JOURNAL OF PHARMA INSIGHTS AND RESEARCH ISSN NO. 3048-5428

REVIEW ARTICLE

A Review on Molecular Pathways of Procyanidin C1 in Modulating Inflammation, Oxidative Stress, and Apoptosis in Senescent Cells

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Publication history: Received on 3rd October 2025; Revised on 17th October 2025; Accepted on 21st October 2025

Article DOI: 10.69613/0dp7yg94

Abstract: The progressive accumulation of senescent cells is a primary factor for tissue dysfunction, organismal aging, and the onset of age-related pathologies. While the therapeutic ablation of these cells, termed senolysis, holds immense promise, the development of agents with high selectivity and minimal off-target toxicity remains a critical pharmacological challenge. This review focuses on Procyanidin C1 (PCC1), a naturally occurring polyphenolic trimer derived from grape seed extract, which has emerged as a potent senotherapeutic candidate with a unique, dose-dependent dual mechanism. We analyze the molecular underpinnings of PCC1's activity, detailing its capacity to induce apoptosis specifically in senescent cells via the amplification of oxidative stress and the upregulation of Bcl-2 family pro-apoptotic factors, Puma and Noxa. Simultaneously, at lower concentrations, PCC1 acts as a senomorphic agent, remodeling the Senescence-Associated Secretory Phenotype (SASP) by intercepting Nuclear Factor-kappa B (NF-κB) signaling. This paper also presents the structural prerequisites for the compound for activity and its efficacy in diverse biological contexts, from enhancing chemotherapy outcomes to mitigating organ fibrosis, positing PCC1 as a versatile tool in the advancement of longevity medicine.

Keywords: Procyanidin C1; Cellular Senescence; Senolytics; Oxidative Stress; Bcl-2 Family.

1. Introduction

Cellular senescence is a state of stable cell cycle arrest elicited by sublethal damage signals. While historically viewed as a tumor-suppressive mechanism that prevents the propagation of damaged genomes, the chronic persistence of senescent cells exerts deleterious effects on tissue homeostasis. Senescence is not a uniform state but a response to diverse stressors. The primary triggers include telomere attrition (replicative senescence) which activates the DNA Damage Response (DDR) machinery, specifically the ATM/ATR kinases. Additionally, premature senescence can be induced by persistent oxidative stress, mitochondrial dysfunction, and oncogene activation (e.g., RAS overexpression), known as Oncogene-Induced Senescence (OIS) [1]. These pathways converge on the p53/$p21^{CIP1}$ and $p16^{INK4a}$/Rb axes, locking the cell in G1 arrest.

Senescent cells remain metabolically active and secrete a complex milieu of pro-inflammatory cytokines (IL-6, IL-1β), chemokines (CXCL8), growth factors, and matrix-remodeling proteases (MMPs), collectively termed the Senescence-Associated Secretory Phenotype (SASP) [2]. The SASP drives a local environment of chronic inflammation, often referred to as "inflammaging." Crucially, these factors can induce DNA damage and senescence in neighboring healthy cells, a phenomenon known as the "bystander effect," which accelerates tissue deterioration in a feed-forward loop [3]. The pharmacological targeting of senescent cells has largely bifurcated into two streams: senolytics, which induce cell death, and senomorphics, which suppress the SASP without killing the cell. Early senolytics, such as the BCL-2 inhibitor Navitoclax (ABT-263), demonstrated proof-of-concept efficacy. However, BCL-xL is essential for the survival of platelets. Consequently, Navitoclax treatment frequently results in severe thrombocytopenia and neutropenia, limiting its clinical utility [4]. This highlights the necessity for agents that do not indiscriminately inhibit survival pathways in healthy, essential cell types.

Many first-generation senolytics exhibit narrow efficacy, targeting only specific lineages of senescent cells (e.g., adipocytes vs. endothelial cells). For instance, the Dasatinib and Quercetin (D+Q) cocktail is effective primarily against senescent adipocytes and endothelial cells but less effective against fibroblasts [5]. A broad-spectrum agent capable of targeting multiple senescent cell types across different organs is highly desirable.

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Recent high-throughput screenings of natural product libraries have identified grape seed extract (GSE) as a potent source of senolytic activity. In screening campaigns utilizing primary human stromal cells, GSE emerged as a top hit for selectively reducing senescent cell viability. Subsequent fractionation and bioassay-guided isolation pinpointed Procyanidin C1 (PCC1) as the principal bioactive component responsible for this effect, outperforming other flavonoids like quercetin and fisetin in potency and specificity [6]. Unlike its monomeric counterparts, PCC1 exhibits a sophisticated, concentration-dependent pharmacology: it suppresses inflammatory signaling at low doses (senomorphic) while triggering apoptosis at higher doses (senolytic). This distinct profile suggests that PCC1 may offer a wider therapeutic window compared to existing synthetic analogues, warranting a detailed examination of its molecular mechanisms [7].

Table 1. Comparison of Common Senolytic Agents

Senolytic Agent	Origin/Class	Primary Mechanism	Target Cell Specificity	Side Effects
Navitoclax (ABT-263)	Synthetic BCL-2 Inhibitor	Inhibits BCL-2, BCL-xL, and BCL-w	Broad (HUVECs, Fibroblasts, MEFs)	Severe thrombocytopenia and neutropenia due to BCL-xL inhibition in platelets.
Dasatinib + Quercetin (D+Q)	Tyrosine Kinase Inhibitor + Flavonoid	Target ephrins, PI3K, and anti-apoptotic networks	Adipocytes (D), Endothelial cells (Q), but limited effect on fibroblasts	Poor specificity; Dasatinib can cause pulmonary hypertension and fluid retention.
Fisetin	Natural Flavonoid	PI3K/AKT/mTOR pathway inhibition	Adipocytes, Immune cells	Lower potency compared to synthetic agents; requires high doses for efficacy.
Procyanidin C1 (PCC1)	Natural Proanthocyanidin (Trimer)	ROS induction; Upregulation of Puma/Noxa; NF-ϰB inhibition	Broad (Stromal, Fibroblasts, Epithelial cells)	High specificity with minimal cytotoxicity to proliferating cells; safety profile superior to BCL-2 inhibitors.

2. Structural Biochemistry

2.1. Chemical Composition and Structural Prerequisites

Procyanidin C1 belongs to the proanthocyanidin class of flavonoids, specifically defined as a B-type trimer of (-)-epicatechin.

2.1.1. Polymerization Degree and Activity (Monomer vs. Trimer)

The degree of polymerization (DP) is a critical determinant of biological activity. Comparative studies reveal that while monomeric epicatechin (DP=1) and dimeric procyanidins (DP=2) possess potent antioxidant capacity, they lack the specific senolytic efficacy observed with the trimeric C1 form (DP=3) [8]. This suggests that the trimeric structure facilitates specific steric interactions with cellular membrane components or intracellular signaling nodes that are inaccessible to smaller oligomers.

2.1.2. Stability and Isomerization

The structural integrity of the interflavan bonds (C4-C8 or C4-C6) in PCC1 is essential. Under physiological conditions, PCC1 is relatively stable, but it can undergo cleavage or isomerization in highly acidic gastric environments. However, the trimeric form has shown sufficient stability to reach target tissues *in vivo*, likely aided by its binding affinity to plasma proteins which protects it from rapid degradation [9].

2.2. Pharmacokinetics and Cellular Uptake

The bioavailability of proanthocyanidins is often cited as a limiting factor in their clinical translation; however, PCC1 demonstrates sufficient stability and uptake to exert systemic effects.

2.2.1. Membrane Interaction and Lipid Rafts

PCC1 is amphiphilic, possessing both hydrophobic aromatic rings and hydrophilic hydroxyl groups. This allows it to interact with the lipid bilayer of cell membranes. Evidence suggests PCC1 may preferentially interact with lipid rafts cholesterol-rich membrane microdomains which are sites of intense signaling activity, potentially influencing receptor clustering and internalization [10].

Table 2. Physicochemical Properties and Structural Determinants of PCC1 Activity

Parameter	Description/Value	Implication for Efficacy
Chemical Structure	B-type trimer of (-)-epicatechin	Trimeric structure is essential for specific binding and senolytic activity; monomers/dimers lack this potency.
Linkage Type	4β→8 interflavan bonds	Provides specific steric configuration required for interaction with membrane lipids or receptor proteins.
Molecular Weight	~866.77 g/mol	Sufficient size for specific receptor interaction while maintaining bioavailability.
Hydrophilicity	Amphiphilic (Hydroxyl groups + Aromatic rings)	Facilitates interaction with lipid bilayers (membrane integration) and aqueous intracellular environments.
Stability	Sensitive to high pH and high temperature	Formulation must ensure stability; plasma protein binding enhances in vivo half-life.

2.2.2. Intracellular Localization in Senescent Cells

Once internalized, PCC1 exhibits a differential accumulation profile. Due to lysosomal expansion and pH alterations characteristic of senescent cells, PCC1 appears to accumulate more effectively in these cells compared to their proliferation-competent counterparts. This differential accumulation contributes to the selective toxicity observed at therapeutic doses [11].

3. Molecular Mechanisms of Senolysis: The Oxidative Switch

3.1. The ROS Threshold Theory of Specificity

The selectivity of PCC1 for senescent cells is fundamentally grounded in the "ROS threshold theory," exploiting the metabolic fragility of aging cells.

3.1.1. Altered Redox Homeostasis in Senescence

Senescent cells are characterized by mitochondrial dysfunction and elevated basal levels of Reactive Oxygen Species (ROS) [12]. To survive this constitutive oxidative stress, they operate near a toxicity threshold, heavily reliant on upregulated antioxidant defense mechanisms (e.g., SOD2, Catalase). They are essentially "primed" for oxidative death.

3.1.2. PCC1-Induced Superoxide Generation

PCC1 treatment induces a rapid and substantial surge in intracellular ROS generation, specifically superoxide anions and hydrogen peroxide [13]. In healthy cells, which possess a robust reserve of antioxidant capacity and lower basal ROS, this increase is buffered effectively. However, in senescent cells, the PCC1-induced ROS spike overwhelms the already taxed antioxidant defenses, pushing the cell beyond the lethal threshold and initiating catastrophic oxidative damage [14].

3.2. Mitochondrial Depolarization

The mitochondrion serves as the primary executioner organelle in PCC1-mediated senolysis, transducing the ROS signal into an apoptotic cascade.

3.2.1. Disruption of Membrane Potential ($\Delta\psi m$)

The ROS surge triggered by PCC1 directly impacts mitochondrial integrity. Mechanistic studies indicate that PCC1 treatment leads to a profound disruption of the mitochondrial membrane potential ($\Delta\psi m$) [15]. This depolarization compromises ATP production and disrupts the electrochemical gradient required for cell viability.

3.2.2. Cytochrome C Release and Caspase Activation

The loss of potential facilitates the opening of the mitochondrial permeability transition pore (mPTP) or the formation of pores by BCL-2 family proteins. This permeabilization results in the cytosolic release of cytochrome c. Once in the cytosol, cytochrome c binds to APAF-1, forming the apoptosome which activates Caspase-9 and subsequently the executioner Caspase-3, leading to programmed cell death [16].

3.3. The p53-Puma/Noxa Apoptotic Axis

Downstream of mitochondrial stress, PCC1 engages the intrinsic apoptotic machinery through specific members of the Bcl-2 family.

3.3.1. Signal Transduction from ROS to p53

The ROS-induced DNA damage acts as a signal to activate p53, a key tumor suppressor. In the context of PCC1 treatment, p53 acts as a transcription factor that upregulates specific pro-apoptotic BH3-only proteins [17].

3.3.2. Antagonizing BCL-XL and BCL-2 via Puma and Noxa

PCC1 treatment specifically induces the expression of Puma (p53 upregulated modulator of apoptosis) and Noxa [6]. These proteins bind with high affinity to the anti-apoptotic guardians BCL-2 and BCL-xL, neutralizing them. This displacement frees the effector proteins Bax and Bak to oligomerize in the mitochondrial outer membrane, forming the pores that release cytochrome c. This reliance on the p53-Puma/Noxa axis is a defining feature of PCC1's mechanism, distinguishing it from other senolytics that function as direct mimetics of BH3 proteins [18].

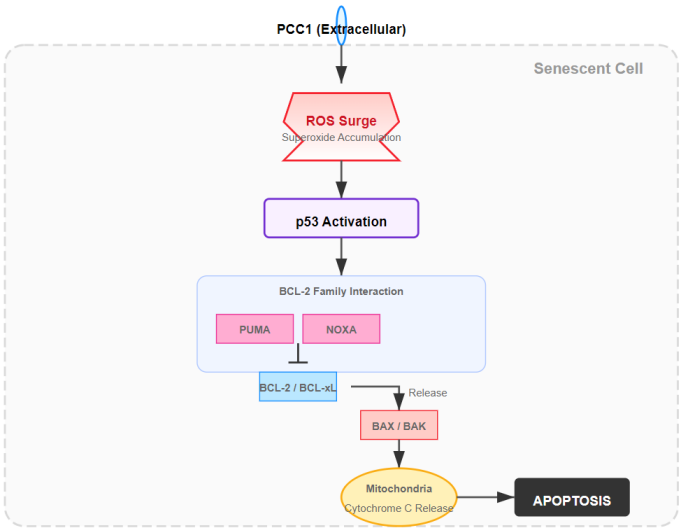

Figure 1. Molecular Pathway of PCC1-Induced Apoptosis

4. Senomorphic Activity and Inflammatory Modulation

4.1. Canonical NF-κB Pathway Inhibition

While high concentrations of PCC1 induce apoptosis, lower concentrations exert a potent "senomorphic" effect. This activity is primarily mediated through the inhibition of the Nuclear Factor-kappa B (NF-κB) signaling pathway, the master transcriptional regulator of inflammation [19].

4.1.1. Targeting IκBα Phosphorylation

In the canonical NF-κB pathway, the inhibitory protein IκBα sequesters the NF-κB dimer (p65/p50) in the cytoplasm. In senescent cells, constitutive stress signals lead to the phosphorylation of IκBα by IKK complex, marking it for proteasomal degradation. PCC1 intervention blocks this phosphorylation step. By stabilizing IκBα, PCC1 prevents the liberation of the active NF-κB complex [20].

4.1.2. Prevention of p65 Nuclear Translocation

By preserving IκBα integrity, PCC1 effectively traps the p65 subunit in the cytoplasm, preventing its nuclear translocation. Without nuclear entry, p65 cannot bind to the promoter regions of target inflammatory genes, thereby silencing the transcriptional program responsible for the SASP [21].

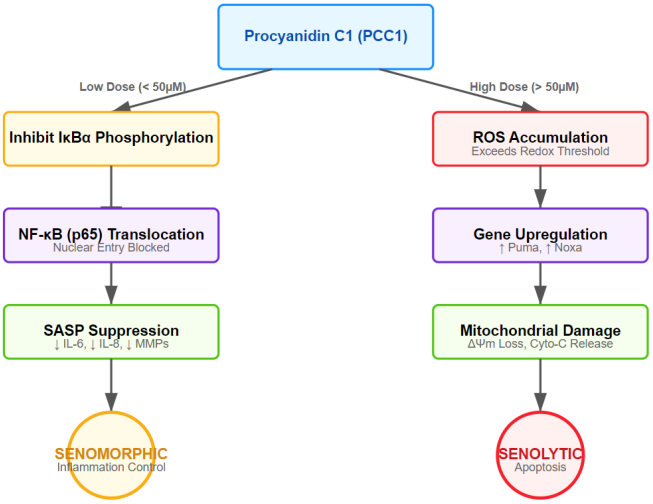

Figure 2. The Dose-Dependent Dual Mechanism of PCC1

Table 3. The Dose-Dependent Dual Mechanism of Procyanidin C1

Concentration	Functional Mode	Primary Molecular Events	Physiological Outcome	Therapeutic Goal
Low Dose (e.g., < 50 μM *in vitro*)	Senomorphic	- Inhibition of IκBα phosphorylation - Blockade of p65 nuclear translocation - Suppression of p38 MAPK	- Reduction of SASP secretion (IL-6, IL-8, MMPs) - Attenuation of paracrine senescence	Anti-inflammatory; Tissue microenvironment remodeling
High Dose (e.g., ≥ 50-100 μM *in vitro*)	Senolytic	- Surge in Intracellular ROS - Mitochondrial depolarization (Δψm loss) - Upregulation of Puma and Noxa	- Activation of Caspase-3/9 - Induction of intrinsic apoptosis - Selective clearance of senescent cells	Cell ablation; Tissue rejuvenation; Fibrosis reversal

4.2. Remodeling the Senescence-Associated Secretory Phenotype (SASP)

The transcriptional blockade of NF-κB by PCC1 leads to a broad-spectrum attenuation of the SASP secretome.

4.2.1. Cytokine Downregulation (IL-6, IL-8)

Transcriptomic profiling of PCC1-treated senescent cells shows a marked downregulation in the mRNA expression of key pro-inflammatory cytokines, most notably Interleukin-6 (IL-6), Interleukin-8 (IL-8), and Interleukin-1β (IL-1β) [22]. These cytokines are the primary mediators of chronic inflammation in aging tissues.

4.2.2. Suppression of Matrix Metalloproteinases (MMPs)

PCC1 also suppresses the secretion of matrix metalloproteinases, specifically MMP-1 and MMP-3. These enzymes degrade the extracellular matrix (ECM) and contribute to tissue laxity and fibrosis. By inhibiting MMP expression, PCC1 helps preserve tissue architecture and prevents the creation of microenvironments favorable to metastasis [23].

4.3. Signal Transduction Cross-talk

Beyond NF-κB, PCC1 modulates parallel signaling pathways that contribute to the senescent phenotype.

4.3.1. EGFR-MAPK Axis Modulation

PCC1 has been observed to modulate the p38 Mitogen-Activated Protein Kinase (MAPK) pathway, a critical driver of SASP regulation. Moreover, it interacts with the Epidermal Growth Factor Receptor (EGFR), binding to it and inhibiting downstream phosphorylation. This blockade suppresses the activation of ERK and AKT pathways, which are often hyperactive in senescent fibroblasts [24].

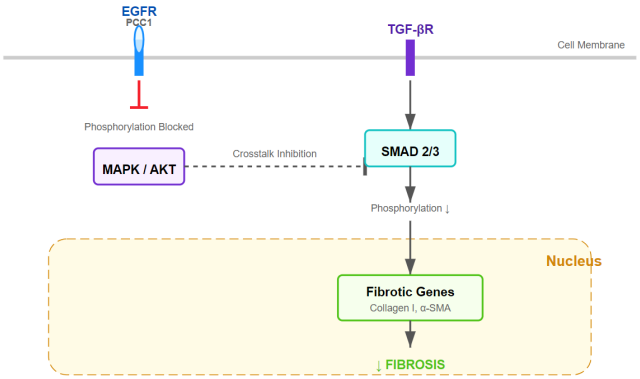

Figure 3. Anti-Fibrotic Mechanism via EGFR/TGF-β Signaling

Table 4. Molecular Signaling Targets Modulated by PCC1

Molecular Target	Regulatory Effect	Pathway Association	Functional Consequence in Senescent Cells
Reactive Oxygen Species (ROS)	Upregulation↑↑)	Oxidative Stress	Triggers DNA damage response; overwhelms antioxidant capacity, leading to lethal stress.
Puma (BBC3)	Upregulation	p53/Apoptosis	Binds to BCL-2/BCL-xL; displaces Bax/Bak to initiate mitochondrial pore formation.
Noxa (PMAIP1)	Upregulation	p53/Apoptosis	Synergizes with Puma to neutralize anti-apoptotic MCL-1 and A1 proteins.
IκBα	Stabilization	NF-κB Signaling	Prevents release of NF-κB dimers; sequesters p65 in the cytoplasm.
EGFR	Inhibition	MAPK/AKT Axis	Blocks downstream phosphorylation of ERK/AKT; reduces fibrotic signaling.
SIRT3	Activation	Mitochondrial Dynamics	Deacetylates FOXO3; promotes mitochondrial homeostasis (observed in nucleus pulposus cells).
TGF-β1	Downregulation	Fibrosis/SMAD	Reduces SMAD2/3 phosphorylation; prevents myofibroblast differentiation.

4.3.2. TGF- β/SMAD Signaling in Fibrosis

In the context of fibrosis, PCC1 targets the Transforming Growth Factor- β(TGF-β) signaling cascade. It inhibits the phosphorylation of SMAD2/3, the canonical effectors of TGF-β. This inhibition prevents the differentiation of fibroblasts into myofibroblasts, thereby reducing collagen deposition and mitigating tissue stiffening [25].

5. Therapeutic Applications and *In Vivo* Efficacy

5.1. Gero protection in Naturally Aged Models

The most compelling evidence for PCC1's potential lies in its systemic effects in naturally aged mice.

5.1.1. Functional Physical Improvements

Intermittent administration of PCC1 (e.g., bi-weekly) significantly reduces the burden of $p16^{Ink4a}$-positive senescent cells. This clearance translates into tangible functional phenotypes: treated aged mice exhibit enhanced maximal walking speed, improved hanging endurance, and superior grip strength compared to vehicle-treated controls [6].

5.1.2. Lifespan Extension Metrics

Most notably, PCC1 treatment was found to extend the remaining lifespan of aged mice by approximately 9% to 60% depending on the treatment regimen (early vs. late life intervention), without increasing late-life morbidity. This suggests a genuine extension of healthspan the period of life spent in good health rather than just expanding the geriatric phase [26].

5.2. Chemotherapy-Induced Senescence and Cancer Therapy

Chemotherapeutic agents often induce senescence in tumor cells and the surrounding stroma (Therapy-Induced Senescence, or TIS).

5.2.1. Clearing Therapy-Induced Senescence (TIS)

While TIS initially halts tumor growth, the resulting SASP can promote tumor relapse and chemoresistance. PCC1 effectively eliminates these chemotherapy-induced senescent cells. In preclinical models, combining PCC1 with mitoxantrone resulted in greater tumor regression than chemotherapy alone [27].

5.2.2. Reducing Tumor Recurrence and Metastasis

PCC1 reduces the likelihood of metastasis by disrupting the stromal support signals (SASP) that protect residual cancer cells. The elimination of senescent stromal cells deprives the tumor of growth factors and angiogenic signals required for resurgence [28].

5.3. Targeted Organ Fibrosis and Degeneration

The therapeutic scope of PCC1 extends to specific organ pathologies driven by senescence.

5.3.1. Renal Fibrosis and Tubular Epithelial Recovery

In models of kidney injury, PCC1 ameliorates fibrosis by clearing senescent tubular epithelial cells. Mechanistically, this restoration involves the downregulation of profibrotic markers (Fibronectin, Collagen I) and the preservation of renal filtration function [29].

5.3.2. Intervertebral Disc: SIRT3/FOXO3 Pathway

Recent findings indicate that PCC1 protects nucleus pulposus cells in the intervertebral disc. This protection is mediated via the activation of the SIRT3/FOXO3 signaling axis. SIRT3 activation by PCC1 deacetylates FOXO3, promoting antioxidant gene expression that maintains mitochondrial dynamics and prevents degeneration under acidic stress [30].

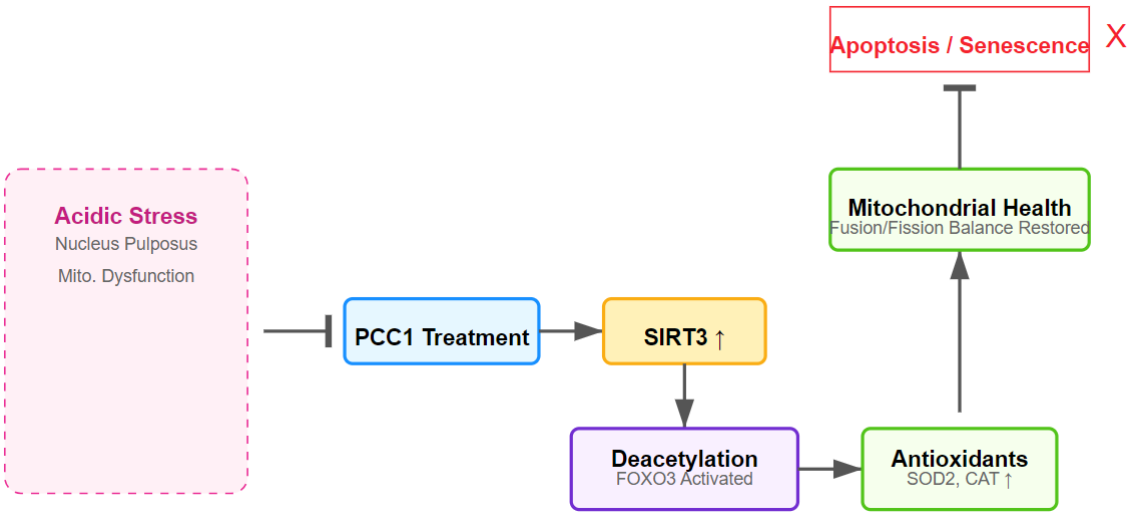

Figure 4. SIRT3-FOXO3 Pathway in Intervertebral Disc Degeneration

5.3.3. Retinal Protection and RPE Senescence

PCC1 has shown promise in ophthalmology, alleviating structural decline in the aged retina. It clears senescent Retinal Pigment Epithelial (RPE) cells, which are central to the pathogenesis of Age-Related Macular Degeneration (AMD), thereby preserving photoreceptor integrity [31].

Table 5. Summary of Preclinical *In Vivo* Efficacy of PCC1

Disease/Aging Model	Treatment Regimen	Target Tissue/Organ	Observed Therapeutic Benefit	Reference
Natural Aging (Mice)	Intermittent (bi-weekly)	Systemic (Liver, Kidney, Muscle)	Increased maximal walking speed, grip strength, and hanging endurance; extended remaining lifespan by ~9-60%.	[6]
Chemotherapy-Induced Senescence (TIS)	Combination with Mitoxantrone	Tumor Microenvironment (Prostate/Breast)	Clearance of senescent stromal cells; reduced tumor size; enhanced chemotherapeutic efficacy; prolonged survival.	[6]
Renal Fibrosis (UUO Model)	Post-injury administration	Kidney (Tubular Epithelial Cells)	Reduction in fibrotic markers (Collagen I, Fibronectin); restoration of renal structure and function.	[29]
Skin Fibrosis (Bleomycin-induced)	Systemic or Topical	Dermis/Epidermis	Reduced epidermal hyperplasia; improved collagen structure; restored Collagen I/III ratio.	[24]
Intervertebral Disc Degeneration (IVDD)	Systemic injection	Nucleus Pulposus	Protection against acidic pH-induced degeneration; preservation of disc height and hydration.	[30]
Retinal Degeneration	Systemic administration	Retina (RPE Cells)	Alleviation of structural decline; clearance of p16+ RPE cells; preservation of visual function markers.	[31]

6. Challenges

6.1. Dosage Windows

While PCC1 exhibits a favorable safety profile in rodents, translation to humans requires precision.

6.1.1. Defining the Senolytic vs. Senomorphic Threshold

The distinct concentration thresholds for senomorphic (low dose) versus senolytic (high dose) effects necessitate precise dosing strategies. A dose that is too low may only suppress symptoms without clearing the root cause, while excessive doses could theoretically impact healthy cells with lower oxidative thresholds [32].

6.1.2. Pharmacokinetics in Human Populations

Phase I clinical trials must rigorously establish the pharmacokinetic parameters (absorption, distribution, metabolism, excretion) in humans. The impact of gut microbiota on the metabolism of trimeric procyanidins into smaller metabolites must also be understood, as this varies significantly between individuals [33].

6.2. Delivery Systems and Clinical Feasibility

6.2.1. Nanoparticle Formulation Strategies

Nano-encapsulation (e.g., liposomes, polymeric nanoparticles) could improve the stability of PCC1 and direct it specifically to tissues with high senescent cell burdens, such as atherosclerotic plaques or arthritic joints, enhancing local efficacy while minimizing systemic exposure [34].

6.2.2. Standardization of Natural Extract Purity

As a natural product derivative, PCC1 faces regulatory challenges regarding purity. Variations in grape seed sources and extraction methods can alter the trimer content. Developing synthetic or semi-synthetic manufacturing routes will be essential to produce pharmaceutical-grade PCC1 consistently for widespread clinical use [35].

7. Conclusion

Procyanidin C1 stands at the forefront of the second generation of senotherapeutics, distinguished by its unique natural origin and dual mechanism of action. By leveraging the intrinsic oxidative vulnerability of senescent cells, PCC1 executes a precise apoptotic program via the ROS-p53-Puma/Noxa axis, while simultaneously dampening the pro-inflammatory SASP via NF-κB inhibition. The compound's efficacy in extending lifespan, enhancing cancer therapy, and reversing organ fibrosis in preclinical models provides a robust rationale for its clinical development. As our understanding of the molecular nuances of PCC1 signaling deepens specifically its interaction with pathways like SIRT3, EGFR, and mitochondrial dynamics PCC1 holds the potential to transform the management of aging and age-related diseases.

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