approximately 7.1 μM, significantly lower than that of gallic acid (12.1 μM) [4]. This enhanced activity results from the presence of multiple galloyl groups, each contributing phenolic hydrogens capable of quenching free radicals [3, 6, 39].

The antioxidant mechanism involves direct radical scavenging, metal chelation, and potentially induction of endogenous antioxidant enzymes [3, 6]. This multifaceted antioxidant activity likely contributes to PGG's protective effects in various disease models involving oxidative stress [3, 4, 6, 40].

5.3 Antimicrobial and Antiviral Activities

PGG demonstrates antimicrobial activity against various bacterial pathogens, including methicillin-resistant Staphylococcus aureus (MRSA), and inhibits bacterial biofilm formation [3, 41]. These effects may involve membrane disruption, inhibition of bacterial enzymes, and interference with quorum sensing [41-43].

Antiviral activity has been documented against the hepatitis B virus (HBV), where PGG reduced extracellular HBV levels and decreased HBsAg production in a dose-dependent manner [44]. The gallate structure appears critical for this anti-HBV activity [44]. PGG also exhibits anti-HCV entry into host cells [45]. PGG's anti-parasitic activity against Trypanosoma cruzi, the causative agent of Chagas disease, was reported with EC_{50} values (67 μM) significantly lower than the standard drug benznidazole [46].

5.4 Anti-Diabetic Potential

PGG has demonstrated anti-diabetic properties in experimental models, including inhibition of α-glucosidase and α-amylase, enzymes responsible for carbohydrate digestion [2, 3, 47-49]. By delaying glucose absorption, PGG may help control postprandial hyperglycemia [4, 47]. Additionally, PGG inhibits islet amyloid polypeptide (IAPP) aggregation, a process implicated in pancreatic β-cell dysfunction in type 2 diabetes [50]. These findings suggest PGG could serve as a lead compound for developing anti-diabetic therapeutics.

5.5 Neuroprotective Effects

Emerging evidence suggests neuroprotective potential for PGG, particularly in Alzheimer's disease [34]. PGG and Paeonia suffruticosa extracts containing PGG demonstrated potent inhibitory effects on amyloid β (Aβ) fibril formation *in vitro* and *in vivo*, suggesting potential for disease-modifying therapy in Alzheimer's disease [51-53]. A scoping review published in 2025 highlighted the promise of PGG in targeting Alzheimer's disease hallmarks, though the authors emphasized the need for further in vivo studies to validate therapeutic potential [34].

5.6 Anti-glycolysis effect

The Warburg effect with excessive glycolytic activity is a hallmark of cancer cell glucose metabolism [54]. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) is a rate-controlling enzyme by catalyzing the conversion of D-glyceraldehyde 3-phosphate to D-glycerate 1,3-bisphosphate in the 6th critical step in glycolysis; therefore, it exerts a metabolic flux control role during aerobic glycolysis as an attractive therapeutic target for cancer treatment [55, 56]. A recent study demonstrated that PGG is a reversible GAPDH inhibitor with Ki = 0.5 μM *via* a NAD^+ and Pi competitive mechanism [57].

Another characteristic feature in aggressive malignancy is the overexpression of lactic acid dehydrogenase-a (LDH-A), a key enzyme in glycolytic flux, leading to pericellular accumulation of lactate [58, 59]. Previous studies showed that PGG was a primary constituent (present at ~9.95 ± 0.34% dry weight) responsible for Galla Chinensis extract-induced LDHA inhibition (IC_{50} < 1 μg/ml) [60]. Further studies suggested that PGG acts through a reversible competitive binding mechanism at the NADH cofactor site with an IC_{50} of 27.32 nM [60].

5.7 Vascular Health Effects

Good vascular health is crucial for preventing life-threatening conditions like heart attack, stroke, and peripheral artery disease [61]. Multiple studies showed that nanoparticle-encapsulated PGG preparation showed reduction in ROS and MMP-2 secretion in mouse myoblast C2C12 cells, an in vitro model for vascular extracellular matrix study, and induced a significant recovery in the elastic properties after enzymatic extracellular matrix (ECM) degradation [62]. This result provided preliminary support for the PGG use in the treatment of abdominal aortic aneurysms (AAA), which is a life-threatening weak-

ening and expansion of the abdominal aorta due to inflammatory cell infiltration and ECM degeneration [63]. Consistently, in a mouse model, nanoparticles loaded with PGG *via* the intravenous route at a dose of 10 mg/kg of body weight reversed the AAA by decreasing matrix metalloproteinases MMP-2/9 and the macrophage infiltration in the medial layer [64]. Further investigation is warranted for PGG use in vascular health, as outlined [5].

6. Future Perspectives and Conclusion

6.1 Challenges and Opportunities

The development of PGG as a therapeutic agent faces several significant challenges, chief among them being poor oral bioavailability. The compound's instability in intestinal conditions, extensive metabolism, and low permeability collectively limit systemic exposure following oral administration. Overcoming this barrier will require innovative formulation strategies, prodrug approaches, or the development of synthetic analogs with improved pharmaceutical properties.

The multi-targeted mechanism of PGG, while potentially advantageous for efficacy, raises questions about selectivity and potential off-target effects. Comprehensive toxicological studies are needed to establish safety profiles and therapeutic windows. Encouragingly, available evidence suggests minimal toxicity in animal models at efficacious doses, but systematic evaluation remains necessary [20].

6.2 Addressing Knowledge Gaps

Despite significant progress, several critical questions remain unanswered regarding PGG's therapeutic potential:

1. Pharmacokinetics and bioavailability: While computational models predict favorable absorption, experimental pharmacokinetic studies in relevant animal models are urgently needed. The high molecular weight and numerous hydrogen bond donors raise questions about oral bioavailability that can only be resolved through *in vivo* assessment. Tissue distribution studies would confirm whether PGG reaches tumor tissues at therapeutically relevant concentrations, and whether accumulation occurs in normal tissues that might be sites of toxicity. A liquid-liquid extraction and reverse-phase HPLC-based protocol for in vivo PK/PD analysis was established [65].
2. Optimal dosing and scheduling: Preclinical studies have employed various concentrations and dosing regimens, but systematic dose optimization studies are lacking. Determination of the maximum tolerated dose, dose-limiting toxicities, and schedule-dependent effects in animal models would inform future clinical trial design.
3. Comprehensive toxicology: Although computational predictions suggest low toxicity, comprehensive GLP toxicology studies are required before first-in-human trials. Particular attention should be paid to gastrointestinal effects, given the compound's polyphenolic nature and structural similarity to tannins that can cause gastrointestinal irritation at high doses.
4. Biomarker identification: The identification of HER2 as a PGG target raises the possibility that HER2 expression or amplification could serve as a predictive biomarker for patient selection. Similarly, baseline JAK-STAT activation status might identify tumors most likely to respond. Retrospective analysis of preclinical models and prospective biomarker validation in clinical trials would facilitate precision medicine approaches.
5. Mechanistic depth: While direct HER2 binding has been demonstrated, the precise binding site and structural basis of interaction remain to be elucidated. Crystallographic or NMR studies of the PGG-HER2 complex would provide atomic-level insights that could guide analog development. Similarly, whether PGG directly binds JAK kinases or modulates their activity through indirect mechanisms requires further investigation.

6.3 Research Priority areas for future research

1. Structural optimization: Development of PGG analogs with improved bioavailability while retaining biological activity. Structure-activity relationship studies have already identified critical structural features, providing a foundation for rational design [3].
2. Target identification: Continued efforts to identify direct protein targets of PGG, building on the recent identification of HER2 [9]. Understanding the complete target profile will facilitate the prediction of efficacy and toxicity.

3. Combination studies: Systematic evaluation of PGG in combination with approved chemotherapeutic and targeted agents. The observed antagonism with bortezomib in multiple myeloma highlights the importance of such studies [21].
4. Advanced formulations: Development of delivery systems (nanoparticles, liposomes, cyclodextrin complexes) to enhance bioavailability and enable targeted delivery [31].
5. Clinical translation: Progression from preclinical studies to early-phase clinical trials, beginning with topical or locally administered formulations that bypass bioavailability limitations.

6.3 Conclusion

The hydrolyzable tannin 1,2,3,4,6-Penta-O-galloyl-β-D-glucopyranose represents a fascinating natural product with diverse biological activities and significant therapeutic potential. Its anti-cancer effects, mediated through direct protein targeting (including HER2) and modulation of key signaling pathways (PI3K/AKT, MAPK, NF-κB), have been documented across multiple cancer types. Beyond oncology, PGG exhibits anti-inflammatory, antioxidant, antimicrobial, anti-diabetic, and neuroprotective properties that warrant further investigation. The recent identification of HER2 as a direct molecular target provides a mechanistic framework for understanding PGG's anti-proliferative effects in HER2-expressing cancers and positions it within the context of targeted cancer therapy. Concurrent advances in understanding its pharmacokinetic limitations highlight both the challenges to clinical translation and potential strategies to overcome them. As research continues, PGG stands as a compelling example of how traditional medicinal plants can yield structurally unique molecules with unexpected therapeutic mechanisms. Whether through development of the natural compound itself, synthetic analogs, or formulation strategies that circumvent bioavailability limitations, PGG holds promise as a contributor to future therapeutic options for cancer and other diseases.

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