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REVIEW ARTICLE

Procyanidins as potential anticancer agents: mechanisms of action, bioavailability challenges and therapeutic opportunities

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Abstract

Procyanidins (PCs), dietary polyphenols found in fruits, vegetables, and beverages, exhibit potent anticancer properties. Their mechanisms of action involve modulating oxidative stress, inhibiting angiogenesis, inducing apoptosis, and preventing tumor progression. Despite promising preclinical and clinical findings, their therapeutic potential remains underexplored. This review aims to provide a comprehensive analysis of the anticancer properties of PCs, including their bioavailability, pharmacokinetics, and safety. A systematic literature search was conducted across databases such as PubMed, Scopus, and Web of Science, utilizing Medical Subject Headings (MeSH) terms and specific keywords. Studies were selected based on predefined inclusion criteria, focusing on in vitro, in vivo, and clinical evidence. PCs demonstrate anticancer effects through multiple pathways, including inhibition of pro-inflammatory cytokines, suppression of the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathways, and regulation of apoptosis-related proteins such as BCL2-associated X protein (BAX), B-cell lymphoma 2 (BCL-2), and caspases. PCs demonstrate anticancer effects through multiple pathways, including inhibition of pro-inflammatory cytokines, suppression of the PI3K/AKT/mTOR and MAPK/ERK pathways, and regulation of apoptosis-related proteins such as BAX, BCL-2, and caspases. However, their low oral bioavailability and metabolic instability pose challenges for clinical application. Current research highlights the need for novel delivery systems, such as nanoparticles and liposomes, to enhance systemic absorption and therapeutic efficacy. Ongoing clinical trials are investigating the potential of PCs as adjuvants in cancer therapy, either alone or in combination with chemotherapeutic agents. Future studies should focus on optimizing their pharmacokinetics, exploring synergistic effects with existing treatments, and conducting large-scale clinical trials to validate their efficacy and safety. PCs hold promise as natural anticancer agents, with the potential to complement conventional therapies and improve patient outcomes.

Keywords Antioxidants · Bioavailability · Cancer prevention · Drug resistance · Flavonoids · Metastasis inhibition

Abbreviations

A549	Lung cancer cells
AOX	Antioxidant
BAK	Pro-apoptotic BCL2 protein
BAX	Apoptosis regulator
BCL-XL	B-cell lymphoma-extra large
BCL2	B-cell lymphoma 2
BIU87	Human bladder cancer cell line
CASP3	Caspase-3
CASP8	Caspase-8
CASP9	Caspase-9
CDK4	Cyclin-dependent kinase 4
CDKs	Cyclin-dependent kinase 4
Cip1/WAF1	Cyclin-dependent kinase inhibitor 1
COX	Cyclooxygenase
CRC	Colorectal cancer cells
cPLA2	Cytosolic phospholipase A2
DPPH	1,1-Diphenyl-2-picrylhydrazyl
DISC	Death-inducing signaling complex
DNA	Deoxyribonucleic acid
EC	Epicatechin
ERKs	Extracellular-Signal-Regulated Kinase
FAS	Apoptosis antigen 1, also named FASR
G1/G0	Growth 1 phase/resting phase
G2/M	Phase arrest of the cell cycle and apoptosis

Extended author information available on the last page of the article

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GSH	Glutathione
HepG2	Cells hepatoblastoma G2 cell line
HMOX1	Heme oxygenase 1 gene
HT29	Human colorectal adenocarcinoma cell line
HTC116	Cell Line human colon carcinoma
IL-1b	Interleukin 1b
IL-2	Interleukin 2
IL-4	Interleukin 4
IL-6	Interleukin 6
IL-8	Interleukin 8
IL-10	Interleukin 10
INF-γ	Interferon gamma
JAK2	Janus kinase 2
JNK1	C-Jun N-amino terminal kinase 1
JNK2	C-Jun N-amino terminal kinase 2
JNKs	C-Jun N-amino terminal kinases
LD50	Lethal dose 50
LOX	Lipoxygenase
MAPK	Mitogen-activated protein kinase
MCF-7	Human breast carcinoma
MDAMB-231	Human breast adenocarcinoma
MIA PaCa-2	Human pancreatic cancer cell line
MMP2	Matrix metalloproteinase 2
MMP9	Matrix metalloproteinase 9
NCM460	Normal human colon mucosal epithelial cell line
NF-κB	Nuclear factor kappa B
NRF2	NF-E2-related factor
Nrf2/ARE	NF-E2-related factor 2/antioxidant responsive element
OVCAR3	Epithelial ovarian cancer cells
PC	Procyanidins
PGE2	Prostaglandin E2
PI3-kinase	Phosphoinositide 3-kinases
PKB	Protein kinase B
QAW42	Epithelial ovarian cancer cells
RANTES	Chemokine (C–C motif) ligand 5
ROS	Reactive oxygen species
SOD	Superoxide dismutase
STAT-3	Signal transducer and activator of transcription 3
SW-480	Colorectal cancer cell
TGF-β	Transforming growth factor beta
TNF-α	Tumor necrosis factor alpha
VEGF	Vascular endothelial growth factor

Introduction

Cancer is a multifactorial and life-threatening disease characterized by the uncontrolled proliferation and invasive potential of abnormal cells, affecting various organs and tissues [1]. It remains the second leading cause of mortality worldwide, posing a significant global health burden and emphasizing the need for advancements in prevention, early detection and innovative therapeutic strategies [2–4]. Cancer cells possess metastatic potential, allowing them to detach from the primary tumor and disseminate to distant organs through hematogenous or lymphatic pathways; this process plays a fundamental role in tumor progression and contributes to intratumoral heterogeneity, as evidenced in colorectal cancer, where distinct histochemical and immunohistochemical variations have been identified [5, 6]. The causative factors of cancer are not known; however, some predisposing risk factors can influence the development of the disease. Individual's genetic makeup, exposure to ionizing radiation or some chemical substances in the environment, and lifestyle (e.g., poor diet, stress, inadequate exercise) play a significant role in the initiation and growth of abnormal cells [7]. Given the complexity of cancer progression and the limitations of conventional therapies, increasing attention has been directed toward natural bioactive compounds with anticancer properties, which exhibit potential in targeting key molecular pathways involved in tumor growth, metastasis and chemoresistance [1, 8, 9]. Procyanidins (PCs) are dietary phytochemicals or polyphenols that belong to a class of flavonoids known as condensed tannins and/or proanthocyanidins. The red pigments, anthocyanidins, are produced when PCs are hydrolyzed by acid [10]. They are present naturally in flowers, nuts, berries (e.g., cranberry and blueberry), grains, red wine, tea, cocoa, soybeans, cinnamon, legumes, leaves, bark, and seeds of various plants. PCs are commonly found in virtually all fruits, but higher contents are found in grapes, apples, persimmon, and bananas [11, 12]. PCs are secondary metabolites, thus protecting plants against diseases and disease-causing organisms [13, 14]. According to their degree of polymerization, they exist as dimers, trimers, tetramers, oligomers, and polymers of flavan-3-ol units, including catechin and epicatechin (EC). Based on the configuration and the degree of polymerization between monomers, PCs are classified into two main categories: A-type and B-type PCs. Ten known types of procyanidin dimers (Fig. 1) result from variations in linkage types and stereochemistry. The most common linkage patterns are B-type, characterized by a single carbon–carbon bond (C4-C8 or C4-C6), and A-type, where an additional ether bond forms between the oxygen at C2 and the carbon at C7 [14]. Furthermore, the stereochemistry of the catechin and epicatechin units (cis or trans configurations) contributes to the diversity of these dimers. The structural variety impacts the biological activities and functional properties of procyanidins, making them important compounds of interest in food science and health research [15]. PCs are utilized as food additives to

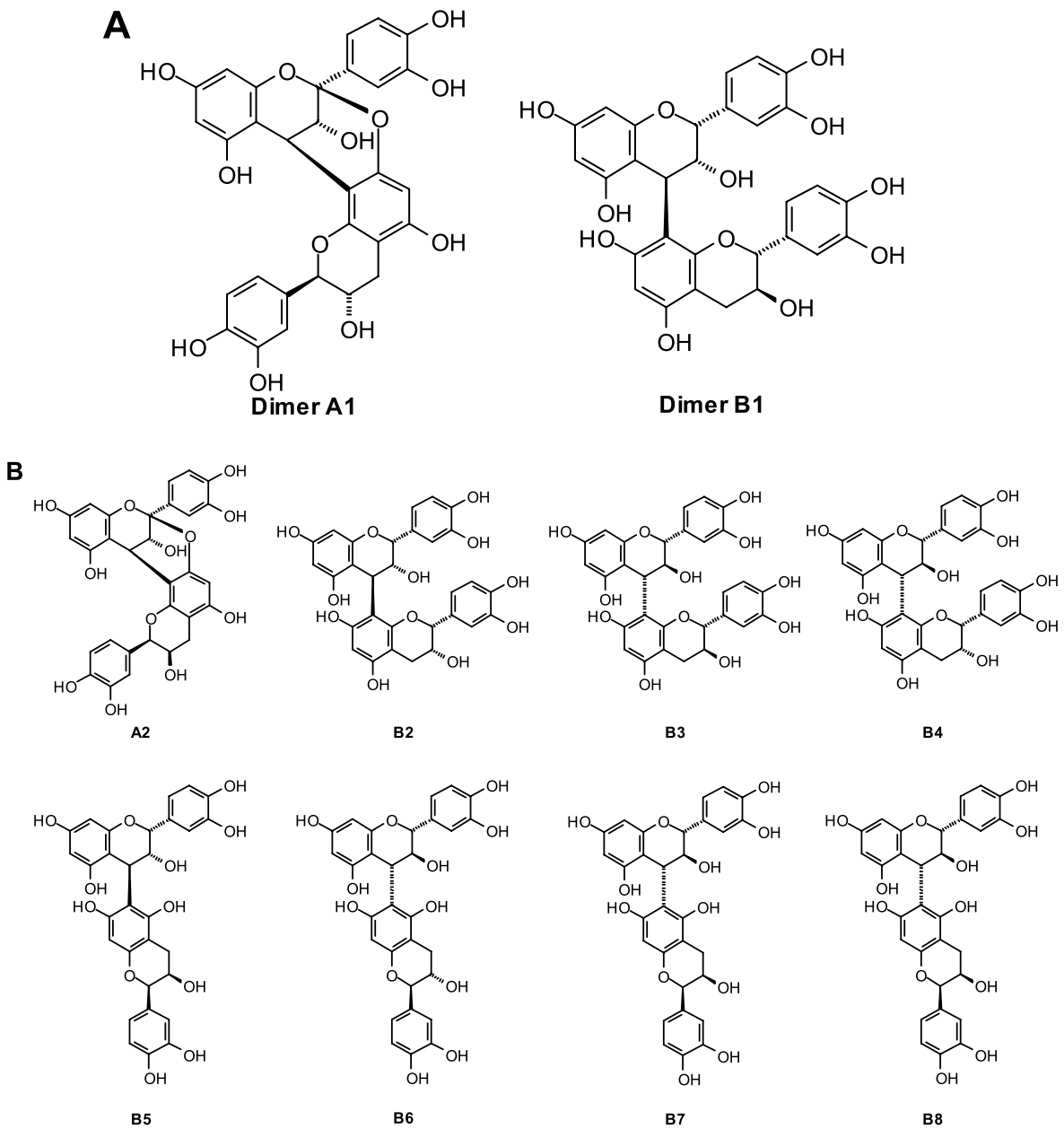

Fig. 1 Procyanidin dimers. Procyanidin dimers are composed of catechin and epicatechin subunits linked by different types of interflavan bonds, contributing to their diverse biological activities. Dimers in the **A** series feature A-type bonds (C2→O→C7), while the **B** series includes B-type bonds (C4→C8 or C4→C6). These structures underline the structural complexity and functional diversity of procyanidins in biological and therapeutic contexts

enhance food products' shelf life, such as fruit juices and wine since they can taste bitter, sour, and sweet and have antimicrobial activity [16, 17].

Other reported pharmacological benefits of PCs are anti-inflammatory, antidiabetic, antibacterial, antiviral, molluscidal, anti-allergic, lipid-lowering, anti-obesity, immunostimulative, and protective properties against many metabolic and chronic degenerative disorders [11, 18]. They can improve vision, blood circulation, vasodilation, and flexibility in joints, arteries, veins, capillaries, and tissues like the heart, inhibit platelet aggregation, and offer protection against ultraviolet radiation[19]. Currently, all the available clinical interventions for the treatment of cancer are costly and come with additional side effects. However, using plants and their bioactive compounds as dietary interventions in managing cancer has recently increased [18, 20]. PCs can inhibit proliferation and induce apoptosis in cancer cells without toxic effects on healthy cells [21]. PCs

from grape seeds have been shown to inactivate the PI3-kinase/PKB pathway and induce apoptosis in a colon cancer cell line [22]. Furthermore, PCs have antioxidant and pro-oxidant activities and can alter gene expression and transcription factors [16, 17]. This review article highlights the emerging role of procyanidins (PCs) as chemopreventive and therapeutic agents, emphasizing their structural diversity and its impact on anticancer efficacy. It provides updated insights into their bioavailability, metabolic transformations, and mechanisms of action, including apoptosis induction and cell cycle regulation. The review also underscores the clinical relevance of PCs, with evidence from preclinical studies and ongoing trials, while addressing safety and toxicity considerations. Future perspectives focus on enhancing bioavailability through advanced delivery systems and exploring their potential in combination therapies for improved clinical outcomes.

Review methodology

The literature search for this review was conducted using electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar. A combination of Medical Subject Headings (MeSH) terms and relevant keywords was used to ensure comprehensive coverage of available studies. The MeSH terms included "procyanidins," "dietary polyphenols," "anticancer properties," "bioavailability," "pharmacokinetics," and "toxicity." Keywords such as "natural compounds", "mechanisms of action", "preclinical studies", "clinical trials", and "safety evaluation" were also included. Boolean operators (AND, OR) were applied to refine the search strategy. Studies were selected based on predefined inclusion and exclusion criteria. Inclusion criteria involved original research articles, systematic reviews, and meta-analyses that focused on the anticancer properties, mechanisms of action, bioavailability, and pharmacokinetics of procyanidins. Articles reporting findings from preclinical (in vitro and in vivo) studies and clinical trials were considered. Only studies published in English and those providing detailed methodologies and outcomes were included to ensure the quality and relevance of the data. Exclusion criteria were applied to articles that did not specifically investigate procyanidins or dietary polyphenols in the context of anticancer properties. Studies with incomplete methodologies, lack of clear outcomes, or those primarily focused on unrelated compounds were excluded. Non-peer-reviewed publications, conference abstracts, editorials, and opinion pieces were also excluded. Duplicate records were identified and removed before the screening process. The most important findings and data, including mechanisms of action, preclinical and clinical evidence, bioavailability, and safety evaluations, are summarized in tables and figures.

Sources, phytochemistry and chemical structure-anticancer activity relationship

PCs are present in different plants and food products like flowers, vegetables, nuts, spices, legumes, cereals, grains, cocoa, chocolate, tea, red wine, cinnamon, pumpkin, bark, leaves, and seeds of plants [12, 23]. Likewise, PCs are found in woody and non-woody plants, including shrubs, arbors, and various herbs, some of which possess antiparasitic properties [24]. The physical and chemical properties of PCs are linked to the phenolic functional groups. The structural unit of PCs comprises flavan-3-ol monomers, catechin and EC [25]. The conjunction of several monomeric units results in procyanidins: 2–5 units for catechin oligomers and over 5 units for catechin polymers. The B-type PCs are the most abundant in plant foods like apples, cocoa, and grape seeds [26]. Generally, the A-type PCs have interflavan bonds and ether linkages between the A-ring hydroxyl group and C-2 of the other A-ring, while the B-type PCs have single interflavan bonds between C-4 of the B-ring and either C-8 or C-6 of the C-ring. The dimer PCs consist of two monomers. Double linkages are formed between C–C bond and C–O–C bond in A-type dimer PCs (e.g., A1, A2, Geranins A and B), while single interflavan linkage is formed between C–C bond in B-type dimer PCs (e.g., B1 and B2) at C-4, C-6, and C-8 [25, 26]. A1 dimer PCs are present in peanut (*Arachis hypogaea*) skin, A2 dimer PCs are found in the shells of horse chestnut (*Aesculus hippocastanum*) fruits, chestnut, cranberry, and peanut, geranins A and B are found in *Geranium niveum* [25, 27, 28]. The trimer PCs comprise three monomers connected by single or two bonds with one or two linkages at C-4 and C-8. The A-type trimer PCs include aesculitannin C and cinnamtannin B1, while B-type trimer PCs are C1 and C2 [29]. Cinnamtannin B1 is present in *Cinnamomum verum* [29]. The tetramers have several different configurations, for example, arecatannin A2 (A-type tetramer PCs) and cinnamtannin A2 (B-type tetramer PCs) [30, 31], they are composed of three single C–C bonds while parameritannin A2 consists of two C–O–C ether bonds. Arecatannin A2 is found in cranberry [30]. The different degrees of polymerization, linkages, and interflavan bonds in the chemical structures of PCs affect their biological activities. The B-type PCs, the most common PCs, have some special biological features. B1 is a better oxygen radical scavenger (e.g., $^{\cdot}O_2^{-}$) than A2. The radical scavenging ability of B2 is enhanced by esterification [32]. Kondo et al. [33] reported that the prodesterification (advanced glycated end-products, e.g., methylglyoxal, carboxymethyllysine, and pentosidine) can be inhibited by B2. B2 and B5 PCs are reported as potent inhibitors of hemolysis [32]. B3 and C2 are hair growth

enhancers, and C2 PCs are promoters of the secretion of tumor necrosis factor-alpha (TNF-α) [33]. However, the A-type and B-type PCs can be inter-converted chemically under some conditions. For example, a radical of 1,1-diphenyl-2-picrylhydrazyl (DPPH) can oxidize B1 to A1 under neutral conditions [25, 34]. The anticancer properties of PCs are significantly influenced by their structures. The degree of polymerization and substituent groups (like hydroxyl and methoxy groups) are crucial to the anticancer effects of PCs [26, 35]. Furthermore, the position of these substituent groups determines the potency. For example, 4′-hydroxyl derivative of flavonols is more potent than the 2′-hydroxyl derivative, and 3-methoxy is more cytotoxic [35]. In addition, oligomers and polymers of PCs produce more potent anticancer properties than monomers and dimers [36]. Quifar-Radar et al. [36] reported that oligomers (particularly hexamers) were more potent in reducing the viability of colon cancer cells. However, Kelm et al. [32] revealed that the PC dimer, B3, had higher inhibition of cancer cell proliferation, but more study is required to ascertain the relationship between the degree of polymerization and anticancer effects.

Semi-synthetic derivatives of procyanidins

In the literature, numerous studies document the synthesis of novel procyanidin derivatives aimed at enhancing their bioactive properties [37]. Notably, derivatives of epicatechin-(4b→8)-catechin-3-*O*-(4-hydroxy)benzoate have been a focal point. These derivatives originate from an extract of *Hamamelis virginiana*, a plant traditionally employed in medicine to address gastrointestinal disorders and inflammation [38]. Various experimental approaches have been employed in their synthesis, including electrospray ionization [39], utilization of reducing agents [40], cationic polymerization catalyzed by Lewis acids [41, 42], and catalytic hydrogenation for debenzylation [43, 44]. Efficient condensation of tannins and subsequent formation of phloroglucinol adducts have been achieved through degradation via acid catalysis [45]. Derivatives from pecan nuts (*Caraya illinoensis*) have been obtained through methylation and acetylation [46]. The diverse array of derivatives, coupled with observed effects on biological activities tied to modifications in functional groups, their positioning, polymerization degree, and stereochemistry, merits a comprehensive review [46–48]. In this context, we will focus on three promising cancer control derivatives. The arrangement of the primary PC dimers serves as the foundation for developing key semi-synthetic derivatives, as indicated in Fig. 2. PC derivative **3** is the first synthesized PC [49]. It was obtained by a condensation reaction between leucocyanidin (flavan-3,4-diol), a free polyphenol, catechin (a flavan-3-ol), and a mild acid catalyzed by the enzyme leucocyanidin reductase, and subsequently accompanied by methylation and acetylation reactions (Fig. 2A). PC derivative **6** (Fig. 2B) was synthesized by Weinges et al. [50] using a Grignard-type coupling reaction involving an 8-lithium derivative of catechin and taxifolin derivative B4 to obtain 4-hydroxyprocyanidin. Subsequently, 4-hydroxyl and benzyl groups were reductively removed by hydrogenolysis, and an acetylation reaction concluded the synthetic process. Several studies have reported the synthesis of other PCs derivatives. In this context, dimer derivative **B3** was synthesized from the condensation reaction between tetrabenzylcatechin **7** and benzylated flavan-3,4-diol derivative **8** in the presence of $TiCl_4$ in CH_2Cl_2 (Fig. 2C). The pure compound was obtained with silica gel preparative thin-layer chromatography [51, 52].

Bioavailability and pharmacokinetics of procyanidins

Studies have demonstrated that the oral bioavailability of PCs is limited in tissues and affected by their different molecular structures after ingestion [53]. Weinert et al. observed that methylated PCs have low bioavailability since the cytosolic catechol-*O*-methyltransferase had monophasic, biphasic, and triphasic reactions [54]. The assimilation and bioavailability of PCs could also be affected by carbohydrates, proteins, digestive enzymes, and fibers through a synergistic or antagonistic effect. For example, the amylose–PC complex is less digestible than PCs [55]. On the other hand, the acidic condition of the stomach pH breaks down the PCs into readily assimilable monomers, improving their assimilation and bioavailability. Subsequently, PCs circulate from the stomach to the colon, and assimilation in the intestinal tract depends on their molecular size. PCs with smaller molecular sizes, such as monomers and dimers, are more easily assimilated than larger molecules. Conjugate PCs are formed in the liver, accumulate in tissues, are present in plasma, and are excreted in the urine. The microbiota in the human colon consists of a vast community of microbes that assist and embellish mammalian enzyme activities in the liver and gut. Hence, the biological activities of PCs are related to their degradative products in the colon [56], which could have more biological relevance than the original PCs [57]. For example, **B1** was shown to be metabolized by the gut microbiota into 5-(3′,4′-dihydroxyphenyl)valerolactone, which is a major metabolite of epicatechin. It has higher antioxidant properties, potentially reducing the risk of colon cancer, promoting the Nrf2/ARE pathway (intrinsic mechanism of defense against oxidative stress), and regulating intracellular proteolysis [58]. The hydrolysis of PC oligomers under acidic conditions resulted in a mixture of EC monomers and dimers like those found in the human

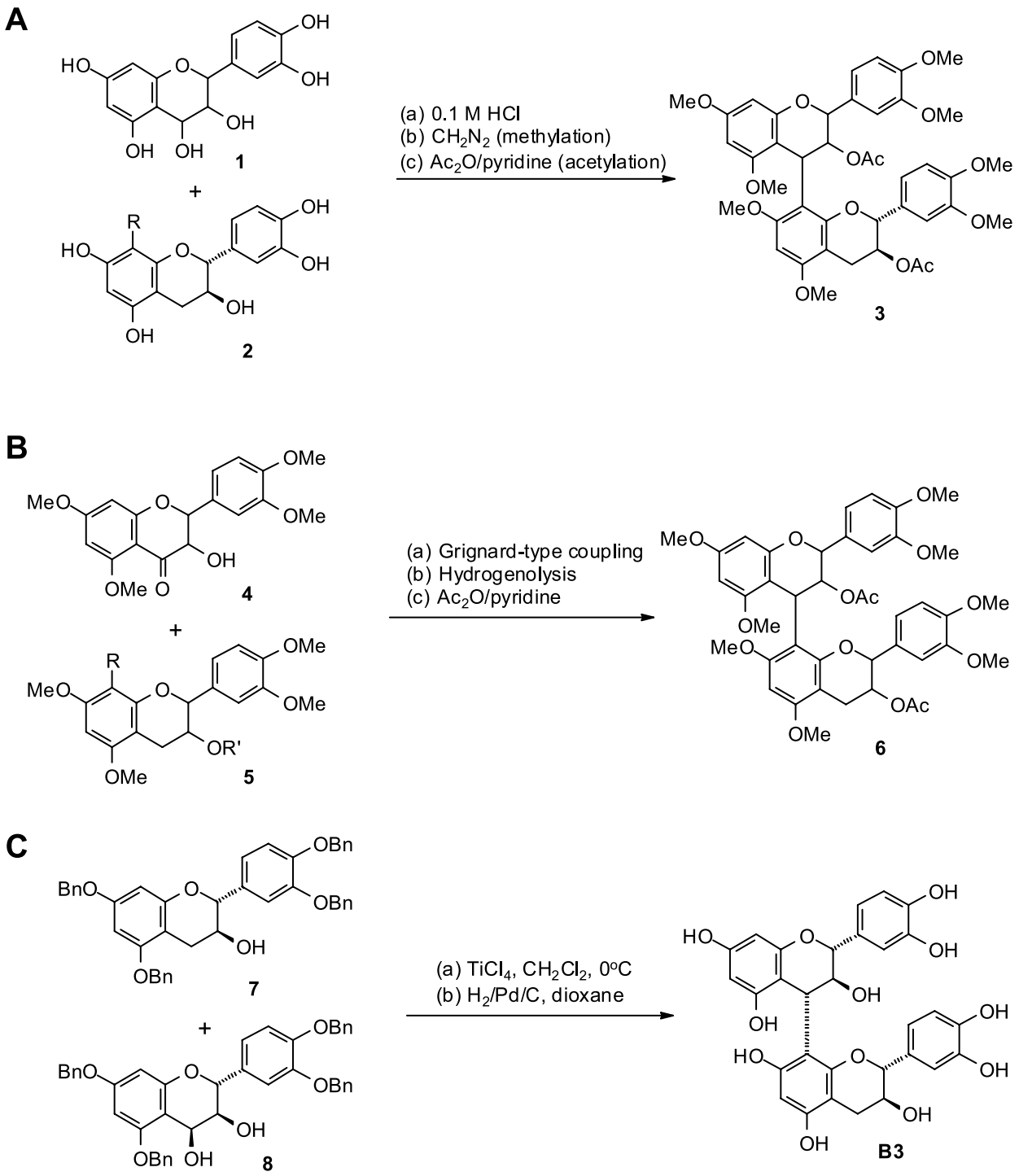

Fig. 2 Semi-synthetic derivatives of procyanidins

stomach [59, 60]. Clinical research on the digestion of PCs in cocoa beverages revealed that PC monomers and dimers were stable [60]. In another similar study that used PC-rich extract from grape seeds in rats, remarkably stabilized PCs were also observed [61]. Zhang et al. [62] reported that when the degree of polymerization of PCs is 5 or more, it results in poor absorption. On the contrary, other research has indicated that PCs exhibiting lower degrees of polymerization, including monomers and dimers, demonstrated favorable intestinal absorption. The findings were validated by testing the Caco-2 monolayer permeation system [63, 64]. In addition, the presence of PC monomers, dimers, and trimers

in the plasma of rats suggested that PCs with less polymerization could be absorbed instantly from the intestine and/or colon [61, 65, 66]. Appeldoorn et al. [67] reported that the PCs dimers, **A1** and **A2**, were well absorbed in rat small intestine than the PC dimer **B2**. The PCs dimers, **B1** and **B2**, were present in serum and plasma after grape seed and cocoa diets and are well absorbed in the human intestine [68, 69]. Wiese et al. suggested that humans did not instantly absorb PCs polymers and oligomers because they were absent in the plasma [70]. After absorption of PCs from the colon, supported by the gut microbiota, they are primarily metabolized in the liver or small intestine into their conjugated and/or methylated forms [62, 71]. Monomeric metabolites in mammals have a higher bioavailability than dimeric metabolites [65, 70]. After ingesting PC monomers and dimers, methylated and conjugated EC and **B1** are present in plasma and urine [70]. Methylation occurs in the liver and is catalyzed by catechol-*O*-methyltransferase [72], while glucuronidation occurs in the small intestine and is catalyzed by uridine 5′diphosphate glucuronosyltransferases [72]. Furthermore, PCs can be metabolized by the colon microbiota [73]. In an in vivo study where rats were fed with cinnamon bark, about 30 PC metabolites (e.g., 3- and 4-hydroxyphenylpropionic acid and phenolic acids) were obtained in the liver, while 3-hydroxyphenylacetic acid and 3,4-dihydroxyphenylacetic acid were the microbial degradative metabolites obtained [29]. Gonthier et al. [74] observed that the microbial degradative metabolites 3-hydroxybenzoic acid, 3-hydroxyhippuric acid, and 3- hydroxyphenylpropionic acid were present in rat urine after ingesting red wine polyphenols. Subsequently, the metabolism of PC dimer **B3**, trimer **C2**, and a polymer isolated from willow tree catkins was compared to catechins in rats. About 16 microbial metabolites (e.g., phenylacetic, phenylpropionic, phenylvaleric, and benzoic acid derivatives) were obtained, reducing total yields from the catechin to the PCs polymer. Thus, the degree of PC polymerization affects microbial metabolism [74, 75]. Moreover, these metabolic products are then distributed into different tissues, organs, and blood. The distribution of PC metabolic products, mainly EC, was studied in rats fed a cocoa diet. Methylated and glucuronidated EC were found in the liver, spleen, testicles, lymphoid tissues, and thymus [76]. The EC metabolic products in the lymph suggest that PCs may modulate immune functions [77]. Likewise, their presence in testicles indicates their potential benefits, including protection from oxidative stress [78]. In another similar research by Serra et al. [79], methylated, sulfated, and glucuronidated catechins were present in the kidney, lung, thymus, testicles, and spleen of rats after ingesting hazelnut extract. In addition, a microbial colon metabolite, protocatechuic acid, was detected in most tissues except testicles, and this could be related to their excretion in urine and the protection of cardiovascular tissues [79, 80]. The metabolic products of PCs can also cross the blood–brain barrier and offer neuroprotection [79, 81]. Excretion occurs after the distribution of PC metabolites into target tissues and organs where they induce their pharmacological effects. The PC dimer, **B2**, and excretion were studied in male rats. After oral administration, about 58% of metabolites were excreted in the urine, while about 41% were excreted in the feces. After intravenous administration, about 76% of metabolites were excreted in urine, while about 28% were excreted in feces [66, 76]. Choy and Waterhouse described that after ingesting the PC dimer **B2**, the metabolized (i.e., methylated, glucuronidated and/or sulfated metabolites of monomers or dimers of flavan-3-ols) and non-metabolized dimer and its colon microbial products were excreted in bile [56]. Therefore, the research suggests that procyanidins are a source of epicatechin and catechins, and their metabolism plays an important role in the properties of all these molecules. It is demonstrated that flavan-3-ol monomers present some advantages in the individual form; however, the efficiency of catechins is lower or nonexistent in some chemical pathways. Therefore, the synergistic effect of various procyanidins and catechins in several diseases and affections supports the need for scientific reports on these compounds employed in high-impact medical conditions such as cancer. Since the necessity of finding new and natural alternatives for world concerns, it is evident that the analysis and evaluation of procyanidins in their different forms and monomers, their interaction in several tissues and tumors, and clinical trials are urgent.

Mechanism of antitumor action of procyanidins

PCs exhibit anticancer properties through multiple mechanisms, including inactivation of enzymatic and chemical processes, modulation of inflammatory pathways, inhibition of cell invasion and metastasis, induction of apoptosis, and cell cycle arrest (Table 1). These activities demonstrate the potential of PCs as therapeutic agents in cancer treatment.

Anti-inflammatory effects, modulation of oxidative stress and redox balance

Inflammation plays a fundamental role in the tumor microenvironment by promoting angiogenesis, proliferation, and immune evasion. PCs mediate anti-inflammatory effects through modulation of cytokine secretion, regulation of inflammatory gene expression, and inhibition of key signaling pathways [82]. PCs can inactivate cyclooxygenase (COX) and lipoxygenase (LOX), which participate in some tumor cells' rapid growth and development [83]. The PC dimer, **B3**, prevents the growth of prostate cancer cells by inhibiting the enzyme histone acetyltransferase and hence,

Table 1 Mechanisms of antitumor action of procyanidins

Mechanism	Molecular targets/pathways	Key findings	References
Anti-inflammatory effects	Cytokines: (IL-1β, IL-2, IL-6, IL-8, TNF-α, INF-γ, IL-10, IL-4, TGF-β NF-κB MAPK COX LOX	PCs modulate cytokine secretion, downregulate NF-κB signaling, Inhibit COX/LOX. PC dimers (e.g., **B2**, **B3**) target histone acetyltransferase and reduce inflammatory cytokines	[82, 84, 85, 111]
Oxidative stress modulation	Reactive oxygen species (ROS) NRF2 Antioxidant enzymes: SOD, catalase	PCs induce ROS-mediated apoptosis in tumor cells and NRF2-mediated antioxidant defense in normal cells Procyanidin **B2** causes oxidative DNA damage and mitochondrial dysfunction in cancer cells	[92, 93]
Macrophage polarization	Peroxisome proliferator-activated receptor gamma (PPARγ) M1/M2 macrophage markers	PCs reprogram tumor-associated macrophages (TAMs) to M1 phenotype, enhancing TNF-α production and reducing tumor-supportive factors	[95]
Cell cycle arrest	p21 Cyclin D1 Cyclin-Dependent Kinases (CDK4) Surviving genes	PCs induce G1 arrest by downregulating cyclin D1, CDK4, and surviving gene expression. This effect is p21-independent in some cancers, such as esophageal adenocarcinoma	[88, 96, 97]
Inhibition of cell invasion/metastasis	Cathepsin B Matrix metalloproteinases (MMPs, e.g., MMP9) VEGF; voltage-gated potassium channels (Kv10.1)	PCs inhibit MMP9 and VEGF expression, reducing metastasis. Procyanidin **B1** targets Kv10.1 channels, reducing migration and proliferation in hepatocellular carcinoma cells	[99, 101]
Apoptosis induction	Death receptors (FAS, DISC) Caspases (CASP3, CASP8, CASP9); BCL2 family proteins; JNK pathway	PCs induce apoptosis via mitochondrial (BCL2 family), death receptor (FAS), and JNK pathways. Procyanidins also reduce mitochondrial membrane potential and increase ROS accumulation	[104, 106, 107, 109]
Paraptosis induction	Calcium mobilization MAPK activation	Oligomeric PCs induce paraptosis-like cell death in glioblastoma cells, involving vacuolization and mitochondrial swelling, independent of apoptosis mechanisms	[112]
Inhibition of tumor angiogenesis	Hypoxia-Inducible Factor-1 Alpha (HIF-1α); VEGF; MMP-2; EGFR-PI3K-AKT-mTOR; MAPK-ERK1/2	PCs downregulate HIF-1α and VEGF pathways, inhibiting angiogenesis and reducing tumor vascularization. PC dimers (e.g., **A2**) block VEGF receptor and downstream signaling	[109, 114, 116]
Enhancement of chemotherapy efficacy	Efflux pumps; calcium channels; mitochondrial membrane potential	PCs potentiate chemotherapy (e.g., doxorubicin) by reducing drug efflux, increasing calcium influx, and disrupting mitochondrial membrane potential to induce apoptosis	[117, 118]

BCL2 B-cell lymphoma 2, *CASP* caspase, *CDK* cyclin-dependent kinase, *COX* cyclooxygenase, *DISC* death-inducing signaling complex, *EGFR* epidermal growth factor receptor, *INF* interferon, *IL* Interleukin, *JNK* c-Jun N-terminal kinase, *LOX* lipoxygenase, *MAPK* mitogen-activated protein kinase, *MMP* matrix metalloproteinase, *NRF2* nuclear factor erythroid 2-related factor 2, *PGE2* prostaglandin E2, *ROS* reactive oxygen species, *SOD* superoxide dismutase, *TAM* tumor-associated macrophage, *TGF* transforming growth factor, *TNF α* tumor necrosis factor alpha, *VEGF* vascular endothelial growth factor

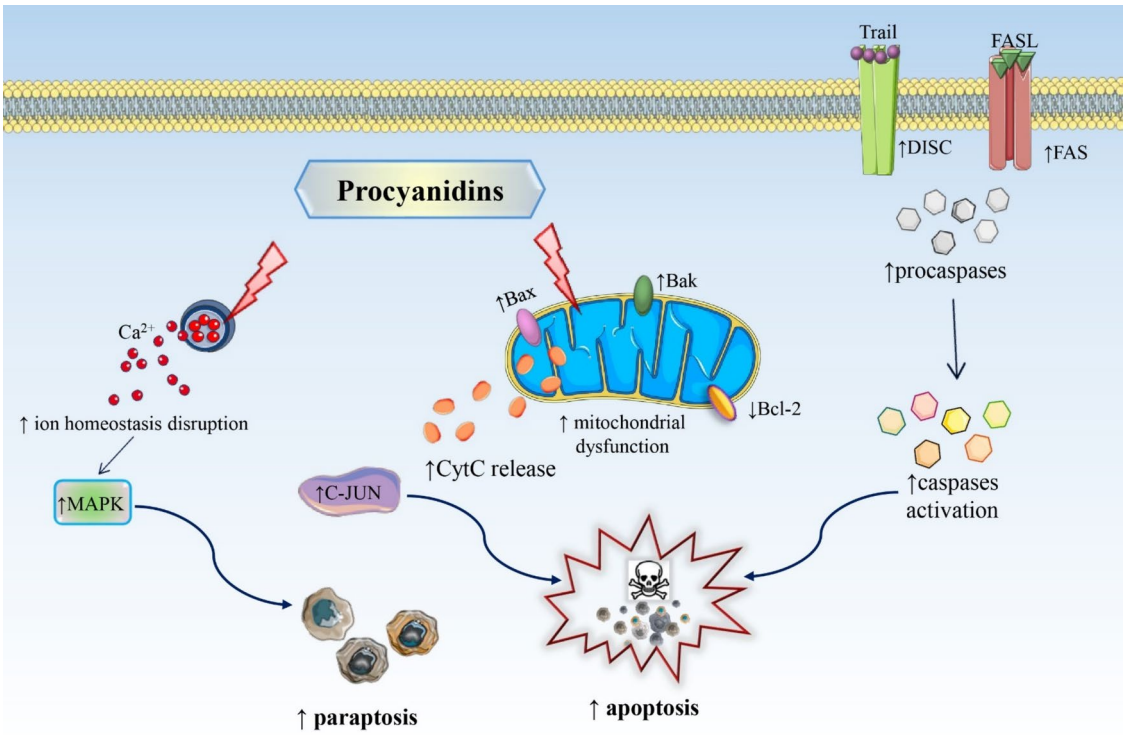

Fig. 3 Summarized scheme regarding the molecular mechanisms by which procyanidins induce paraptosis and apoptosis in cancer cells. Procyanidins disrupt ion homeostasis, leading to calcium (Ca^{2+}) dysregulation and activation of the MAPK pathway, which triggers paraptosis. Concurrently, procyanidins upregulate pro-apoptotic proteins (e.g., Bax and Bak) and downregulate anti-apoptotic proteins (e.g., BCL2), causing mitochondrial dysfunction and cytochrome c (CytC) release. This initiates the apoptotic cascade via caspase activation. Additionally, the extrinsic apoptotic pathway is activated through FASL/FAS and TRAIL/DISC complexes, further amplifying caspase activity and promoting apoptosis. Abbreviations: *Bax* BCL2-associated X protein, *Bak* BCL2 homologous antagonist/killer, *BCL2* B-cell lymphoma 2, Ca^{2+} calcium ions, *CytC* cytochrome c, *DISC* death-inducing signaling complex, *FAS* Fas cell surface death receptor, *FASL* Fas ligand, *HIF-1* hypoxia-inducible factor 1, *MAPK* mitogen-activated protein kinase, *mTOR* mammalian target of rapamycin, *p70S6K* p70 S6 kinase, *TNF-α* tumor necrosis factor-alpha, *TRAIL* TNF-related apoptosis-inducing ligand

suppressing the acetylation of the p300-mediated androgen receptor required to develop prostate cancer cells [84]. This highlights the role of specific PC dimers in targeting epigenetic regulators of tumorigenesis. PCs reduce the production of inflammatory cytokines like IL-1β, IL-2, IL-6, IL-8, TNF-α, INF-γ, and prostaglandin E2 (PGE2) [85, 86]. Also, PCs increase the expression of IL-10, IL-4, NRF2, TGF-β, and other target antioxidant genes that encode superoxide dismutase (SOD) and catalase [87, 88]. In addition, PCs induce anti-inflammatory effects by inhibiting NF-κB and mitogen-activated protein kinase (MAPK) pathways [89, 90]. Mackenzie et al. [91] reported that the PC dimer, **B2**, inhibited the secretion and expression of cytokines by reducing NF-κB DNA binding and downregulating its gene expression in Hodgkin/Reed-Sternberg cells. This inhibitory effect on NF-κB is a recurring mechanism in the anticancer actions of procyanidins, also contributing to their ability to overcome chemoresistance. Procyanidins exhibit a dual role in oxidative stress modulation. In tumor cells, procyanidins selectively increase reactive oxygen species (ROS), disrupting redox homeostasis and leading to apoptosis. For instance, procyanidin **B2** induces oxidative DNA damage by interacting with H_2O_2 and metal ions in cancer cells, which results in the activation of caspase-3 and mitochondrial dysfunction [92]. Conversely, in normal cells, procyanidins function as antioxidants by upregulating NRF2-mediated expression of antioxidant enzymes, such as superoxide dismutase (SOD) and catalase, to protect against oxidative damage [93]. Tumor-associated macrophages often exhibit an M2-like phenotype that supports tumor growth, angiogenesis, and immune evasion [94]. Procyanidins reprogram TAMs to an M1-like phenotype, enhancing their antitumor activity. Procyanidin **B2** activates peroxisome proliferator-activated receptor gamma (PPARγ), inducing M1 macrophage markers such as Arg1, Ym1, and Fizz1. This macrophage polarization promotes inflammatory cytokine production (e.g., TNF-α) and inhibiting tumor-supportive factors [95].

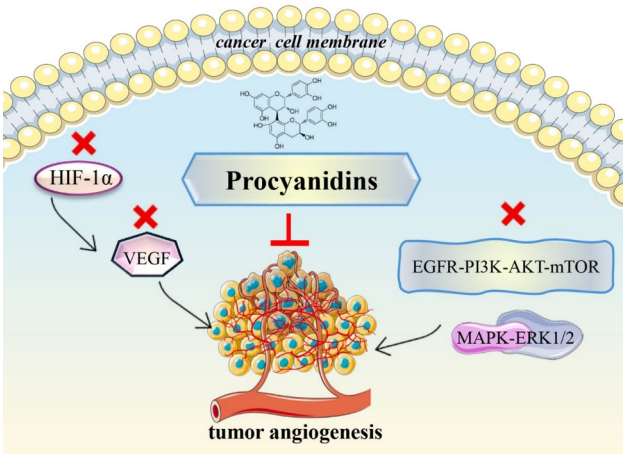

Fig. 4 Summarized scheme regarding antiangiogenetic effect of procyanidins. Procyanidins suppress hypoxia-inducible factor 1-alpha (HIF-1α), leading to the downregulation of vascular endothelial growth factor (VEGF), a key factor in angiogenesis. Additionally, procyanidins inhibit critical pro-angiogenic signaling pathways, including the epidermal growth factor receptor (EGFR)-phosphoinositide 3-kinase (PI3K)-protein kinase B (AKT)-mammalian target of rapamycin (mTOR) axis and the mitogen-activated protein kinase (MAPK)-extracellular signal-regulated kinase 1/2 (ERK1/2) pathway. These inhibitory effects contribute to the suppression of tumor blood vessel formation, ultimately restricting tumor growth and progression. Abbreviations: *EGFR* epidermal growth factor receptor, *ERK1/2* extracellular signal-regulated kinase 1/2, *HIF-1α* hypoxia-inducible factor 1-alpha, *MAPK* mitogen-activated protein kinase, *mTOR* mammalian target of rapamycin, *PI3K* phosphoinositide 3-kinase, *VEGF* vascular endothelial growth factor

Cell cycle arrest

Kaur et al. indicated that PCs arrest the cell cycle, modulating the expression of the p21 gene [96]. A recent study that utilized PC to treat esophageal cancer cells reported that the downregulation of the p21 gene did not cause any effect on the induction of G0/G1 cell cycle arrest. The procyanidin-mediated induction of apoptosis and cell cycle arrest in esophageal adenocarcinoma cells is not dependent on p21 (Cip1/WAF1). Hence, the p21 gene may not be responsible for the induction of cell cycle arrest by PCs. Treating cancer cells with PCs caused G1 arrest and inhibited the expression of cyclin D1, CDK4, and surviving genes [88]. Chung et al. [97] reported that cancer cells treated with PCs exhibited G1 cell cycle arrest and decreased cyclin D1, E, A, and B1 gene expression. Thus, the ability of PCs to induce cell cycle arrest could be related to the knock-down of cyclin D1, cyclin-dependent kinases (CDKs, particularly CDK4), and surviving genes. Since cell cycle arrest can prevent the growth and development of malignant cells, it is believed to be a potent way of treating cancer.

Inhibition of cell invasion and metastasis

The invasion and metastasis of tumor cells are critical to cancer development [98]. PCs can inhibit this invasion and metastasis by knocking down the expression of critical molecules and genes associated with angiogenesis and metastatic progression. Wu et al. [99] and Li et al. [100] revealed that PCs inhibited human cervical cancer cell migration via the down-regulation of cathepsin B expression. The MMPs and vascular endothelial growth factor (VEGF) are essential for cell migration. PCs inhibited the expression of MMP9 in colon cancer (SW-480) cells and, thus, prevented invasive and metastatic activities [90]. Voltage-gated potassium channels, such as Kv10.1, are overexpressed in several cancers and play an important role in cell proliferation, migration, and tumor progression [101]. Procyanidin **B1** specifically inhibits Kv10.1 with an IC_{50} of 10.38 μM, reducing the migration and proliferation of hepatocellular carcinoma cells in vitro and suppressing tumor growth in xenograft mouse models without affecting normal tissues (Na et al., 2020). This demonstrates the potential of procyanidins as targeted therapies for Kv10.1-expressing tumors.

Apoptosis and paraptosis induction

Procyanidins induce apoptosis via multiple, often overlapping pathways, including both mitochondrial (intrinsic) and death receptor-mediated (extrinsic) routes. These involve key regulators such as caspases (CASP3, CASP8, CASP9), BCL2 family proteins, and Cytochrome c release (Fig. 3) [102–105]. In MCF-7 and A549 cells, procyanidins activate caspase-9 via the mitochondrial apoptosome and suppress anti-apoptotic BCL2, as shown in several cancer models [106, 107]. PCs alter mitochondrial membrane permeability through modulation of BAX, BAK, and BCL2, triggering Cytochrome c release and caspase cascades [107–110]. ROS accumulation also contributes to this process, particularly in cancer cells with weakened antioxidant defenses [85, 108–111]. PCs additionally activate the JNK pathway to enhance apoptosis through c-Jun signaling [112]. Oligomeric procyanidins isolated from grape seeds induce paraptosis-like cell death in U-87 glioblastoma cells. This involves calcium mobilization, MAPK activation, and protein synthesis, independent of nuclear fragmentation or apoptotic body formation [112]. This unique mechanism offers an alternative pathway to eliminate apoptosis-resistant tumor cells.

Inhibition of tumor angiogenesis

Tumor angiogenesis is driven by hypoxia-inducible factor-1 alpha (HIF-1α) and vascular endothelial growth factor (VEGF), which are key targets for cancer therapy [113] (Fig. 4). Procyanidins suppress HIF-1α expression and its downstream effectors (e.g., VEGF, MMP-2) via the EGFR-PI3K-AKT-mTOR and MAPK-ERK1/2 pathways, inhibiting angiogenesis and reducing tumor vascularization in vitro [114]. Taparia and Khanna [109] described that PCs extracted from cocoa cause down-regulation of MMP2 in ovarian cancer cell lines. PCs also inhibited the expression of the VEGF gene in human breast cancer (MDAMB-231) cells and reduced angiogenesis [115]. In addition, the PC dimer **A2** inhibited the migration of vascular smooth muscle cells via kinase insert domain receptor (VEGF receptor) and JAK2/STAT-3/cPLA2 signaling pathways [116]. This demonstrates the ability of PCs to act as broad-spectrum inhibitors of the molecular pathways underlying tumor metastasis. This anti-angiogenic effect limits tumor growth and metastasis.

Enhancement of chemotherapy efficacy and reversal of drug resistance

The enhancement of chemotherapy efficacy and the reversal of drug resistance are essential strategies in cancer therapy, focusing on addressing the molecular mechanisms of resistance, including drug efflux, dysregulated survival signaling, and impaired apoptosis, to improve therapeutic outcomes and overcome treatment challenges [117]. Procyanidins potentiate the efficacy of chemotherapeutic agents like doxorubicin by overcoming multidrug resistance (MDR). In doxorubicin-resistant K562/DOX cells, procyanidins enhance intracellular drug accumulation by decreasing efflux pump activity, elevate intracellular calcium levels, and disrupt mitochondrial membrane potential, leading to increased apoptosis [118].

Modulation of microRNAs (miRNAs)

Procyanidins have been shown to modulate the expression of specific microRNAs (miRNAs), which play critical roles in cancer progression and therapeutic resistance. For example, Mao et al. demonstrated that grape seed-derived PCs down-regulate oncogenic miRNAs such as miR-19a, miR-19b and miR-106b in lung cancer models[119]. These miRNAs are known to regulate eicosanoid signaling and apoptosis-related pathways, suggesting that PCs exert part of their anticancer effects through epigenetic regulation. Targeting miRNAs may offer a novel strategy to enhance the selectivity and durability of PC-based therapies [120].

Preclinical anticancer studies

Several in vitro cell and in vivo animal models of anticancer activities have been employed to evaluate PCs. The representative preclinical anticancer studies of PCs are presented in Table 2.

Clinical studies

While limited scientific reports are available on human clinical studies evaluating the anticancer therapeutic potential of procyanidins (PCs), preclinical and in vitro findings suggest promising outcomes. Various studies have demonstrated the potential of PCs to inhibit tumor growth, modulate oncogenes, and enhance key signaling pathways involved in cancer progression. For example, recent research has highlighted the role of PCs in combination therapies and their effects on cancer-related biomarkers. Several clinical trials have been conducted or are currently underway to further explore these findings, assessing the efficacy of PCs across different cancer types. Table 3 summarizes critical clinical trials related to the use of procyanidins in cancer treatment, along with their outcomes or current status.

Synergistic effects of procyanidins in cancer therapy

The synergistic effects of procyanidins with chemotherapeutic agents, radiotherapy, and bioactive compounds are mediated by several mechanisms. Procyanidins enhance apoptosis by upregulating pro-apoptotic proteins such as Bax and caspases, while simultaneously downregulating anti-apoptotic proteins like BCL2. They increase intracellular drug concentrations by inhibiting P-glycoprotein, a protein responsible for drug efflux, thereby overcoming chemoresistance [134]. Procyanidins also inhibit key survival pathways such as AKT, ERK, and NF-κB, thus sensitizing cancer cells to chemotherapy and radiotherapy [135]. Furthermore, they promote radiosensitivity by inducing oxidative stress and enhancing radiation-induced DNA damage, leading to increased cancer cell death [135].

Synergy with chemotherapy

Procyanidins enhance the effects of various chemotherapeutic agents by improving their efficacy and reducing the required therapeutic dose, thus minimizing side effects (Table 4). For example, a study demonstrated that grape seed proanthocyanidins significantly enhanced the anticancer

Table 2 Preclinical anticancer studies of procyanidins

Type of cancer	Cell line/model	Concentrations IC_{50}/doses	Mechanisms	Results	Reference
Breast cancer	MDA-MB-231 cells In vitro	25–75 μM	Induction of cell cycle arrest and apoptosis Reduced expression levels of VEGF	Inhibits cell invasiveness Inhibits MMP-9	[115]
Prostate cancer	Hodgkin and reed-sternberg (H-RS) cell line In vitro	2.5–100 μM	Modulation of NF-κB, IL-6, TNF-α, and RANTES signaling pathways	Inhibition of the release and expression of NF-kB-dependent cytokines and anti-apoptotic proteins	[91, 121]
Bladder cancer	BIU87 cells In vitro	Not available	Induction of cell cycle arrest	G1 phase cell cycle arrest Inhibition of CDKs	[88]
	T24 and 5637 bladder cancer cells In vitro	50 mg/mL	PCs robustly suppress the migration and invasion of bladder cancer cells by reversing the epithelial-mesenchymal transition (EMT), and this effect is achieved through the inhibition of the TGF-β signaling pathway	The treatment inhibited migration, invasion, and MMP-2/-9 secretion	[122]
Colorectal cancer	Caco-2 cells In vitro	10–30 μM	Arresting the cell cycle in G2/M phase Inducing apoptosis via the mitochondrial pathway	The treatment inhibited cell migration, invasion, and adhesion, decreasing the activity of matrix metalloproteinases (MMP-2/9)	[123]
	Caco-2 cells In vitro	100–500 nM	Attenuating EGF-induced EGFR dimerization and NADPH oxidase-dependent phosphorylation at Tyr 1068, decreasing EGFR location at lipid rafts, and inhibiting the downstream activation of pro-proliferative and anti-apoptotic pathways, i.e., Raf/MEK/ERK1/2 and PI3K/Akt	decrease EGFR phosphorylation and inhibit cell growth	[124]
	HCT116, HT29 HCT116 CRC cells In vitro	10.0 μg/mL 50 mg/kg	Inhibition of progression and proliferation of tumor growth Increased apoptosis	Treatment did not induce cell toxicity to NCM460 cells, and this specifies anti-proliferative effects only for cancer cells The apoptotic cells increased from 5.4 to 6.5%	[125]
Colon cancer	Caco-2 cells In vitro	10 μM	Reduction in plasma levels of inflammatory factors Modulation of ERKs and JNKs signaling pathways	Inhibition of caspase-3 enzyme activity GSH depletion and ROS generation was prevented	[110, 126]
Lung cancer	A549 cancer cells In vitro	200 mM	PCs enhanced the expression of the pro-apoptotic protein Bax while suppressing the expression of the anti-apoptotic protein BCL2. It also inhibited the epithelial-mesenchymal transition (EMT) process in A549 cells. The JAK2/STAT3 signaling pathway inhibitor, AG490, synergized with PCs to effectively impede the invasion and migration of A549 cells	The treatment inhibited the migration and invasion of A549 cells and induced apoptosis and G2/M cell cycle arrest	[99]

Table 2 (continued)

Type of cancer	Cell line/model	Concentrations IC_{50}/doses	Mechanisms	Results	Reference
Gastric cancer	BGC-823 SGC-7901 cells In vitro	50 mM	Induction of caspase-3 and -9 activities The treatment-induced autophagy, evidenced by heightened LC3 staining and elevated expression of Beclin1 and Atg5, and reduced the protein expression of p-Akt and p-mTOR	The treatment induced an increased apoptosis rate of gastric cancer cells	[127]
Liver cancer	Nude mice In vivo	100–200 mg/kg	They suppress the phosphorylation of mitogen-activated protein kinase (MAPK) pathway-associated proteins, namely p-JNK, p-ERK, and p-p38 MAPK, while concurrently decreasing survivin expression	The treatment inhibited the growth of HepG2 cells in nude mice without causing observable toxicity and autophagy	[128]
Lung cancer	MLE-12, BEAS/2B, LLC A549 cells In vitro	20 mg/mL	Differential regulation of the MAPK signaling pathway Regulated secretion of cytokines IL-6 and IFN-γ and expression of p53 and Ki67	The treatment inhibited tumor growth and played a synergistic killing effect with radiotherapy	[129]

BAX BCL2-associated X protein, *BCL2* B-cell lymphoma 2, *BEAS/2B* human bronchial epithelial cell line, *BIU87* human bladder cancer cell line, *CDKs* cyclin-dependent kinases, *CRC* colorectal cancer cells, *EGFR* epidermal growth factor receptor, *EMT* epithelial-mesenchymal transition, *ERKs* extracellular signal-regulated kinases, *GSH* glutathione, *HCT116* human colorectal carcinoma cell line, *HT29* human colorectal adenocarcinoma cell line, *IFN-γ* interferon gamma, *IL-6* interleukin 6, *JAK2* Janus kinase 2, *JNKs* c-Jun N-terminal kinases, *Ki67* cellular proliferation marker, *MAPK* mitogen-activated protein kinase, *MDA-MB-231* human breast adenocarcinoma cell line, *MLE-12* mouse lung epithelial cell line, *MMP-2* matrix metalloproteinase-2, *MMP-9* matrix metalloproteinase-9, *NCM460* normal human colon mucosal epithelial cell line, *PCs* procyanidins, *PI3K* phosphoinositide 3-kinase, *p-JNK* phosphorylated c-Jun N-terminal kinase, *p-ERK* phosphorylated extracellular signal-regulated kinase, *p-mTOR* phosphorylated mammalian target of rapamycin, *Raf/MEK/ERK1/2* mitogen-activated protein kinase signaling pathway, *ROS* reactive oxygen species, *STAT3* signal transducer and activator of transcription 3, *TGF-β* transforming growth factor beta, *TNF-α* tumor necrosis factor alpha, *VEGF* vascular endothelial growth factor

Table 3 Summary of clinical studies investigating the anticancer potential of procyanidins (PCs)

Clinical trial	Study focus	Outcome/conclusion	References
Tadanobu et al	Anticancer activity of *Andrographis paniculata* with oligomeric PCs in patient-derived tumor organoids from colorectal cancer patients	Synergistic and enhanced anti-proliferative effects and tumor growth inhibition were observed. Increased expression of the HMOX1 gene (heme oxygenase-1) suggested a potential mechanism involving ferroptosis as a regulator of the antitumor effect	[125]
Mao et al	Phase I study on grape seed procyanidin extract for lung cancer	Modulation of oncogenes miR-19a, -19b, and -106b, with effects on eicosanoid signaling pathways. Indirect biomarker (SEBM) associated with lung carcinogenesis was significantly altered. The study suggests that the grape seed procyanidin extract complexed with soy phospholipids is a promising candidate for lung cancer prevention	[119]
NCT03465345	Combination of procyanidin complexes and metformin for prostate cancer	Ongoing; results pending. Expected to provide insights into the role of PCs in prostate cancer therapy	[130]
NCT00041223	Grape seed extract for breast cancer prevention in postmenopausal women	Ongoing; results pending. The study focuses on potential cancer-prevention benefits of grape seed extract	[131]
NCT04515004	Early treatment of lung cancer with procyanidins	Ongoing; results pending. The trial explores the application of procyanidins in early-stage lung cancer treatment	[132]
NCT03482401	Treatment of breast cancer patients with procyanidins	Ongoing; results pending. Investigate the therapeutic potential of procyanidins in breast cancer treatment	[133]

Table 4 Synergistic effects of procyanidins in cancer therapy

Combination strategy	Cancer type/cell line	Mechanism of action	Outcomes	References
Procyanidins + chemotherapy (doxorubicin)	Leukemia cells (In vitro, In vivo mouse model)	Increased intracellular DOX concentration, reduction in mitochondrial membrane potential, Increased intracellular calcium	Enhanced apoptosis and tumor growth suppression compared to DOX alone	[136]
Procyanidin B2 + Docetaxel	Prostate and breast cancer cells (In vitro)	↑ BAX ↑caspase-9 ↓BCL2	Increased apoptosis and effectiveness in overcoming drug resistance	[137]
Low-molecular-weight procyanidins + 5-Fluorouracil (5-FU)	Colon cancer cells (In vitro)	↓ AKT ↓NF-κB	Enhanced cytotoxicity and apoptosis compared to 5-FU alone	[138]
Procyanidins from *Uncaria rhynchophylla* + 5-FU	Breast cancer cells (In vitro)	Induction of G2/M cell cycle arrest ↑ ROS ↑Alteration of Bax/BCL2 ratio	More effective against drug-resistant breast cancer than either agent alone	[139]
Procyanidins + Radiotherapy (X-ray)	Lung adenocarcinoma (SPC-A-1) cells (In vitro)	Reduction in mitochondrial membrane potential, ↑Apoptosis ↑ Cell cycle arrest	Increased radiosensitivity and enhanced therapeutic effects	[141]
Peanut skin-derived procyanidins + Resveratrol	Colorectal cancer cells (In vitro)	↓ AKT ↓ERK ↓NF-κB pathways	Inhibited cell proliferation, induced apoptosis, and arrested cell cycle at G0/G1 phase	[135]
Apple-derived procyanidins + Lysosomotropic drugs	Colon cancer cells (In vitro)	↑ Lysosomal membrane permeability	Amplified growth inhibition and apoptosis	[142]
Procyanidins + Green tea polyphenols (EGCG) + Cisplatin	Lung cancer cells (In vitro)	↑Apoptosis ↑Cell cycle arrest	Reduced cisplatin toxicity while maintaining efficacy	[143]

AKT protein kinase B, *BAX* BCL2-associated X protein, *BCL2* B-cell lymphoma 2, *DOX* doxorubicin, *EGCG* epigallocatechin gallate, *ERK* extracellular signal-regulated kinase, *G0/G1* growth 0/G1 phase of the cell cycle, *G2/M* growth 2/mitosis phase of the cell cycle, *NF-κB* nuclear factor kappa B, *ROS* reactive oxygen species, *5-FU* 5-fluorouracil. Symbols:↑ increase

effect of doxorubicin (DOX) in leukemia cells and in mouse models. The combination therapy increased intracellular DOX concentrations, leading to greater apoptosis and tumor growth suppression compared to DOX alone. The mechanism included reductions in mitochondrial membrane potential and increased intracellular calcium, which collectively enhanced the chemotherapeutic effect [136]. Similarly, procyanidin B2, when combined with docetaxel, significantly increased apoptosis in prostate and breast cancer cells. This synergy was attributed to the upregulation of apoptosis-related genes such as BAX and caspase-9 while downregulating the expression of anti-apoptotic proteins [137]. The combined therapy was especially effective in overcoming resistance in hormone-related cancers, offering a potent approach to treating these malignancies [137]. Another study highlighted the combination of low-molecular-weight procyanidins with 5-fluorouracil (5-FU) in colon cancer cells. The procyanidins not only enhanced the cytotoxicity of 5-FU but also surpassed the chemotherapeutic agent's efficacy in reducing cell viability in vitro [138]. This effect was attributed to the ability of procyanidins to inhibit survival pathways such as AKT and NF-κB, leading to increased cancer cell apoptosis and decreased cell proliferation Procyanidins from *Uncaria rhynchophylla* have also shown synergistic effects with 5-FU in breast cancer cells. This combination-induced G2/M cell cycle arrest and apoptosis by increasing ROS levels, disrupting mitochondrial function, and altering the Bax/BCL2 ratio. The combined treatment was more effective than either agent alone, making it a promising strategy for drug-resistant breast cancer [139].

Synergy with radiotherapy

Procyanidins have demonstrated radiosensitizing effects, enhancing the efficacy of radiotherapy in cancer treatment [140]. A study on lung adenocarcinoma cells (SPC-A-1) showed that grape seed procyanidins significantly increased the sensitivity of cancer cells to X-ray radiotherapy. The combined treatment-induced apoptosis, reduced mitochondrial membrane potential, and caused cell cycle arrest. These findings highlight the potential of procyanidins to act as natural radiosensitizers that improve the therapeutic outcomes of radiotherapy [141].

Synergy with other bioactive compounds

Procyanidins also exhibit synergistic effects when combined with other natural bioactive compounds. For instance, peanut skin-derived procyanidins, when combined with resveratrol, demonstrated strong anticancer activity in colorectal cancer cells. The combination significantly inhibited cell proliferation, induced apoptosis, and arrested the cell cycle at the G0/G1 phase. Mechanistically, this synergy was mediated through the inhibition of the AKT, ERK, and NF-κB signaling pathways, which are crucial for cancer cell survival and proliferation [135]. Similarly, apple-derived procyanidins, when combined with lysosomotropic drugs, amplified growth inhibition and apoptosis in colon cancer cells. The combination worked by increasing lysosomal membrane permeability, a novel mechanism that adds another dimension to the potential uses of procyanidins in cancer therapy [142]. Another example is the combination of procyanidins with green tea polyphenols (EGCG) and cisplatin in lung cancer cells. The tripartite combination significantly enhanced apoptosis and cell cycle arrest compared to the individual components. This synergy allowed for the use of lower doses of cisplatin, reducing its associated toxicity while maintaining efficacy [143]. The synergistic interactions of procyanidins with chemotherapy, radiotherapy, and other bioactive compounds highlight their potential as powerful adjuncts in cancer therapy. These natural polyphenols not only enhance the efficacy of conventional treatments but also reduce their toxicity, offering a promising approach to multimodal cancer treatment. Further research and clinical trials are essential to fully realize the therapeutic potential of procyanidins in combination therapies.

Safety profile and translational outlook

Earlier studies reported that PCs were relatively regarded to be safe because they initially believed that they were not absorbed from the gut. However, subsequent studies have shown that PC monomers, dimers, and the hydrolyzed products of oligomers and polymers are absorbed [70, 144, 145]. Lluis et al. [146] and Yamakoshi [147] carried out several mutation tests (micronucleus, chromosomal aberration, and reverse mutation) on PC-rich extracts from grape seeds and skins and discovered that the PC-rich extracts were not mutagenic when orally administered to mice. The acute toxicity test further showed that the LD_{50} of this extract was reported to be higher than 5000 mg/kg in the tested mice [146]. Several studies have been carried out to ascertain the safety of PCs. In an in vitro study by Segal et al. [148], the mutagenicity of Oligopinr, a PC oligomer-rich extract from French maritime pine bark was investigated in human and bacterial and lymphocytes. It was observed that PCs did not produce mutation in the genes. Similarly, an in vivo study carried out by Segal et al. to ascertain the toxicity of Oligopinr in orally administered rats [148] demonstrated that the PC oligomer did not cause any adverse effect at the different doses (1000 mg/kg and 2000 mg/kg) tested. In another in vitro study by Frevel et al. on the toxicity of Enzogenolr, a PC oligomer-rich extract from pine bark, no mutagenic activity was observed when a bacterial reverse mutation test was carried out [149]. Sano [150] tested a PC-rich extract

from grape seed on healthy Japanese subjects and reported that it was generally safe (the highest dose tolerated when administered orally was 2500 mg/day for 4 weeks). Despite these promising findings, further evaluation of chronic toxicity, immunogenicity, and long-term safety in diverse populations remains essential before widespread clinical application. To bridge preclinical efficacy and clinical translation, several critical steps must be addressed. These include a good pharmacokinetic profiling, development of reproducible formulations, and execution of well-controlled early-phase clinical trials. Encapsulation of PCs into nanocarriers, such as polymeric nanoparticles, liposomes, or lipid-based systems, has been shown to enhance bioavailability and stability. Functionalizing these nanocarriers with ligands like folic acid or hyaluronic acid (HA) enables active targeting to tumor tissues that overexpress folate or CD44 receptors, respectively. This strategy may significantly improve tumor accumulation and reduce systemic toxicity.

Frevel et al. evaluated the toxicity of Enzogenolr on hematology and biomarkers of liver and kidney functions [149]. The PC oligomer consumed at 960 mg/day for 5 weeks and 480 mg/day for 6 months by healthy subjects did not produce adverse effects. Evans et al. administered whole grape extract to pre-diabetic, pre-hypertensive, and overweight subjects for 6 to 14 weeks, and no adverse effect was observed in the parameters evaluated [151]. Translating procyanidins from bench to bedside involves several critical steps, including preclinical validation, pharmacokinetic profiling, formulation optimization, and early-phase clinical trials. Recent studies on related flavonoids such as baicalein and crocin underscore the importance of such translational frameworks to assess therapeutic viability, safety, and combinatorial potential in oncology settings [152, 153].

Conclusion and future perspectives

Procyanidins (PCs), widely present in fruits, vegetables, cocoa, and other plant-based foods, have shown significant potential as anticancer agents due to their ability to modulate inflammatory pathways, inhibit angiogenesis, induce apoptosis, and prevent tumor invasion and metastasis. Their diverse structural forms, especially dimers and oligomers, contribute to these biological activities with enhanced efficacy observed in specific subtypes. While preclinical and emerging clinical evidence underscores their therapeutic promise, challenges such as low oral bioavailability and complex metabolism remain significant barriers to their clinical application. The existing data on their safety profile, including high LD_{50} values and minimal toxicity in both animal and human studies, suggests that PCs are well-tolerated at therapeutic doses, but further investigation is necessary to fully establish their safety for long-term use.

Despite the promising preclinical and mechanistic findings, several limitations must be acknowledged. The current body of clinical evidence remains sparse and largely preliminary, limiting our ability to draw firm conclusions about therapeutic efficacy. Additionally, procyanidins suffer from poor oral bioavailability, structural variability, and rapid metabolic degradation, which complicate standardization and dose optimization. These factors pose significant barriers to clinical translation and highlight the need for well-designed pharmacokinetic studies and delivery innovations. Moreover, the heterogeneity in study designs and cancer models across existing research makes cross-comparison challenging. To fully exploit the therapeutic potential of procyanidins, several future research directions must be pursued. First, addressing the issue of low bioavailability is critical. Innovative delivery systems, including nanoemulsions, micelles, and liposomes, offer promising solutions to enhance their stability and absorption. Encapsulation strategies utilizing nanoparticles designed for targeted and controlled release can further improve their pharmacological efficacy by ensuring higher systemic bioavailability and site-specific delivery. Second, the synergistic effects of PCs when combined with chemotherapy, radiotherapy, and other bioactive compounds require further exploration. These combinations have the potential to reduce the required doses of conventional treatments, thereby minimizing side effects and improving patient outcomes. Studies focusing on the molecular mechanisms underlying these synergies are essential to establish optimized therapeutic protocols. Additionally, future research should explore the role of PCs in targeting specific cancer types and pathways. For instance, the ability of PCs to inhibit Kv10.1 ion channels and reprogram tumor-associated macrophages demonstrates their promise in precision oncology. Omics-based approaches, including proteomics and transcriptomics, could provide deeper insights into their molecular targets and mechanisms of action. Furthermore, well-designed clinical trials are urgently needed to translate preclinical findings into clinical applications. These trials should focus on determining optimal dosing regimens, safety, and efficacy across diverse populations, as well as evaluating their potential as both chemopreventive and therapeutic agents. Long-term toxicity studies are equally important to ensure the safety of PCs in chronic use, alongside investigations into potential interactions with other medications and dietary components, particularly for applications in integrative oncology. The development of semi-synthetic derivatives of PCs offers another avenue for future exploration. Structural modifications designed to enhance stability, bioavailability, and pharmacological activity could overcome many of the current limitations associated with natural PCs. These derivatives could be tailored to specific therapeutic needs, potentially enhancing their anticancer efficacy while reducing any undesirable effects. In

conclusion, procyanidins hold immense promise as natural resources for cancer prevention and therapy. However, it is important to note that while preclinical findings are promising, current clinical evidence remains limited. Most available human studies are preliminary, and robust, large-scale clinical trials are needed to validate the efficacy, safety, and therapeutic applicability of procyanidins in oncology. With advancements in formulation technologies, targeted delivery systems, and combination strategies, they can complement existing treatment modalities, offering a less toxic and more effective approach to cancer management. Continued efforts in research and development will be crucial to overcoming current limitations and translating the therapeutic potential of PCs into widespread clinical success.

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