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Posted Date: 19 February 2026

doi: 10.20944/preprints202602.1086.v1

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Review

Translational Potential and Pharmacokinetic Challenges of Procyanidin C1 as a Next-Generation Senotherapeutic Agent

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Abstract

Procyanidin C1 (PCC1), a B-type procyanidin trimer derived from natural sources, has recently garnered significant attention in preclinical models due to its potential to specifically induce apoptosis in senescent cells (senolytic activity) and extend healthspan. However, existing data reveal a pronounced pharmacological paradox: the *in vitro* induction of apoptosis in senescent cells typically requires high micromolar concentrations (>50 μ M), whereas *in vivo* peak plasma concentrations following intraperitoneal (i.p.) injection in mice are distributed around the 2-15 μ M range, and oral (p.o.) administration yields nanomolar exposure levels (~0.04 μ M), often falling below this threshold. This study aims to construct an objective translational medicine evaluation framework by systematically integrating cellular pharmacodynamic thresholds, *Caco-2* transmembrane transport mechanisms, and *in vivo* pharmacokinetic (PK) data. The analysis indicates that even with i.p. administration, systemic plasma concentrations of PCC1 struggle to sustainably reach the cytotoxicity thresholds established *in vitro*; its *in vivo* efficacy is likely derived from high accumulation and localized concentration effects within specific tissues (e.g., adipose, lymphoid tissue). Further analysis points out that high-dose application may face dual barriers of safety risks and economic costs. It is postulated that combining modern nanodelivery technologies with synthetic biology to enhance bioavailability and achieve dosage minimization represents a critical pathway for the safe, economical, and efficient clinical translation of PCC1.

Keywords: procyanidin C1; senolytics; pharmacokinetics; bioavailability; drug delivery systems; translational medicine

1. Positioning of PCC1 in Senescence Intervention and PK Bottlenecks

In the context of interventions targeting cellular senescence, the development of pharmacological agents capable of selectively eliminating senescent cells (senolytics) while simultaneously suppressing the senescence-associated secretory phenotype (SASP) represents a pivotal strategy for mitigating age-related physiological decline and treating age-related diseases [1,2]. Early synthetic precursors such as Navitoclax (ABT-263) demonstrated significant clearing efficacy, yet their application in prophylactic settings for healthy populations is substantially constrained by off-target toxicities, most notably thrombocytopenia [3–5]. Against this backdrop, Procyanidin C1 (PCC1), a polyphenolic compound abundant in grape seed extracts (GSE) and peanut skins, has been identified as a potential next-generation senolytic candidate owing to its observed lifespan-extending effects in murine models and its relatively favorable safety profile [6].

Research by Xu *et al.* first proposed that PCC1 specifically induces apoptosis in senescent cells by triggering reactive oxygen species (ROS) generation, leading to mitochondrial dysfunction [7]. However, the clinical translation of PCC1 should withstand the scrutiny of pharmacokinetic (PK)

laws. It is imperative to examine the physiological barriers this molecule faces when transitioning from *in vitro* to *in vivo* environments under a rigorous pharmacokinetic/pharmacodynamic (PK/PD) framework. Failure to effectively bridge the gap between the high effective concentrations required *in vitro* and the actual low exposure levels *in vivo* may lead to directional uncertainty regarding the prospects of PCC1 clinical translation and practical application.

2. Pharmacodynamic Landscape of PCC1

A comprehensive analysis of reported biological effects indicates that the action mode of PCC1 is characterized by a distinct dose-dependent biphasic profile rather than a single linear relationship. This mechanistic stratification is supported by data across multiple cellular models.

Table 1. Statistical Summary of PCC1 Effective Dosages and *in vitro* Pharmacological Effects.

Cell Type	Tissue Origin	Induction Method	Concentration (μM)	Time	Pharmacological Effect (Mechanism)	Ref.
PSC27	Human Prostate Stroma	Bleomycin / Replicative	50-200 μM	72h	Senolytic: Dose-dependent apoptosis induction; upregulation of PUMA/NOXA; increased ROS.	[7]
PSC27	Human Prostate Stroma	Bleomycin	< 50 μM	72h	Senomorphic: Inhibition of NF-κB nuclear translocation; reduction in IL-6/IL-8 secretion.	[7]
HK2	Human Renal Tubular	Radiation / UUO Model	50-100 μM	24-48h	Senolytic: Elimination of p21+ cells via ANGPTL4/NOX4 signaling.	[8]
Lung Fibroblasts	Murine Primary Lung	Radiation (10 Gy)	100 μM	48h	Senolytic: Selective clearance of senescent myofibroblasts; inhibition of ECM deposition.	[9]
L929	Murine Fibroblasts	D-Galactose (D-Gal)	12.5-25 μM	5d	Senomorphic: Downregulation of senescence (p16, p21) and fibrotic markers (α-SMA).	[10]

HCT116	Human Colorectal Cancer	Tumor Model	5-10 μ M	24-72h	Antitumor: Modulation of miR-501-3p/HIGD1A axis; inhibition of proliferation and metastasis.	[11]
RAW 264.7	Murine Macrophage	LPS / IFN- γ	10-50 μ M	24h	Immunomodulation: Activation of NF- κ B and MAPK pathways; promotion of Th1 polarization.	[12]

The aggregated data in **Table 1** indicate that PCC1 demonstrates a broader spectrum of anti-aging activity compared to other natural senolytics such as quercetin and fisetin, with effects covering cell types of diverse tissue origins [13–18]. This suggests that if PCC1 can be successfully applied to humans, it could be utilized for anti-aging at a broader organ and tissue level. However, achieving comparable senolysis (direct induction of cell death) in human cell models typically requires maintaining extracellular concentrations above 50 μ M. The determination of this threshold may be influenced by the chemical properties of polyphenolic compounds [19,20].

Literature indicates that polyphenols are often classified as Pan-Assay Interference Compounds (PAINS), whose catechol-rich structures are prone to non-specific binding with serum proteins (e.g., albumin) in culture media [21]. This implies that the nominal concentration in *in vitro* experiments may be higher than the actual effective free fraction. Consequently, the *in vitro* requirement of 50 μ M likely includes a certain proportion of protein-binding loss. On the other hand, data from Table 1 reveal a potential low-dose therapeutic window: in the 10-25 μ M range, while PCC1 does not induce widespread apoptosis, it significantly inhibits the NF- κ B signaling pathway, thereby blocking SASP release. This senomorphic effect provides a pharmacological basis for dose optimization.

3. Translational Medicine Challenges: Physiological Barriers and Exposure Disparities

To evaluate the feasibility of achieving the aforementioned effective concentrations in the human body, it is necessary to analyze administration routes and physical barriers from a PK perspective. **Table 2** presents statistics on the administration cycles and intervention effects of PCC1 in different animal models. Intraperitoneal (i.p.) injection of dosages above 20 mg/kg is currently the general dosage and administration method in animal research. Significantly, it is also reported that daily oral gavage of 8 mg/kg PCC1 over the long term enhanced retinal and bone marrow hematopoietic functions in mice [6,18]. When adjusted for body surface area, this regimen translates to a daily intake of *ca.* 45 mg for a 75-kg human.

Table 2. Dosage Cycles of PCC1 and Efficacy Statistics in Animal Models.

Disease Model	Strain	Dosage	Route	Frequency	Therapeutic Goal & Outcome	Ref
Natural Aging	C57BL/6	20 mg/kg (Phosal/PEG system)	i.p.	Every 2 weeks	Extended remaining lifespan (64.2%); reduced all-cause mortality.	[7]
Chemo-induced Senescence	NOD-SCID	20 mg/kg (Phosal/PEG system)	i.p.	Weekly	Clearance of chemotherapy-induced senescent stromal cells in tumor microenvironment.	[7]
Renal Fibrosis (UUO)	C57BL/6	20 mg/kg	i.p.	Twice weekly	Clearance of Senescent-TECs; reversal of renal interstitial fibrosis.	[8]
Lung Fibrosis (BLM)	C57BL/6	20 mg/kg	i.p.	Weekly	Promotion of apoptosis in senescent myofibroblasts; improvement of lung function.	[9]
Colorectal Cancer	BALB/c Nude	40 mg/kg	i.p.	Every 3 days	Inhibition of tumor growth and liver/lung metastasis.	[11]
Natural Aging (Retina)	C57BL/6	8 mg/kg (Diet)	p.o.	Daily	Alleviation of structural and functional decline in the aged retina.	[6]
Natural Aging (Immune)	C57BL/6	8 mg/kg (Diet)	p.o.	Daily	Increased proportion of B cells and HSCs; restoration of immune homeostasis.	[18]

3.1. PK Limitations of i.p. Injection

Although i.p. injection is commonly used in animal experiments, the blood concentration of PCC1, as a procyanidin trimer, remains physiologically limited. Due to the lack of direct PK data for PCC1, the key PK parameters (**F** and **Vd**) based on structurally similar homologs are estimated in **Table 3**. In parallel, the PK profiles of PCC1 were evaluated in C57BL/6 mice using i.p. injection (20 mg/kg) and alternative delivery formulations in our lab recently.

Given that the vast majority of existing literature employs aqueous PCC1 solutions for intraperitoneal administration, with only one notable exception utilizing a Phosal/PEG system [7], we evaluated the pharmacokinetic limitations of PCC1 (20 mg/kg) when administered in a standard

PBS vehicle. Although the compound exhibited rapid absorption kinetics ($T_{max} = 15 \text{ min}$) consistent with a true solution, the observed C_{max} of 12–15 μM deviated significantly from the theoretical stoichiometric projection of $\sim 57.7 \text{ }\mu\text{M}$. This substantial bioavailability deficit ($\sim 75\%$ loss) could suggest that the aqueous formulation promotes absorption primarily *via* the visceral peritoneum into the portal venous system, rather than the lymphatic pathway utilized by lipid-based carriers [7]. Consequently, the drug is subjected to extensive hepatic first-pass metabolism immediately upon absorption, which severely curtails systemic exposure. As a result, the circulating concentration remains restricted to a senomorphic window, insufficient to reach the $>50 \text{ }\mu\text{M}$ threshold required for inducing ROS-mediated apoptosis in senescent cells.

Table 3. Inferential Pharmacokinetic Estimation for PCC1 (i.p., 20 mg/kg).

Parameter	Theoretical Value (Math Model)	Actual Value (Observed)	Key Insight
Input Dose	20 mg/kg	20 mg/kg	Identical input.
C_{max} (Peak)	Ca. 57.7 μM ^a	12 - 18 μM ^b	75% Loss: Massive first-pass metabolism by the liver.
T_{max} (Time)	10 - 20 min	15 min	Rapid Absorption: Behaves as a true solution.
Bioavailability	100% (Ideal)	$\sim 25\%$ (Calculated)	Portal Vein Route: Forces drug through liver before circulation.

a: Calculation (Source of 57.7 μM): Based on formula: $C_{max} = \text{Dose} / V_d$; Assumed $V_d = 0.4 \text{ L/kg}$ (extracellular fluid distribution); Calculation: $20 \text{ mg/kg} / 0.4 \text{ L/kg} = 50 \text{ mg/L} = 57.7 \text{ }\mu\text{M}$ (MW: 866.77). **b:** Data Source of 12-18 μM : Unpublished data derived from our lab work: C57BL/6 mice administered 20 mg/kg PCC1 (Pure) in PBS *via* i.p. injection.

Above data suggests that the current *in vivo* efficacy of PCC1 observed in most studies may not be primarily driven by transient plasma concentrations but is likely related to its tissue distribution characteristics. Polyphenols typically possess relatively high lipophilicity, tending to distribute from the systemic circulation to specific tissues. Data from Wang *et al.* confirmed the enrichment of PCC1 in mesenteric white adipose tissue [22]. Therefore, the localized accumulation concentration in target tissues may exceed circulating plasma concentrations, thereby achieving effective therapeutic levels within the local microenvironment. In future, the clinical application strategy for PCC1 may need to focus on this unique high tissue accumulation characteristic. In specific pathological states, tissue-specific distribution of the drug may compensate for insufficient systemic exposure. For example, in intestinal disease models, PCC1 may demonstrate local therapeutic advantages. Drug remaining in the intestinal lumen after p.o. administration can directly contact damaged epithelial cells; concurrently, drug components transported via the lymphatic system may enrich in mesenteric lymph nodes [24,25].

3.2. Bioavailability Barriers of p.o. Administration

Compared to the aforementioned i.p. injection, p.o. administration faces more significant physical barriers. *In vitro* studies by Hemmersbach *et al.* confirmed that transmembrane transport of PCC1 is restricted by Caco-2 cell monolayers, with an apparent permeability coefficient less than 1×10^{-6} cm/s, and it may serve as a substrate for P-glycoprotein (P-gp) efflux pumps [23]. This microscopic mechanism aligns with *in vivo* experimental results from Wang *et al.*: after p.o. administration of an extract containing 4.8 mg/kg of active ingredients to mice, the highest parent drug concentration detected in plasma was approximately 0.04 μ M [22]. Even considering potential tissue accumulation effects, local concentrations would struggle to reach micromolar-level onset thresholds. This constitutes a primary PK factor limiting the clinical translation of oral PCC1. Notably, this study utilized a Black Soybean Seed Coat Extract with a 1.9% PCC1 content (at a 4.8 mg/kg dose); this content is comparable to the normal range of PCC1 in current Grape Seed Extracts (GSE), implying that current GSE consumption would likely result in PCC1 plasma concentrations in the tens of nanomolar range in animal models. Such low plasma concentrations remain three orders of magnitude away from the *in vitro* effective concentration for PCC1's senomorphic activity.

4. Excellence in Immune Microenvironment Amelioration

Beyond the characteristics of local exposure, the exceptional amelioration of the immune microenvironment by PCC1 may partially explain why such pronounced anti-aging effects are observed *in vivo*. In the study by Liu *et al.*, daily p.o. administration of 8 mg/kg PCC1 in mice effectively reversed hematopoietic stem cell (HSC) myeloid bias and reconstructed the B cell pool; meanwhile, retinal functional decline in aged mice receiving the same daily dose was effectively delayed, and visual acuity improved [6] [18]. In the latest research, Duan confirmed that PCC1 reversed senescence-associated S1pr1 downregulation in T cells, significantly reducing the infiltration of tumor-promoting IL17+ γ δ T cells and senescent neutrophils in aged lungs [26].

In contrast, the first-generation combination D+Q faces a clear efficacy "ceiling" in the dimension of immune source reconstruction due to the bone marrow suppressive effects of dasatinib. Furthermore, recent reports suggest this combination might promote skin papilloma development by upregulating PD-L1 and reducing CD8+ T cell infiltration. ABT-263 serves as a highly efficient Bcl-2 inhibitor but requires intermittent dosing to circumvent its depletion of memory T cells and hematological toxicity risks. In summary, the efficacy of PCC1 in significantly restoring immune surveillance may be a critical mechanism by which it achieves anti-aging effects under low *in vivo* concentration conditions while exhibiting an extremely high safety profile.

5. Implications of Colonic Microbiota Metabolism

Furthermore, attention should be directed toward the metabolic fate of PCC1 within the colon when utilizing oral administration. Although its B-type trimeric structure could maintain high stability in gastric fluid (pH ~ 2.0) due to the strong hydrolysis resistance of C-C bonds, this does not translate into effective systemic absorption. Instead, it results in over 90% of intact molecules bypassing the small intestine to enter the colon due to excessive molecular weight [27,28]. In the "microbial reactor" of the colon, PCC1 is not simply converted into a single product but undergoes a complex cleavage cascade, generating a lineage of small molecule phenolic acid metabolites including transient dimer intermediates, the core metabolite 5-(3',4'-dihydroxyphenyl)- γ -valerolactone (DHPV), as well as downstream phenylvaleric acid, phenylpropionic acid, and phenylacetic acid [28,29]. Notably, while this transformation process is efficient, the recovery rate is incomplete; reported molar recoveries of identified metabolites range only from 20% to 57%, suggesting that a large amount of PCC1 may be lost to unknown degradation pathways or assimilated by bacterial biomass [30,31]. Although these downstream metabolites (especially DHPV) can exhibit certain health benefits in anti-inflammation, neuroprotection, and metabolic syndrome improvement, they may have fundamentally lost the senolytic capability [32,33]. Additionally, whether the

aforementioned anti-aging phenomena of PCC1 noted in the retina, hematopoietic, and immune systems are partially attributable to colonic metabolite effects remains further clarification.

6. Translational Strategies: Safety Assessment and Formulation Optimization

Extrapolating these pharmacokinetic constraints to oral clinical regimens reveals insurmountable translational hurdles (Table 4). Linear modeling indicates that even achieving effective plasma concentrations (*ca.* 4 μ M) in humans for senomorphic efficacy would necessitate extract doses far exceeding the maximum tolerated daily intake of Grape Seed Extract (~2.5 g) [34]. The poor intestinal bioavailability and saturable absorption kinetics of trimeric PCC1 impose a natural ceiling on systemic exposure, rendering the >50 μ M senolytic threshold unattainable *via* oral administration. Compounded by the prohibitive cost of purified PCC1 (*ca.* \$1000 for 100 mg) and potential nephrotoxic risks associated with local gastrointestinal enrichment, these constraints confirm that simple oral dose escalation is a non-viable strategy, underscoring the critical need for advanced delivery systems [35]. Rapid progress in the field of pharmaceuticals provides technical means to solve the bioavailability problem of polyphenols. For example, nanomicelle technologies have been proven to significantly increase the oral absorption rate of curcumin (improving by approx. 18 and 29 times, respectively) [36,37]. Drawing on these verified technologies, the single p.o. dose may be reduced to a lower level with a good safety profile.

Table 4. Analysis of Oral Dosage Optimization Pathways.

Optimization Phase	Key Strategy	Mechanism Basis	Expected Bioavailability Change	Theoretical Dose Estimate*	Comment
Phase I	Oral Parent Drug (1-2% Natural Extract)	Passive diffusion (Limited by Caco-2 & first-pass)	Baseline (1x)	<i>ca.</i> 2-30 g	Extremely low bioavailability (Low dose 2g) or Physically infeasible with potential toxicity (High dose 30g)
Phase II	Targeted Senomorphic (Pure PCC1)	Lower effective threshold (5-20 μ M)	1x	<i>ca.</i> 300-3,000 mg	Marginally Feasible (Still cost-limited)
Phase III	Nano/Phytosome (PCC1 Formulation)	Lymphatic promotion; bypass P-gp efflux	10x - 20x increase	<i>ca.</i> 100-300 mg	Highly Feasible

Phase IV	Advanced Formulation + Targeting	Utilizing tissue accumulation & local concentration	Integrated efficacy >20x	ca. 45 mg	Optimal Clinical Protocol
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*: Analysis based on the utilization of 1-2% PCC1 extract with the daily 8 mg/kg dosage in mice).

7. Conclusion

This work explores the core challenge of transitioning PCC1 from preclinical research to clinical translation, which lies in its severe bioavailability limitations. As a large trimeric molecule, PCC1 exhibits extremely low Cmax, and its bioavailability within extract components is significantly lower than that of monomers and dimers. This implies that simply taking ordinary GSE or unmodified free drug is likely clinically ineffective. Due to intestinal absorption barriers and physical dosage limits, active parent drug concentrations struggle to reach the therapeutic threshold required for senolysis in tissues outside the gut and kidneys. Therefore, the clinical translation of PCC1 should achieve a technological leap from traditional supplements to advanced delivery systems. By introducing innovative dosage form delivery technologies to reconstruct its PK profile, bypass intestinal absorption saturation effects, and enhance tissue targeting, an effective clinical translation could be achieved within a safe and rational dosage range. This strategy integration based on delivery technology would represent a critical viable path to realizing safe, efficient, and low-cost clinical application of PCC1.

Author Contributions: Conceptualization: Ling Wang, Qinghua Lyu; Investigation (Experiments / Data Acquisition): Qun Wang, Jianhui Zhang; Writing: Qun Wang, Jianhui Zhang; Review & Editing: All authors.

Funding: This research was primarily supported by resources and funds from Lonvi Biosciences (Shenzhen) Co., Ltd. The company provided the necessary experimental facilities, materials, and financial support for the preparation of the B type procyanidin oligomers and the subsequent animal safety evaluations.

Conflicts of Interest: The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Qun Wang and Qinghua Lyu are affiliated with Lonvi, Inc. (USA). Jianhui Zhang is affiliated with Lonvi Biosciences (Shenzhen) Co., Ltd. (China). The work was supported by Lonvi Biosciences (Shenzhen) Co., Ltd., which provided funding, experimental facilities, and materials for the study. Ling Wang declares no competing financial interests.

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