



The role of proanthocyanidins as dietary bioactive compounds in cancer prevention and therapy: Mechanisms and perspectives

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ABSTRACT: Cancer is one of the leading causes of death worldwide, and its high incidence and mortality pose a significant threat to public health. Studies show that more than two-thirds of cancer-related deaths could be prevented through changes in lifestyle, especially dietary patterns. Proanthocyanidins, as a class of polyphenolic compounds widely present in the diet, have attracted wide attention due to their high safety and good biological tolerance. Studies have found that proanthocyanidins have shown multifaceted potential in cancer prevention and treatment. Their mechanisms involve inducing cell apoptosis and cell cycle arrest, improving the tumor immune microenvironment, regulating tumor-related signaling pathways, inhibiting angiogenesis, and suppressing invasion and metastasis, etc. This paper systematically reviews the research mechanisms, different research models, and the development of novel delivery systems of proanthocyanidins in cancer prevention and treatment. It also explores the challenges of current research and future translational directions, providing theoretical basis for promoting the translation of proanthocyanidins from basic research to clinical applications.

Keywords: Proanthocyanidins, cancer, antitumor mechanisms, delivery system, clinical translation

1. Introduction

Cancer poses a significant threat to global human health. According to updated global cancer estimates from the International Agency for Research on Cancer, there were nearly 20 million new cancer cases (including nonmelanoma skin cancers [NMSCs]) and 9.7 million cancer-related deaths (including NMSC) in the year 2022 ^[1]. These estimates indicate that approximately one in five men or women develop cancer in their lifetime, whereas about one in nine men and one in twelve women die from the disease. Lung cancer was the most common cancer worldwide in 2022, with about 2.5 million new cases (12.4% of all cancers), followed by female breast cancer (11.6%), colorectal cancer (9.6%), prostate cancer (7.3%), and stomach cancer (4.9%). Lung cancer was also the leading cause of cancer death, accounting for an estimated 1.8 million deaths (18.7%), followed by colorectal cancer (9.3%), liver cancer (7.8%), female breast cancer (6.9%), and stomach cancer (6.8%) ^[1]. Breast cancer and lung cancer were the most common cancers both incidence and mortality among women and men, respectively. Based on the projected changes in population

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growth and aging, and assuming that overall cancer incidence remains unchanged, it is predicted that more than 35 million new cancer cases (including NMSCs, except basal cell carcinoma) will occur in the year 2050, an increase of 77% from the estimated 20 million cases in 2022. Demographic predictions suggest that there will be 35 million new cancer cases by 2050 ^[1].

Common therapeutic methods for cancer include surgery, chemotherapy, radiotherapy, molecular targeted therapy, and immunotherapy ^[2]. Surgical intervention is most effective when cancer is detected at an early stage. However, chemotherapy is often limited by systemic side effects and the development of drug resistance. Similarly, radiotherapy carries the risk of damaging adjacent healthy tissues and organs ^[2]. In contrast, targeted therapy offers higher precision and fewer side-effect profile compared to conventional chemotherapy, its application is limited to patients with specific genetic mutations. Furthermore, it is often associated with the development of drug resistance and entails high treatment costs ^[3]. Cancer immunotherapy has significant advantages in providing durable treatment responses and a wide range of treatment indications. However, its disadvantages such as a unique toxicity profile, complex management requirements, variable response rates, and high treatment costs cannot be ignored ^[4].

Natural products play an important role in the discovery and development of anticancer drugs. Many modern anticancer drugs are directly derived from natural products or their derivatives ^[5]. It is estimated that more than 50% of the approved anti-cancer drugs are natural source-based ^[6], with approximately 75% of anti-cancer drugs are plant-based ^[7]. Paclitaxel, a drug isolated from the bark of *Taxus brevifolia*, presents one of the most successful cases in anti-cancer drug discovery from natural product ^[8]. Natural products offer several advantages in anti-cancer therapy, including low toxicity, reduced side effects, the ability to overcome drug resistance, wide sources, and low cost ^[5]. Nanotechnology has demonstrated significant potential in enhancing the solubility, stability, and targeted delivery of natural products. For example, the use of nanocarriers to deliver paclitaxel and other natural compounds to tumor sites can improve therapeutic outcomes while minimizing adverse effects ^[9]. Furthermore, the combination of natural products with conventional anti-cancer drugs or other treatment methods-such as radiotherapy and immunotherapy-has emerged as a key research focus, aiming to achieve synergistic effects and enhance overall treatment efficacy ^[9].

In recent years, despite significant advances in cancer therapy, the global incidence and mortality of cancer continue to rise. Consequently, there is a growing focus on prevention as a strategy for cancer management. It has been estimated that over two-thirds of cancer-related deaths could be prevented through modifications in lifestyle, particularly dietary patterns ^[10]. In this context, growing attention has been directed toward plant-based foods rich in polyphenolic compounds. Proanthocyanidins, a class of polyphenols widely distributed in plants, are notably abundant in foods such as grape seeds, cranberries, red goji berries, pomegranates, red rice, and red wine ^[11]. They are recognized for their high safety profile and good tolerability ^[12, 13]. Owing to their antioxidant, anti-inflammatory, and anti-cancer properties, among other biological activities, proanthocyanidins have attracted considerable research interest ^[11]. Proanthocyanidins have shown

great anti-cancer potential by inhibiting tumor cell proliferation, inducing cell apoptosis and cell cycle arrest, improving the tumor immune microenvironment, regulating tumor-related signaling pathways, inhibiting angiogenesis, and suppressing invasion and metastasis. This paper systematically reviews current studies on the anti-cancer effects of proanthocyanidins, including their mechanism, research models, novel delivery systems, current challenges, and future prospects, thereby providing a comprehensive reference for researchers. Through this review, limitations and gaps in existing research are identified, which may guide future investigations. Furthermore, this review aims to establish a scientific basis for the clinical application of proanthocyanidins in cancer prevention and treatment, facilitating the translation of laboratory findings into clinical practice. Thus, the anti-cancer research of proanthocyanidins has important significant scientific and practical value.

2. Chemical structures and sources

Proanthocyanidins, also known as condensed tannins, represent one of the most abundant classes of phenolic compounds in the plant kingdom ^[14]. They are widely distributed in various plant organs-such as flowers, fruits, barks, and seeds-where they contribute to defense mechanisms against biotic and abiotic stresses ^[15]. Chemically, proanthocyanidins are products of the flavonoid biosynthetic pathway and consist of flavan-3-ol units linked by carbon-carbon bonds, forming oligomeric or polymeric structures. Their biological activity is largely determined by the degree of polymerization and the types of monomeric units involved. Proanthocyanidins are generally categorized into two main structural types: type B and type A. As illustrated in **Figure 1** ^[16], type B proanthocyanidins are composed of flavan-3-ol units linked through C4→C8 and/or C4→C6 bonds. In contrast, type A proanthocyanidins are flavan-3-ol units linked through C4→C8 and C2→O7 bonds ^[17, 18]. In addition to these types, there are more complex structures existing in the form of gallate esters or double-bond linkages ^[18]. Among these, type B proanthocyanidins are the most commonly encountered in the human diet ^[19]. Dietary sources rich in proanthocyanidins include grape seeds, cranberries, Chinese wolfberries, red goji berries, pomegranates, red rice, and red wine, among others ^[11]. At present, the main source of proanthocyanidins on the market is grape seeds ^[11].

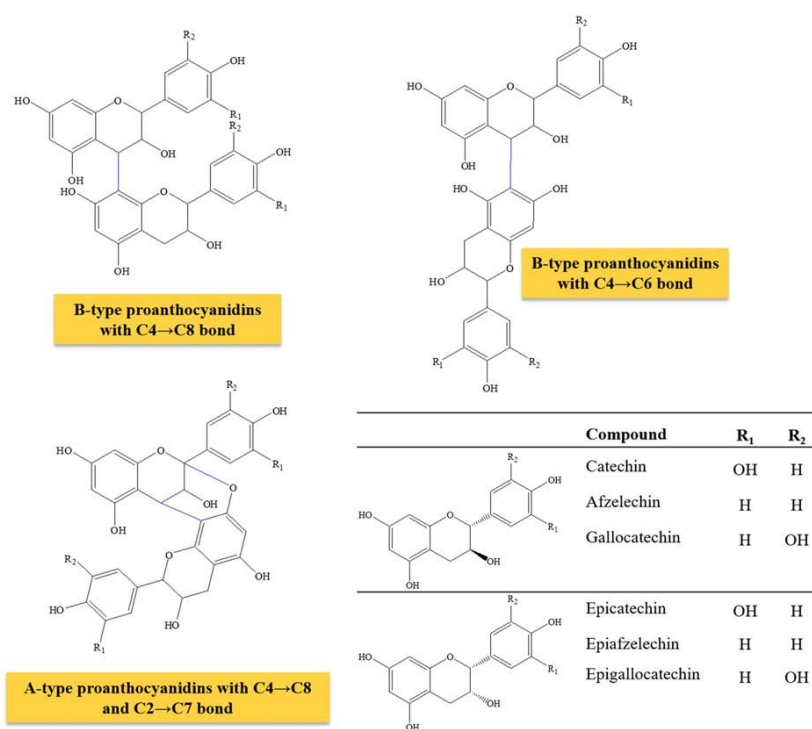


Figure 1 Basic chemical features of B- and A-type proanthocyanidins and their monomeric units.

3. Pharmacokinetic properties and bioactivity of proanthocyanidins

A comprehensive understanding of the pharmacokinetics and pharmacodynamics of proanthocyanidins—including their absorption, distribution, metabolism, and excretion—is essential to advance their application in cancer therapy and to establish an optimal dosage and administration regimen.

3.1 Digestion and absorption

Proanthocyanidins are capable of forming complexes with salivary proteins and polysaccharides in the oral cavity, which influences their solubility and stability [20]. Such interactions may reduce the bioaccessibility of proanthocyanidins, although the underlying mechanisms remain incompletely elucidated. Current *in vitro* research findings regarding the gastric stability of proanthocyanidins remain controversial, and this inconsistency may be attributed to variations in factors including the type and source of proanthocyanidins, experimental methods and conditions, and the duration of gastric exposure [20].

Studies have shown that proanthocyanidin oligomers (mainly monomers and dimers) can be partially absorbed directly through the small intestine, whereas polymers with a higher degree of polymerization require degradation by the gut microbiota in the colon into smaller metabolites before absorption [21]. The absorption rate of proanthocyanidin dimers is approximately 5%–10% of that of (-)-epicatechin, with trimers and tetramers exhibiting even lower absorption rates, and highly polymerized proanthocyanidins hardly being absorbed directly [22]. Specifically, after ingestion of 256 mg of cocoa-derived proanthocyanidin dimers, the plasma concentration of B2 reached only 0.041 $\mu\text{mol/L}$; after ingestion of 18 mg of grape seed-derived proanthocyanidin B1, the plasma concentration of B1 was approximately 0.011 $\mu\text{mol/L}$ [23].

Polymerization degree is one of the key structural factors affecting the absorption efficiency of proanthocyanidins. Generally, the absorption efficiency of proanthocyanidins decreases with the increase of

their polymerization degree. Among them, oligomeric proanthocyanidins (OPCs, with a polymerization degree of 2-4) are more easily absorbed by the human body due to their lower molecular weight and better water solubility. In contrast, highly polymerized proanthocyanidins with a polymerization degree greater than 4 are poorly absorbed directly by small intestinal epithelial cells, and must undergo degradation into oligomers or monomers in the intestinal tract prior to entering the circulatory system ^[24]. In addition, proanthocyanidins with different polymerization degrees also exhibit differences in their stability within the gastrointestinal environment and in their effects on the gut microbiota. Studies indicated that oligomers demonstrate greater stability in simulated digestive systems and are more effective in promoting the growth of beneficial bacterial populations. Conversely, highly polymerized proanthocyanidins were more sensitive to gastrointestinal conditions but display stronger inhibitory effects on harmful bacteria ^[25].

The linkage patterns of proanthocyanidins (type A and type B) also significantly affect their absorption behavior. Type B proanthocyanidins, which link monomeric units only through C-C bonds (mainly C4→C8 or C4→C6), possess a relatively simple structure and lower stability. Some oligomeric type B structures may be partially absorbed in the small intestine, but their overall bioavailability remains limited. In contrast, type A proanthocyanidins form an additional C-O-C ether linkage on the basis of the C-C bond, making their molecular structure more stable and hydrophobic. This structural characteristic results in a lower absorption rate of type A proanthocyanidins in the small intestine. Most of them could not be directly absorbed and instead enter the colon, where they were metabolized by the gut microbiota into small-molecule phenolic acids and other metabolites prior to systemic utilization ^[26]. However, current studies on the specific differences in absorption between type A and type B proanthocyanidins remain limited, and the underlying mechanisms requires further investigation.

Although proanthocyanidins themselves are poorly absorbed, their physiological effects may not rely solely on the direct absorption of the parent compounds. The metabolic transformation mediated by the gut microbiota generates various low-molecular-weight metabolites, which may exhibit bioactivities distinct from those of the parent compounds and may exert important effects on host health ^[21].

Some B-type proanthocyanidin oligomers were reported to be absorbed in the small intestine following oral administration of black soybean seed coat extract ^[27]. In general, proanthocyanidins with a high degree of polymerization (polymerization degree > 4) are poorly absorbed in the small intestine, whereas monomers and dimers can be absorbed via the passive paracellular pathway ^[28]. Proanthocyanidins are absorbed through passive diffusion rather than through specific transporters. Owing to the abundance of hydrophilic hydroxyl groups in their molecular structure, proanthocyanidins are unlikely to cross the lipid bilayer via the transcellular pathway. Therefore, paracellular diffusion is regarded as the main mechanism for their absorption ^[29]. Relatively high concentrations of free proanthocyanidins oligomers and (-)-epicatechin were detected in mesenteric fat, indicating that these compounds may be absorbed through the lymphatic pathway ^[27]. Additionally, food matrices significantly affect the oral absorption of proanthocyanidins. For example, a carbohydrate-rich diet has been shown to markedly reduce their absorption in rats ^[29].

Owing to their high molecular weight, the majority of proanthocyanidins are not absorbed in the small intestine but reach the colon, where they are metabolized by the gut microbiota into low molecular weight phenolic compounds, phenylvalerolactones, and phenolic acids [20, 28, 29]. These microbial metabolites exhibit higher bioavailability and enhanced bioactivity compared to the parent proanthocyanidin compounds. It should be noted, however, that interindividual variations in gut microbiota composition lead to considerable differences in proanthocyanidins metabolism and host response.

3.2 Intestinal distribution

Distinct concentration profiles of proanthocyanidins and their metabolites were observed in the luminal contents of the rat cecum, proximal colon, mid-colon, and distal colon. Following oral administration, proanthocyanidins reached their peak concentrations in all colonic segments at approximately 3 hours post-gavage, whereas the metabolites attained their maximum levels between 3 and 18 hours [30]. Higher molecular weight metabolites, such as 1-(3',4'-dihydroxyphenyl)-3-(2'',4'',6''-trihydroxyphenyl) propane-2-ol, were detected early and accumulated to higher concentrations in the cecum and proximal colon, followed by gradual degradation. In contrast, lower molecular weight metabolites, including phenylacetic acids and benzoic acid derivatives, reached high concentrations during the mid to late phases in the distal colon, suggesting that they are late products of proanthocyanidins [30]. Furthermore, both free and conjugated forms of proanthocyanidin oligomers and (–)-epicatechin were identified in multiple tissues, including the small intestine, liver, kidney, muscle, mesenteric fat, epididymal fat, and perirenal fat [27].

3.3 Gut microbial metabolism

The biotransformation of proanthocyanidins in vivo primarily relies on the metabolic activity of the gut microbiota. The gut microbiota involved in their metabolism includes well-taxonomically defined species, such as *Adlercreutzia equolifaciens*, *Eubacterium oxidoreducens*, *Streptococcus thermophilus* and *Lactobacillus casei-01*. In addition, a large number of microbial species that have not yet been precisely classified also play a crucial role in this metabolic degradation [22]. These microbial communities gradually degrade proanthocyanidins into a series of bioactive low-molecular-weight metabolites through complex metabolic networks.

There is a bidirectional regulatory relationship between proanthocyanidins and gut microbiota. On the one hand, proanthocyanidins exerted prebiotic-like effects and could selectively promote the proliferation of beneficial bacteria. For instance, studies have demonstrated that they can increase the abundance of species such as *Akkermansia muciniphila*, which is closely associated with the improvement of metabolic syndrome and the enhancement of intestinal barrier function. Meanwhile, proanthocyanidins could inhibit the growth of some potential pathogenic bacteria, such as *Bacteroides* and *Prevotella* genera, which are associated to obesity and chronic inflammation [22]. Furthermore, proanthocyanidins modulated gut microbiota composition at a macroscopic level, for example by reducing the *Firmicutes/Bacteroidetes* ratio, whose imbalance is considered one of the characteristics of obesity and metabolic syndrome [22]. On the other hand, proanthocyanidins could also promote the growth of probiotics including the genera *Bifidobacterium* and

Lactobacillus, which may be one of the important pathways through which they exert health-promoting effects [21].

At the metabolite level, the primary bioactive compounds generated from the depolymerization and degradation of proanthocyanidins by the gut microbiota include phenylacetic acids, phenylpropionic acids, phenylvaleric acids, and phenylvalerolactones. These metabolites are typically formed through meta- or para-monohydroxylation modifications, and the diversity of their chemical structures determines varied biological activities [31]. The above-mentioned types of metabolites have been directly identified using in vitro fermentation models of the human gut microbiota [32]. In animal studies, researchers have detected 16 microbial-derived metabolites in rats, identified as derivatives of phenylvaleric acid, phenylpropanoic acid, phenylacetic acid, and benzoic acid [22]. Notably, the total production rate of these metabolites decreased significantly with increasing degree of polymerization of proanthocyanidins: from catechin monomers ($10.6 \pm 1.1\%$) to dimers ($6.5 \pm 0.2\%$), trimers ($0.7 \pm 0.1\%$), and polymers ($0.5 \pm 0.1\%$), indicating that the polymerization degree is a key factor affecting the intestinal metabolic efficiency of proanthocyanidins [22].

The linkage pattern of proanthocyanidins also significantly influences their metabolic pathways in vivo. Type B proanthocyanidins can be partially degraded by the colonic microbiota, mainly generating small-molecule metabolites such as phenolic acids and γ -valerolactones. Among them, type B structures with low polymerization degrees are more susceptible to such biotransformation. Metabolites like γ -valerolactones have been demonstrated to exhibit potential health benefits such as antioxidant and anti-inflammatory activities [33]. In contrast, type A proanthocyanidins may also be degraded by gut microbes, but their specific degradation products and rates may vary due to structural complexity. Although type A proanthocyanidins may also be degraded by intestinal microbiota and generate bioactive metabolites, current studies on their precise metabolic pathways, metabolite profiles, and associated biological effects remain relatively limited, requiring further systematic investigation [33].

3.4 Excretion

It was found that 58% of the carbon-14 labeled proanthocyanidin dimer B2 was excreted through urine after oral administration, and 76% was excreted through urine after intravenous injection, indicating that proanthocyanidins and their metabolites are excreted mainly in the urine [28]. Structurally related (epi)catechin metabolites (SREMs), 5-carbon side chain ring-fission metabolites (5C-RFMs), and other phenolic acids and aromatic metabolites were detected in urine, indicating that some proanthocyanidins were metabolized and excreted in the body. The presence of SREMs, 5C-RFMs, and other phenolic and aromatic metabolites in urine further confirms that a portion of proanthocyanidins undergoes metabolic transformation before being excreted. After ingestion of red wine proanthocyanidin-rich (RWP) extracts, 11% of RWPs and 7% of grape seed proanthocyanidins (GSPs) underwent microbial degradation, and these degradation products were mainly excreted through urine [34]. Monomeric catechins and their methylated metabolites, along with proanthocyanidin dimers and trimers were detected in the urine of rats after oral administration of grape seed extract. Notably, a new tetramethylated proanthocyanidin dimer metabolite (m/z 633) was also detected [35].

3.5 Antitumor activity of proanthocyanidins

Emerging evidence highlights the significant potential of proanthocyanidins as adjunctive agents in combinatorial cancer regimens. Their integration with conventional chemotherapy, radiotherapy, or other bioactive compounds frequently yields synergistic anti-tumor effects. This synergy not only enhances therapeutic efficacy but also holds promise for reducing the required effective doses of cytotoxic drugs or radiation. Consequently, such combinations can mitigate adverse effects and overcome dose-limiting toxicities, improving the therapeutic index. Furthermore, proanthocyanidins may help counteract acquired resistance mechanisms, thereby re-sensitizing malignancies to standard treatments. This sensitizing role underscores their translational value in developing more effective and tolerable multimodal cancer therapies.

The combination of curcumin and OPCs demonstrates a synergistic interaction, yielding more potent anti-tumor effects than either agent administered alone. In models of colorectal cancer, this combination regimen effectively suppresses cell proliferation and promotes apoptosis. Mechanistic studies indicate that its superior efficacy stems from the concurrent modulation of multiple critical cellular processes, including DNA replication, cell cycle progression, protein export, glutathione metabolism, and porphyrin metabolism. These findings posit the curcumin-OPC combination as a promising, naturally derived adjunct to conventional chemotherapy. Such a strategy holds potential not only to enhance therapeutic efficacy but also to mitigate the development of drug resistance, thereby improving overall treatment outcomes [36].

Similarly, the combination of GSPs and resveratrol exhibits a marked synergistic inhibitory effect on human breast cancer cells. This synergy is evident not only in the impairment of short-term cell viability but also in the sustained suppression of long-term clonogenic survival. Mechanistic insights reveal distinct cell death pathways in different breast cancer subtypes. In triple-negative MDA-MB-231 cells, the combination potently induces apoptosis, characterized by the upregulation of the pro-apoptotic protein Bax and concomitant downregulation of the anti-apoptotic protein Bcl-2. Conversely, in estrogen receptor-positive MCF-7 cells, it primarily triggers a non-apoptotic form of cell death. Beyond direct cytotoxicity, this phytochemical combination demonstrates significant epigenetic modulatory activity, notably reducing the enzymatic activity of DNA methyltransferase and histone deacetylase. This suggests an additional mechanism through which it may reactivate silenced tumor suppressor genes, contributing to its overall anticancer efficacy [37].

Synergy is also observed with conventional chemotherapy. Proanthocyanidins, particularly procyanidin B2, demonstrate a multifaceted synergistic interaction with docetaxel, significantly enhancing its anti-tumor efficacy through several interconnected mechanisms. Primarily, the combination potently enhances cytotoxicity and anti-proliferative effects against various cancer cell lines (e.g., prostate and breast cancer), often exceeding the efficacy of docetaxel monotherapy. This is coupled with a substantial increase in the induction of apoptosis, achieved through the modulation of key regulators such as Bax and Caspase-9. A critical aspect of this synergy is the chemosensitizing effect of proanthocyanidins, which render cancer cells more susceptible to docetaxel, thereby lowering the effective therapeutic dose. At the molecular level, the

combination orchestrates favorable alterations in gene expression, notably upregulating tumor suppressor genes (e.g., CDKN1A) and epithelial integrity markers (e.g., E-cadherin), while downregulating pro-survival signals. Furthermore, proanthocyanidins contribute an anti-metastatic dimension by inhibiting cancer cell migration and invasion. Collectively, these mechanisms enhanced direct cytotoxicity, amplified apoptosis, chemosensitization, pro-differentiation gene modulation, and migration suppression provide a robust mechanistic rationale for the superior anti-tumor activity of the proanthocyanidin-docetaxel combination, highlighting its promising translational potential [38].

A particularly notable and therapeutically valuable property of GSPs is their capacity to function as a dual-modifying agent in radiotherapy. GSPs demonstrate a selective, context-dependent modulation of cellular response to radiation: they exert a radioprotective effect on normal lung tissue while concurrently acting as a radiosensitizer in lung cancer cells. This differential effect is mediated through the precise modulation of the mitogen-activated protein kinase (MAPK) signaling pathway. In normal cells, GSPs mitigate radiation-induced damage by downregulating specific MAPK components, thereby reducing oxidative stress and apoptosis. Conversely, in malignant lung cancer cells, they potentiate radiotherapy by selectively upregulating the stress-activated kinases JNK and p38, pathways that enhance radiation-induced cell death. This dual, tissue-specific action highlights the unique potential of GSPs as a sophisticated adjuvant to improve the therapeutic index of lung cancer radiotherapy by simultaneously enhancing tumor control and normal tissue sparing [39].

The polymerization degree of proanthocyanidins is one of the factors influencing their antitumor activity. Research indicates that OPCs, primarily consisting of monomers to trimers, exhibit significantly superior antitumor effects compared to unfractionated grape seed extract, which contains a higher proportion of polymeric components. In various colorectal cancer cell lines, OPCs could more effectively inhibit cell proliferation, induce cell cycle arrest and apoptosis, and significantly reduce tumor growth in xenograft animal models [40]. In *in vivo* experiments, OPCs at different concentrations all exhibited stronger tumor inhibitory effects than grape seed extract. This difference may be related to their higher bioavailability, as proanthocyanidins with a high polymerization degree are generally poorly absorbed in the intestine [40]. Although highly polymeric proanthocyanidins have low bioavailability, emerging evidence suggests that they may exhibit unique bioactivities in specific tumor types. For example, compared with monomers (such as (-)-epicatechin) and trimers, hexameric proanthocyanidins showed the most potent inhibitory effects on colorectal cancer cell viability [41]. This finding indicates that highly polymeric proanthocyanidins may exert their antitumor effects through mechanisms different from those of OPCs. Therefore, when evaluating the antitumor activity of proanthocyanidins, it is essential to comprehensively consider the differences in their polymerization degree, bioavailability and underlying mechanisms of action.

4. Safety of proanthocyanidins

A comprehensive understanding of the toxicological profile of proanthocyanidins, including safety and toxicity, is essential for their safe application as dietary supplements or therapeutic drugs.

Generally, proanthocyanidins are considered safe when consumed as part of a balanced diet, with no significant adverse effects reported at typical dietary intake levels. However, as with other bioactive compounds, their safety profile depends on the dose, exposure time, and the specific form of ingestion [42]. Epidemiological studies have not reported any notable adverse effects associated with regular consumption of proanthocyanidin-rich foods, supporting their safety at common dietary levels [13]. Early clinical trials primarily assessed the safety, tolerability, and pharmacokinetics of proanthocyanidins, consistently reporting that these compounds were well-tolerated with minimal adverse effects [12]. Furthermore, studies have shown that proanthocyanidins have a good safety profile even at higher doses. For example, grape seed extract rich in proanthocyanidins has been administered in clinical trials at doses of up to 2500 mg per day without significant adverse outcomes [43].

Proanthocyanidins have been recognized as safe at recommended levels by several regulatory agencies, including the U.S. Food and Drug Administration (FDA) and the European Food Safety Authority. For example, the FDA regards grape seed extract and other supplements rich in proanthocyanidins as generally recognized as safe when produced in compliance with good manufacturing practices [44]. Additionally, grape-seed extract has been approved as a safe food by the U.S. FDA and is commercially marketed as a dietary supplement listed in the U.S. Food Additives Database [45]. Despite this favorable safety profile, potential interactions with medications or other bioactive compounds should be considered, particularly in individuals with underlying health conditions or those undergoing long-term pharmacotherapy.

A series of toxicological studies on grape seed extracts rich in proanthocyanidins have confirmed their safety for use in various dietary supplements. The study showed that acute oral toxicity was not observed in rats administered grape seed extract at doses of 2 g/kg and 4 g/kg. Further assessments, including reverse mutagenesis tests using *Salmonella typhimurium*, chromosome aberration assays in Chinese hamster lung cells, and micronucleus tests in ddY mice, revealed no evidence of mutagenicity [46]. In a 90-day subchronic toxicity study, rats fed diets containing 0.02%, 0.2%, and 2% (w/w) proanthocyanidin-rich grape seed extract exhibited no apparent adverse effects [46]. The no observed adverse effect level of grape seed extract in subchronic toxicity studies was 2% in the diet, equivalent to 1410 mg/kg body weight/day in men and 1501 mg/kg body weight/day in women [46]. In a single-dose toxicity study, rodents administered patented product (Oligonol®) containing catechin-type monomers and proanthocyanidins oligomers at 2000 mg/kg body weight for four weeks exhibited no signs of toxicity, such as abnormal behavior or alopecia [47]. Additionally, a human trial involving 30 healthy volunteers demonstrated that daily intake of the same product at doses of 100 mg or 200 mg over 92 days was well-tolerated, with no clinically significant alterations in liver and renal function, or hematological parameters [47].

Studies in rodent models have demonstrated a favorable safety profile for proanthocyanidins, with no significant toxic effects observed in major organs or systems even at relatively high doses. Acute toxicity studies support this conclusion, for instance, the median lethal dose (LD₅₀) of grape seed extract in rodents has been reported to exceed 5000 mg/kg body weight, indicating very low acute oral toxicity [48]. In subchronic

toxicity studies, studies have shown no significant changes in body weight, food intake, or hematological and biochemical parameters in animals fed high doses of proanthocyanidins for up to 6 months [49]. Furthermore, reproductive and developmental toxicity studies suggest no adverse effects on fetal development or reproductive health. One study in pregnant rats reported that oral administration of grape seed extract produced no teratogenic effects or other impairments in fetal development [50].

However, attention still needs to be paid to their potential toxicological risks and limitations regarding drug interactions to objectively assess the safety of proanthocyanidins. Although current research is limited, available studies suggest that proanthocyanidins may produce adverse effects under specific conditions. For example, one study indicated that polymeric proanthocyanidins can induce non-alcoholic steatohepatitis in C57BL/6 mice. The mechanism is associated with the reduction in the expression of intestinal epithelial tight junction proteins and the disruption of intestinal barrier function caused by polymeric proanthocyanidins. This change facilitates the translocation of lipopolysaccharides from gut bacteria into the liver, where they accumulate, thereby triggering inflammation and liver injury. Notably, supplementation with exogenous probiotics promoted the biotransformation of polymeric proanthocyanidins into structurally simpler, absorbable, and non-hepatotoxic metabolites, effectively alleviating polymeric proanthocyanidins-induced liver damage [51]. Furthermore, *in vitro* studies have shown that grape seed extract inhibits the activity of CYP2C9, CYP2D6, and CYP3A4 in human liver microsomes. These enzymes play important roles in drug metabolism, and their inhibition could potentially affect the metabolism of co-administered drugs [52]. However, research on the interactions between proanthocyanidins and clinical drugs remains limited, and the related mechanisms and potential risks require further in-depth investigation.

Although current evidence from toxicological studies supports the safety of proanthocyanidins, several limitations of these studies must be recognized. Firstly, the majority of safety assessments have been conducted in animal models, and their findings may not be fully translatable to humans. Furthermore, the long-term health implications of chronic exposure to proanthocyanidins, particularly through high-dose dietary supplements, remain inadequately characterized and require further investigation.

5. Antitumor mechanisms of proanthocyanidins

Proanthocyanidins demonstrate broad-spectrum antitumor properties mediated by a diverse array of molecular mechanisms. These include, but are not limited to, inducing cell apoptosis and cell cycle arrest, improving the tumor immune microenvironment, regulating tumor-related signaling pathways, inhibiting angiogenesis, and suppressing invasion and metastasis. A comprehensive overview of these core molecular mechanisms is systematically presented in **Figure 2**.

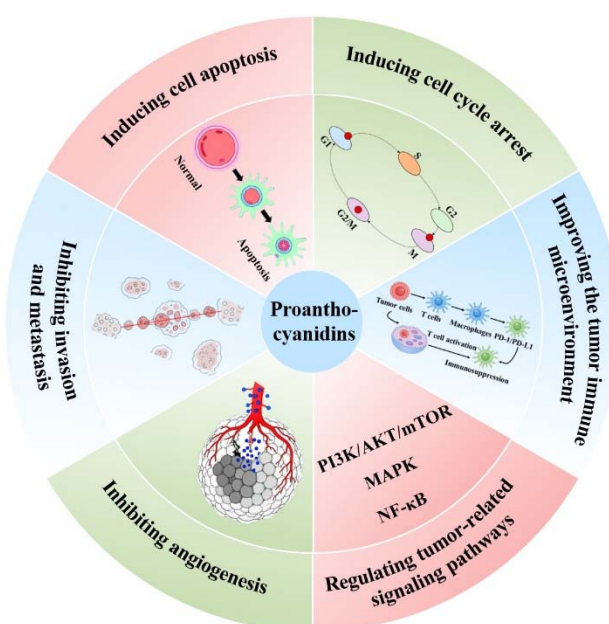


Figure 2 Antitumor mechanisms of proanthocyanidins.

5.1 Inducing cell apoptosis

The induction of apoptotic cell death represents a well-established therapeutic approach in cancer treatment, targeting one of the hallmark capabilities of malignancies [53]. Among various natural compounds investigated for this purpose, proanthocyanidins have shown considerable promise in triggering apoptosis across a spectrum of cancer types. Proanthocyanidins have been demonstrated to promote apoptotic cell death across various cancer types, including cervical cancer [54], breast cancer [55], hepatocellular carcinoma (HCC) [56], prostate cancer [57], and colorectal cancer [58]. The consistent pro-apoptotic activity observed in such diverse malignancies underscores the broad potential of proanthocyanidins as multi-target agents within oncology, warranting further investigation into their underlying molecular mechanisms and therapeutic applicability.

The pro-apoptotic effects of proanthocyanidins across these malignancies are predominantly mediated through the intrinsic mitochondrial pathway. This mechanism is characterized by a disruption of mitochondrial integrity and the activation of downstream caspase cascades. For instance, in cervical cancer models, GSPs were found to initiate apoptosis by modulating key Bcl-2 family proteins, specifically downregulating the anti-apoptotic Bcl-2 while upregulating the pro-apoptotic Bak-1. This imbalance precipitated a loss of mitochondrial membrane potential (MMP), subsequent activation of caspase-3, and ultimately led to significant inhibition of tumor growth in both cellular and animal studies [54]. Similarly, in MDA-MB-231 breast cancer cells, *Uncaria rhynchophylla* proanthocyanidins (UPAs) induced apoptosis by elevating the Bax/Bcl-2 ratio, depleting MMP, increasing intracellular reactive oxygen species, and enhancing levels of cleaved caspase-3 [55].

Further corroborating the centrality of the mitochondrial pathway, research on lipophilic grape seed proanthocyanidins (LGSPs) in PC3 prostate cancer cells demonstrated cleavage of caspase-9 and caspase-3, alongside PARP cleavage—a hallmark of apoptosis. This was accompanied by a decreased Bcl-2/Bax ratio. In

vivo xenograft models reinforced these findings, showing that LGSP treatment not only reduced the proliferation marker Ki67 but also significantly increased cleaved caspase-3 levels ^[57]. Beyond canonical Bcl-2 regulation, apoptotic induction can involve other regulatory nodes. In HepG2 HCC cells, a proanthocyanidin-rich fraction (PRFR) from red rice suppressed survivin expression and increased cleavage of PARP-1, caspase-8, and caspase-3, suggesting a potential cross-talk between pathways ^[56]. Finally, in HT-29 colorectal cancer cells, the pro-apoptotic outcome of proanthocyanidin treatment was quantified by a significant increase in the proportion of early and late apoptotic cells, as definitively measured via Annexin V/PI dual staining ^[58].

At the cellular level, researchers evaluated the protective effects of seven microbial metabolites of proanthocyanidins (3-phenylpropionic, 4-hydroxyphenyl acetic, 3-(4-hydroxyphenyl) propionic, p-coumaric, benzoic acid, pyrogallol, and pyrocatechol) using human lung epithelial cells (BEAS-2B) and human fetal hepatic cells (WRL-68) exposed to the chemical carcinogen 4-[(acetoxymethyl) nitrosamino]-1-(3-pyridyl)-1-butanone. The results demonstrated that pyrogallol significantly alleviated cytotoxicity and DNA damage in BEAS 2B cells, while pyrocatechol exerted similar protective effects in WRL 68 cells. Mechanistic studies revealed that pyrogallol and pyrocatechol mitigated carcinogen-induced oxidative stress by regulating DNA damage response pathways such as ATR-Chk1 and ATM-Chk2, respectively, enhancing total antioxidant capacity and glutathione peroxidase activity, and reducing reactive oxygen species accumulation. Meanwhile, both pyrogallol and pyrocatechol suppressed the activation of the extrinsic apoptotic pathway (caspase 3 and 8) provoked by 4-[(acetoxymethyl) nitrosamino]-1-(3-pyridyl)-1-butanone. These findings suggest that microbial metabolites of proanthocyanidins may play a potential role in the chemoprevention of lung and liver cancers by attenuating DNA damage and regulating oxidative stress and apoptotic signaling ^[59].

Collectively, these studies delineate a consistent mechanistic theme wherein proanthocyanidins converge on the mitochondrial apoptotic pathway, tipping the balance of pro- and anti-apoptotic proteins, compromising mitochondrial function, and executing cell death through caspase activation.

5.2 Inducing cell cycle arrest

The orderly progression of the cell cycle is fundamental to controlled cellular proliferation, and its dysregulation constitutes a canonical hallmark of cancer pathogenesis. Consequently, the targeted induction of cell cycle arrest has emerged as a well-established therapeutic strategy to suppress uncontrolled tumor growth ^[60]. Natural compounds, including proanthocyanidins, have garnered significant interest for their ability to modulate key cell cycle checkpoints. Accumulating in vitro evidence demonstrates that proanthocyanidins can effectively induce cell cycle arrest across a diverse spectrum of cancer cell lines. This inhibitory activity has been documented in cervical cancer ^[54], breast cancer ^[55], HCC ^[56], prostate cancer ^[57], and colorectal cancer ^[58]. The consistent observation of cell cycle perturbation across these distinct malignancies underscores the broad potential of proanthocyanidins as multi-target agents capable of disrupting a core mechanism of cancer cell viability and propagation.

The specific phase of cell cycle arrest induced by proanthocyanidins, along with the associated molecular mechanisms, exhibits variation across different cancer types, highlighting their context-dependent bioactivity. In cervical cancer models, GSPs induced G2/M phase arrest in both HeLa and SiHa cell lines, an effect closely linked to their potent anti-proliferative activity ^[54]. Similarly, a G2/M phase arrest was observed in MDA-MB-231 breast cancer cells following treatment with UPAs ^[55]. This pattern extends to HCC, where PRFR obtained from red rice germ and bran extract triggered G2/M arrest in HepG2 cells. Mechanistically, this was associated with a significant downregulation of key G2/M transition regulators, cyclin B1 and cdc25 ^[56]. Consistent with these findings, proanthocyanidins also induced G2/M phase arrest in HT-29 colorectal cancer cells, directly confirming their capacity to halt proliferation by disrupting cell cycle progression ^[58].

In contrast, a distinct arrest profile was reported in prostate cancer. LGSPs induced a G1 phase arrest in PC3 cells. This effect was driven by the downregulation of G1/S promoting proteins (cyclin D1 and CDK4) concurrent with the upregulation of the cyclin-dependent kinase inhibitors p21 and p27, thereby reinforcing the G1 checkpoint ^[57].

5.3 Improving the tumor immune microenvironment

Proanthocyanidins, as a natural polyphenolic compound, have demonstrated significant application potential in the field of tumor immunotherapy in recent years. They can improve the tumor immune microenvironment through multiple pathways, providing new strategies for enhancing the efficacy of immunotherapy.

Regarding the regulation of T cells, studies have shown that proanthocyanidins can regulate the protein stability of programmed death-ligand 1 (PD-L1) through a dual mechanism. On the one hand, they activated the AMPK signaling pathway by stabilizing the LKB1 protein, inducing phosphorylation of PD-L1 and retention in the endoplasmic reticulum. On the other hand, they directly bound to the E3 ubiquitin ligase SYVN1, promoting K48-linked ubiquitination of PD-L1 and its subsequent degradation via the proteasome pathway. This mechanism effectively reversed the tumor immunosuppressive state, and promoted the infiltration and functional restoration of cytotoxic CD8⁺ T cells, while simultaneously inhibiting the immunosuppressive activity of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) ^[61]. In addition, OPCs could downregulate PD-L1 expression by inhibiting the nuclear factor- κ B (NF- κ B) and STAT3 signaling pathways, further enhancing the anti-tumor activity of CD8⁺ T cells and improving the tumor immune microenvironment ^[62].

In terms of macrophage regulation, proanthocyanidins also drove the polarization of tumor-associated macrophages towards the M1 phenotype through the aforementioned PD-L1 degradation mechanism, remodeling the anti-tumor immune microenvironment and enhancing anti-tumor immune responses ^[61]. In terms of cytokine regulation, proanthocyanidins could downregulate the expression of pro-inflammatory cytokines such as TNF- α , IL-6 and IL-1 β by inhibiting the NF- κ B and MAPK signaling pathways, inducing tumor cell apoptosis and suppressing metastasis ^[63].

Proanthocyanidins have been shown to inhibit HCC progression by regulating the gut microbiota and its metabolites. Research indicated that proanthocyanidins not only act directly on tumor cells but also reshape the composition of the gut microbiota, increase the abundance of the beneficial bacterium *Lactobacillus murinus*, and promote its production of the key metabolite 5-hydroxytryptophan. This metabolite further activated the MAPK signaling pathway in B cells and the antitumor immune response of CD8⁺ T cells, ultimately inhibiting HCC growth [64]. This finding provides a scientific basis for proanthocyanidins as a potential adjuvant therapy for HCC and highlights the importance of the gut microbiota-metabolite-immunity axis in cancer intervention.

Notably, the combined application of proanthocyanidins with immune checkpoint inhibitors (such as anti-CTLA-4 antibodies) has demonstrated significant synergistic anti-tumor effects in colorectal cancer and lung cancer models. This combination strategy not only improves tumor control rates but also may prolong patient survival. Mechanistically, the combined therapy significantly enhanced the infiltration of CD8⁺ T cells in tumor tissues and reduced the proportion of immunosuppressive cells (such as Tregs and MDSCs), further improving the tumor immune microenvironment [61]. This synergistic effect may result from the complementarity of multiple immunomodulatory mechanisms, providing a new theoretical basis for optimizing existing immunotherapeutic strategies.

In summary, proanthocyanidins demonstrate broad prospects for combined application with immunotherapy by regulating PD-L1 expression, remodeling immune cell functions, and improving the immune microenvironment.

5.4 Regulating tumor-related signaling pathways

The aberrant activation of signaling pathways plays a core regulatory role in tumorigenesis and progression. In recent years, the natural product proanthocyanidins have attracted significant attention due to their multi-target, multi-pathway antitumor activities. Studies have demonstrated that proanthocyanidins can inhibit tumor cell proliferation, induce apoptosis, and block invasion and migration by regulating key signaling pathways including phosphatidylinositol 3-kinase /protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR), MAPK, and NF- κ B.

The PI3K/AKT/mTOR pathway is one of the most frequently activated signaling axes in human cancers and is involved in regulating various biological processes including cell proliferation, survival, invasion, migration, apoptosis, and DNA repair [65]. Proanthocyanidins exert antitumor effects by directly or indirectly targeting key nodes of this pathway. For example, proanthocyanidin B2 bound to the catalytic and PH domains of AKT, specifically inhibiting its kinase activity, with Lys297 and Arg86 as key binding sites. Mutations at these sites can abolish the antitumor effects of proanthocyanidin B2 [66]. In osteosarcoma cells, proanthocyanidin B2 significantly reduced the mRNA and protein expression levels of PI3K and AKT, and the PI3K agonist 740Y-P partially reversed its regulatory effects on cell proliferation and apoptosis, further confirming the critical role of this pathway [67]. GSPs decreased the expression of the PI3K regulatory subunit p85 and catalytic subunit p110, and inhibited Akt phosphorylation at Ser473. PI3K siRNA

interference experiments further validated the essential role of the PI3K/Akt pathway in the antitumor effects [68]. In colorectal cancer Caco-2 cells, hexameric proanthocyanidins inhibited cell growth by suppressing the PI3K/Akt signaling pathway and downregulating the phosphorylation levels of Bad and GSK-3 β . Combined treatment with the Akt inhibitor MK-2206 enhanced the antiproliferative effect of hexameric proanthocyanidins, suggesting a key role for Akt signaling in the anti-colorectal cancer activity of Hex [41]. Furthermore, procyanidin B2 significantly reduced the phosphorylation levels of Akt and mTOR in gastric cancer cells without markedly affecting their total protein expression, and combined treatment with LY294002 further enhanced its antiproliferative effects [69]. In ovarian cancer A2780/CP70 cells, proanthocyanidins from Chinese bayberry leaves (BLPs) inhibited the phosphorylation of Akt and its downstream signaling molecules mTOR, p70S6K, and 4E-BP1, thereby downregulating the expression of hypoxia-inducible factor-1 α (HIF-1 α) and vascular endothelial growth factor (VEGF) and suppressing angiogenesis [70].

The MAPK signaling pathway is a critical network regulating cell proliferation, differentiation, apoptosis, and stress responses, and its abnormal activation is closely associated with tumor progression [71]. The regulatory effects of procyanidins on this pathway are in their differential impacts on the three main sub-pathways: ERK, JNK, and p38 MAPK. In head and neck cutaneous squamous cell carcinoma SCC13 cells, GSPs reduced cell invasion by inhibiting ERK1/2 phosphorylation. The MEK inhibitor UO126 similarly suppressed cell invasion, suggesting that ERK signaling was a key mediator of the anti-invasive effects of GSPs [72]. In human esophageal adenocarcinoma cells, procyanidin activated JNK and p38 MAPK, and induced the phosphorylation and expression of c-Jun. Knockdown of JNK1, JNK2, or JUN gene expression attenuated the regulatory effects of procyanidin on cell proliferation and apoptosis [73]. In lung cancer cells, GSPs enhanced radiosensitivity and inhibited tumor growth by activating p38 MAPK and JNK. In contrast, in normal lung tissue, GSPs suppressed the p38 MAPK, JNK, and ERK pathways, alleviating radiation-induced damage and demonstrating a dual regulatory effect [39].

The NF- κ B signaling pathway plays a critical role in the survival, anti-apoptosis, metastasis, and therapeutic resistance of tumor cells [74]. Proanthocyanidins exert anti-tumor effects by interfering with I κ B α degradation, inhibiting NF- κ B nuclear translocation and downregulating the expression of its downstream target genes. Dimeric procyanidin B2 could block the binding of NF- κ B to DNA, inhibit constitutively activated NF- κ B in Hodgkin's lymphoma cells, and downregulate the expression of its downstream cytokines (IL-6, TNF- α and RANTES) and anti-apoptotic proteins (Bcl-xL, Bcl-2, XIAP and cFLIP) [75]. GSPs could inhibit lipopolysaccharide and receptor activator of nuclear factor- κ B ligand-induced NF- κ B/p65 nuclear translocation and I κ B α degradation in drug-resistant ovarian cancer A2780/T cells [76]. In tongue squamous cell carcinoma Tca8113 cells, GSPs significantly suppressed I κ B kinase phosphorylation and NF- κ B nuclear translocation, blocking its transcriptional activity [77]. Furthermore, GSPs extract inhibited the activation of the NF- κ B pathway in esophageal squamous cell carcinoma ECA109 cells, reduced the secretion of the inflammatory factors IL-6 and COX-2, upregulated the expression of the apoptotic proteins caspase-3 and

Bax, and downregulated the anti-apoptotic protein Bcl-2, thereby inducing apoptosis and inhibiting proliferation, migration, and invasion [78].

At the molecular regulatory level, proanthocyanidin metabolites can also exert antitumor activity by modulating microRNA expression. Studies have shown that under homeostatic conditions, miRNA target genes regulated by proanthocyanidin metabolites (rather than proanthocyanidins) are enriched in pathways related to kinase signaling, Wnt signaling, growth factor signaling, cell cycle and apoptosis regulation, as well as specific cancer-related pathways. Under inflammatory conditions, cranberry proanthocyanidin extract and its metabolite 3,4-dihydroxyphenylacetic acid were shown to reverse the abnormal expression of 16 and 2 IL-1 β -induced miRNAs, respectively, thereby modulating inflammation- and tumor-related pathways [79]. This study reveals miRNA regulation as a novel mechanism underlying the intestinal bioactivity of proanthocyanidins, and suggests that gut microbiota is essential for this process under homeostasis and certain inflammatory conditions.

5.5 Inhibiting angiogenesis

Antiangiogenic therapy represents a well-established modality in oncology, founded on the principle of inhibiting tumor-induced angiogenesis. By targeting the development of neovasculature that supplies essential nutrients and oxygen to growing tumors, this therapeutic strategy effectively restricts tumor expansion, metastatic dissemination, and disease progression. The central mechanisms of antiangiogenic action predominantly involve the suppression of key molecular pathways, most notably the VEGF/vascular endothelial growth factor receptor (VEGFR) signaling axis. Additionally, modulation of other critical regulators of angiogenesis, such as HIF-1 α and angiopoietin, constitutes an important facet of this multifaceted approach [80]. Together, these interventions disrupt the vascular network that sustains tumor survival and growth, thereby providing a valuable component of combination therapy in numerous cancer types.

A growing body of evidence indicates that proanthocyanidins possess significant antiangiogenic properties across various experimental tumor models. Proanthocyanidins inhibit tumor angiogenesis by suppressing the expression of HIF-1 α and VEGF. HIF-1 α and VEGF are key factors driving tumor angiogenesis. Proanthocyanidins effectively reduced tumor vascular formation by downregulating the expression of these molecules [81]. Furthermore, proanthocyanidins inhibited tumor angiogenesis by blocking the EGFR-PI3K-AKT-mTOR and MAPK-ERK1/2 signaling pathways [81]. These signaling pathways play important roles in tumor angiogenesis and progression, and the multi-target inhibitory effects of proanthocyanidins enhance their anti-angiogenic efficacy. Research on GSPs demonstrated their capacity to suppress angiogenesis and tumor growth in colon cancer. This effect was mediated through the scavenging of reactive oxygen species, leading to a marked reduction in the expression of key proangiogenic factors, VEGF and angiopoietin 1, in SW620 human colon cancer cells [82]. In a similar vein, grape procyanidins were found to inhibit both tumor angiogenesis and growth, a phenomenon associated with the downregulation of VEGF expression and a consequent decrease in microvessel density [83].

Further mechanistic insights were provided by studies on specific procyanidin fractions. For instance, oligomeric procyanidins (F2) isolated from grape seeds significantly inhibited tumor angiogenesis and cell invasion by targeting HIF-1 α . The antitumor mechanism of F2 primarily involved the suppression of the EGFR-PI3K-AKT-mTOR and MAPK-ERK1/2 signaling pathways. This suppression resulted in reduced translation and accumulation of HIF-1 α , thereby downregulating the expression of its downstream target genes, including VEGF, GLUT-1, and MMP-2 ^[84]. In parallel, BLPs exerted a dose-dependent inhibitory effect on the expression of VEGF and HIF-1 α in the cisplatin-resistant human ovarian cancer cell line A2780/CP70. BLPs also reduced intracellular reactive oxygen species levels, further contributing to the inhibition of VEGF and HIF-1 α expression. The antiangiogenic effect in this context was shown to be mediated through the suppression of the Akt signaling pathway ^[70].

More recently, research on procyanidin B2 (PB2) in oral squamous cell carcinoma (OSCC) revealed its inhibitory action on the VEGF/VEGFR2 signaling pathway and tumor angiogenesis in SCC-25 cells. Importantly, the activation of the VEGF/VEGFR2 pathway was shown to attenuate the inhibitory effects of PB2 on OSCC cell growth and metastasis, underscoring the critical role of this axis in mediating the antitumor efficacy of PB2 ^[85]. Collectively, these studies highlight the multi-target potential of proanthocyanidins in disrupting tumor angiogenesis through the modulation of pivotal signaling pathways and key regulatory factors.

5.6 Inhibiting invasion and metastasis

The inhibition of tumor invasion and metastasis constitutes a cornerstone of modern cancer therapeutics, directly targeting the lethal process of cancer dissemination. This strategic approach aims to impede the multi-step metastatic cascade-whereby malignant cells detach from the primary tumor, intravasate into the circulation, and ultimately colonize distant organs-thereby preventing the formation of secondary lesions that are largely responsible for cancer-related mortality ^[86]. The underlying mechanisms are multifaceted, involving coordinated interventions against several key biological drivers of metastasis. Principal strategies include the downregulation of matrix metalloproteinases to preserve the integrity of the extracellular matrix and basal lamina, the inhibition of the epithelial-mesenchymal transition (EMT) program that enhances cellular motility and invasiveness, and the restoration of cell-cell adhesion by enhancing the expression and function of molecules such as E-cadherin, among others ^[86]. By disrupting these interconnected processes, therapeutic agents can effectively constrain the invasive potential of tumor cells and halt metastatic progression.

Accumulating evidence indicates that proanthocyanidins can effectively impede tumor invasion and metastasis by targeting multiple critical steps in the metastatic cascade. Research on hawthorn proanthocyanidin extract (HPOE) demonstrated its ability to inhibit colorectal carcinoma metastasis by impairing the migration and invasion of HCT116 cells. Mechanistically, HPOE significantly downregulated mRNA and protein levels of key EMT-related markers (N-cadherin, Vimentin, and β -catenin) while upregulating E-cadherin, indicating that its anti-metastatic effect is mediated through the suppression of the

EMT^[87]. Similarly, PB2 markedly inhibited the migration and invasion of OSCC SCC-25 cells. This activity was associated with the downregulation of MMP2 and MMP9, an increase in E-cadherin, and a decrease in Vimentin expression, confirming the compound's role in suppressing EMT^[85].

GSPs also exhibit broad anti-metastatic potential. In bladder cancer models, GSPs inhibited cell migration, invasion, and the secretion of MMP-2/9. They reversed TGF- β -induced EMT by blocking the activation of the TGF- β signaling pathway, including the phosphorylation of Smad2/3, Akt, Erk, and p38^[88]. Additionally, GSPs suppressed migration and invasion of human tongue squamous cell carcinoma Tca8113 cells and reduced secretion of MMP-2 and MMP-9^[77].

Furthermore, PRFR obtained from red rice significantly inhibited the invasion and migration of TNF- α -induced A549 lung cancer cells. The underlying mechanism involved the downregulation of multiple invasion-related proteins, including MT1-MMP, uPA, uPAR, COX-2, and MMP-9, along with the suppression of MMP-9 secretion^[89].

Collectively, these studies highlight that proanthocyanidins from diverse sources function as multi-targeted agents against tumor invasion and metastasis, primarily through the dual strategy of inhibiting EMT progression and downregulating key proteases involved in extracellular matrix degradation.

6. Research models in the antitumor studies of proanthocyanidins

6.1 Cellular models

Cellular models *in vitro* have been widely employed to investigate the antitumor effects of proanthocyanidins. For instance, Chen et al. studied the effects of GSPs on the growth and apoptosis of human cervical cancer HeLa and SiHa cells. Their findings demonstrated that GSPs could induce apoptosis in cervical cancer cells through the mitochondrial pathway, thereby suppressing cell growth^[54]. In another study, Chen et al. reported that UPAs effectively inhibited proliferation and migration, and induced apoptosis in human breast cancer MDA-MB-231 cells^[55]. Similarly, research by Suganya et al. indicated that proanthocyanidins inhibited the growth of human colorectal cancer HT-29 cells by inducing apoptosis^[58].

Further evidence comes from studies on prostate cancer. Chen & Yu observed that LGSP exerted anti-proliferative and pro-apoptotic effects on PC3 and DU145 prostate cancer cells. The mechanisms included cell cycle arrest, activation of caspase pathways, modulation of the Bcl-2/Bax ratio, and upregulation of the tumor suppressor proteins p21 and p27^[57]. Additionally, Upanan et al. demonstrated that PRFR exhibited significant anti-tumor effect against human HCC HepG2 cells by inhibiting proliferation and inducing apoptosis^[56].

Collectively, these cellular studies highlight the broad anti-cancer potential of proanthocyanidins across multiple cancer types, primarily through the induction of apoptosis and suppression of proliferation.

6.2 Animal models

Transitioning from *in vitro* to *in vivo* studies is essential for evaluating the anti-cancer potential of proanthocyanidins within a complex biological context. The cell-derived xenograft (CDX) model, in which

human tumor cells are implanted into immunodeficient mice, is commonly employed for this purpose. Studies using CDX models have consistently demonstrated that proanthocyanidins can effectively suppress tumor growth.

For instance, Chen et al. used a cervical cancer xenograft model in nude mice and reported that supplementing drinking water with GSPs significantly inhibited the growth and reduced the weight of HeLa and SiHa tumors. Increased apoptosis in tumor tissue was confirmed by TUNEL assay ^[54]. Similarly, Chen & Yu showed that oral administration of LGSP markedly inhibited tumor growth and decreased tumor volume and weight in a PC3 prostate cancer xenograft model ^[57]. More recently, Chen et al. observed that proanthocyanidins suppressed colorectal tumor growth in nude mouse xenografts ^[90].

These *in vivo* findings corroborate *in vitro* evidence and highlight the potential of proanthocyanidins as candidates for further anti-cancer development.

6.3 Organoid models

Organoids are three-dimensional, miniaturized organ-like structures derived from stem cells including adult stem cells and pluripotent stem cells through advanced three-dimensional culture techniques. These models are capable of simulating the structural and functional characteristics of organs *in vivo*. These models can self-organize, differentiate, and exhibit similar cell types and tissue architecture to their counterparts *in vitro* ^[91].

Organoid models possess several features. They demonstrate high physiological relevance, closely mirroring the structure and function of real organs and reflecting fundamental physiological properties. Their self-organization capability allows them to autonomously assemble and renew into complex tissue structures without external intervention. Additionally, organoids maintain genetic stability, preserving the genetic profile of the original patient tissue, which makes them particularly suitable for personalized medicine research. They also offer scalability, as they can be subcultured long-term in culture to generate ample material for experiments. Finally, their experimental operability enables diverse manipulations such as genetic editing and drug screening, thereby facilitating investigations into organ development and disease mechanisms ^[91].

Organoid models can not only be used in basic research, but also play an important role in drug screening, disease modeling and personalized medicine, regenerative medicine, toxicology research, etc. ^[91].

Organoid models offer several advantages over traditional two-dimensional (2D) cell cultures, including higher physiological relevance, enhanced cellular diversity, and the capacity for long-term culture. Compared with animal models, organoids reduce interspecies discrepancies, shorten experimental timelines, alleviate ethical concerns, and hold strong potential for personalized medicine applications ^[91]. Recognized as the “Method of the Year 2017” in the life sciences by Nature Methods, organoid technology provides an ethically acceptable platform for studying human development, new platforms for drug screening, and a highly informative complement to conventional 2D cultures and animal models.

Recent years have witnessed significant progress in using organoids to screen natural compounds for therapeutic efficacy across multiple research fields. Among these applications, drug screening based on tumor organoids represents the most established and widely adopted approach. Cancer patient-derived organoids (CPDOs) faithfully preserve the molecular and cellular heterogeneity of primary tumors and closely recapitulate their histopathological features^[92]. These characteristics make CPDO a reliable preclinical model for drug efficacy evaluation, high-throughput screening, and mechanism research. Furthermore, co-culturing immune cells with tumor organoids offers an ideal model for studying the tumor immune microenvironment and developing novel immunotherapeutic strategies. In addition, organoids have been used for personalized medication guidance. The response of patients to specific drugs can be predicted by conducting drug sensitivity tests on CPDOs, achieving precision oncology^[91].

Organoid models have been used to explore the anti-tumor effects of polyphenolic compounds such as curcumin^[93, 94], resveratrol^[95], genistein^[96], luteolin^[97, 98], fisetin^[99], and OPCs^[40, 100]. Notably, OPCs have been shown to suppress the formation and growth of CPDOs.

Toden et al. demonstrated that OPCs effectively inhibit colorectal cancer organoid formation and growth while modulating the expression of cell cycle-related genes, which is consistent with results from traditional cell line and mouse xenograft models^[40, 100]. Furthermore, a combination of curcumin and OPCs exhibited a significant inhibitory effect on the formation and growth of organoids derived from a colorectal cancer patient. This combinatorial treatment also led to the downregulation of key genes associated with tumor proliferation and drug resistance, such as IHH, PDE3B, cyclin D1, and HSPA5^[40].

A comparative summary of the anti-tumor effects of proanthocyanidins across cell models, animal models, and organoid models is shown in **Table 1**.

Table 1 A comparative summary of the anti-tumor effects of proanthocyanidins across cellular models, animal models, and organoid models

Models	Characteristics	Advantages	Disadvantages
Cellular models	Uncontrolled proliferation capacity: Cell lines possess the ability to proliferate continuously <i>in vitro</i> , supporting large-scale cultivation and experimental throughput.	Cost-effectiveness: Culturing and maintaining cell lines is relatively inexpensive, making it suitable for large-scale drug screening.	Limited physiological relevance: The 2D culture environment lacks 3D architecture and cell-cell interactions <i>in vivo</i> , thereby failing to faithfully recapitulate microenvironments <i>in vivo</i> .
	Genetic stability: Cell lines usually maintain relatively stable genetic characteristics after long-term subculturing.	Simple operation: The associated experimental protocols are straightforward and can be readily mastered.	Genetic drift: Long-term sub-culturing may lead to changes in genetic characteristics, affecting experimental results.
Animal models	Standardization potential : Cell lines are easy to standardize, facilitating reliable inter-laboratory comparison and replication of results.	High-throughput screening: Cell lines are suitable for automated and high-throughput drug screening platforms.	Differences in drug response: The drug response in 2D-cultured cell lines often do not correlate with <i>in vivo</i> efficacy.
	Holistic physiological environment: Animal models are capable of recapitulating an integrated physiological context, including systemic features such as immune responses and multi-organ interactions.	Comprehensive evaluation: Animal models enable integrated assessment of multiple pharmacological properties, including efficacy, toxicity, pharmacokinetics, and pharmacodynamics.	Interspecies translational limitations: Physiological and metabolic differences between animal models and humans can compromise the accurate prediction of drug responses and disease mechanisms.

Organoid models 3D architecture: Organoids are three-dimensional (3D) culture systems capable of recapitulating the complex tissue architecture and key functions of organs <i>in vivo</i>. Self-organization capacity: Organoids have the self-organization capacity and can form specific tissue structures through cell-cell interactions. Patient specificity: Patient-derived organoids (PDOs) retain the genetic, molecular, and phenotypic features of the original tissue, enabling patient-tailored disease modeling and drug testing.	Critical preclinical platform: They serve as an essential evaluative stage prior to clinical trials, helping to identify potential safety and efficacy issues early, thereby reducing the likelihood of clinical trial failure. High physiological relevance: Organoids closely recapitulate key physiological functions and pathological alterations observed in native tissues, offering a biologically faithful <i>ex vivo</i> model. Personalized medicine potential: PDOs are particularly suitable for personalized medicine applications, as they can be used to predict individual patient responses to specific therapeutic drugs. Long-term culture: Organoids can be cultured <i>in vitro</i> for a long time, providing a stable model for continuous drug screening and disease modeling. Cost and time: Animal studies are typically costly, time-consuming, and require complex ethical approval as well as experimental design. Ethical considerations: The use of animals in research necessitates adherence to strict welfare regulations and ethical review protocols. Challenges in establishment: The generation of organoids often depends on high-quality patient samples and professional techniques, with variable success rates across sample types and protocols. Costs and time: Establishing and maintaining organoid cultures can be costly and time-consuming, and scaling up to obtain sufficient material for high-throughput assays may require extended culture periods. Standardization challenge: The standardization of organoids remains a challenge and results may vary between laboratories.
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7. Novel delivery system for proanthocyanidins

Advances in nanotechnology have significantly increased the potential of phytochemicals, such as proanthocyanidins, in cancer therapy. To enhance the bioavailability and therapeutic efficacy of proanthocyanidins, a variety of targeted delivery systems, including nanoparticles and liposomes have been developed. Improved targeted delivery through intelligent and biocompatible systems could improve tumor specificity while reducing off-target effects on healthy tissues.

Nanotechnology has demonstrated considerable potential for enhancing drug solubility, stability, and bioavailability through the design of nanoparticle-based carriers for drugs or bioactive molecules. For instance, a novel multifunctional PEG-modified $\text{CeO}_2@\text{SiO}_2$ nanoparticle (CSP-NPs) system was successfully developed. When loaded with food-derived proanthocyanidins (PAC) or curcumin (Cur), the resulting PAC-NPs and Cur-NPs exhibited favorable drug loading and release profiles. These formulations showed significant anti-proliferation effects on HepG2 and HeLa cells ^[101].

In another study, biodegradable and targeted chitosan nanoparticles loaded with PAC (PAC-CSNPs) were designed. PAC-CSNPs displayed notable anti-cancer effect in HT-29 cells by inducing cell cycle arrest and apoptosis, mediated through reactive oxygen species overproduction and downregulation of cell cycle regulatory proteins. Toxicity evaluation *in vivo* in zebrafish revealed no significant adverse effects on embryos and larvae at low concentrations, indicating good biocompatibility ^[102].

Additionally, a complex coacervates-based drug carrier for delivering grape seed proanthocyanidins (CCDC-PA) was developed. This system significantly improved the stability and bioavailability of proanthocyanidins and suppressed the proliferation, migration, and invasion of OSCC cells via inhibition of the Akt signaling pathway. The encapsulation enhanced the anti-cancer efficacy of GSPs, supporting CCDC-PA as a promising delivery system for cancer therapy ^[103].

The conjugation of phytochemicals with targeted ligands, such as antibodies and peptides, can enhance their delivery specificity and therapeutic efficacy ^[104]. Recent advances in nanotechnology have made it possible to develop proanthocyanidin-loaded nanoparticles conjugated to targeted ligands, allowing for precision drug delivery to cancer cells without damaging healthy tissue. Studies indicate that antibody-conjugated proanthocyanidin nanoparticles exhibit increased cellular uptake and improved therapeutic outcomes in CDX models ^[105, 106]. For instance, a targeted natural drug system has been developed through the coassembly of phosphatidylcholine (PC), doxorubicin (DOX), proanthocyanidins (PA), and epigallocatechin gallate (EGCG) into PC@DOX-PA/EGCG nanoparticles. These nanoparticles were further modified on the surface with HER2, ER, and PR targeting ligands. Both studies *in vitro* and *in vivo* demonstrated that these nanoparticles effectively targeted multiple breast cancer cell lines, including BT-474, MCF-7, EMT-6, and MDA-MB-231, and significantly inhibited cancer cell growth. These findings suggest a promising strategy for addressing heterogeneous breast cancer ^[106].

Nanotechnology provides a new solution for drug delivery. The targeting, stability and bioavailability of drugs can be improved by designing nanocarriers. Among commonly used nanocarriers, liposomes are noted for their favorable biocompatibility and capacity to encapsulate both hydrophilic and hydrophobic drugs. However, conventional liposomes are often limited by issues such as drug leakage and insufficient stability. PLAROsomes represent a novel class of liposomes in which the incorporation of alkyl resorcinols, such as 2-methylresorcinol, improves stability and prevents drug leakage ^[107]. In a recent study, Bhinge et al. prepared proanthocyanidin-loaded PLAROsomes using the thin-film hydration, aiming to improve the stability and bioavailability of proanthocyanidins. PLAROsomes with ideal particle size and drug release profiles were obtained by optimizing the preparation process. MTT assay and trypan blue staining showed that the inhibitory effect of proanthocyanidin-loaded PLAROsomes on MCF-7 breast cancer cells was significantly higher than that of free PACY. Furthermore, flow cytometry analysis revealed that treatment with proanthocyanidin-loaded PLAROsomes markedly increased the percentage of early apoptotic MCF-7 cells (45.07%) relative to free proanthocyanidins (11.36%) ^[107].

To facilitate the clinical translation and application of proanthocyanidins in tumor therapy, this section compares the advantages and limitations of different delivery systems, with the results summarized in **Table 2**.

Table 2 Advantages and limitations of different delivery systems for proanthocyanidins

Delivery systems	Advantages	Limitations
Nanoparticles	Drug-loading capacity: Nanoparticles, particularly those composed of polymers (such as PLGA) or inorganic materials (such as silica), generally exhibit high drug-loading capacity and can effectively encapsulate and	Toxicity: Certain nanomaterials may exhibit a certain level of toxicity, particularly with long-term or high-dose administration. Therefore, when

	protect PACs to prevent their degradation <i>in vivo</i>. For example, PAC-CSNPs and CeO₂@SiO₂-PEG nanoparticles have both demonstrated favorable drug-loading performance. Stability: Nanoparticles exhibit good stability both <i>in vitro</i> and <i>in vivo</i>, and can maintain structural integrity for an extended period in blood circulation, ensuring effective drug delivery. Specifically, surface-modified nanoparticles, such as PEG-modified nanoparticles, can further reduce the chance of being recognized and eliminated by the immune system. Targeting capability: Nanoparticles can achieve active targeting, enabling precise drug delivery to diseased tissues or cells through surface modification with specific ligands or antibodies. This targeting capability can significantly enhance the therapeutic efficacy of drugs and reduce side effects.	selecting nanoparticles as drug carriers, their biocompatibility and toxicity must be carefully evaluated. Complexity of preparation: The preparation process of nanoparticles can be relatively complex, requiring precise control over various parameters to ensure that the particle size, shape, and surface properties meet the requirements.
Liposomes	Drug-loading capacity: Liposomes, composed of a phospholipid bilayer, are capable of encapsulating both hydrophilic and hydrophobic drugs, thus exhibiting excellent drug-loading capacity. They are particularly suitable as carriers for proanthocyanidins, compounds that contain both hydrophilic and hydrophobic components. Biocompatibility: Liposomes possess good biocompatibility and can be naturally degraded <i>in vivo</i>, reducing the potential toxicity risks. Targeting capability: Active targeted delivery can be achieved by modifying the liposomal surface. For example, conjugating antibodies or ligands to the liposomal surface can guide them to bind specifically to target cells.	Stability: Liposomes have relatively poor stability <i>in vivo</i> and are susceptible to rupture or fusion induced by blood components and enzymes, resulting in premature drug release. Preparation and storage: The preparation process for liposomes can be relatively complex. Furthermore, their storage conditions are demanding, requiring low temperature preservation to prevent degradation.
Complex delivery systems (such as complex coacervates)	Drug-loading capacity: Complex delivery systems, such as complex coacervates, encapsulate drug molecules through non-covalent interactions (e.g., electrostatic interactions, hydrogen bonding, etc.), exhibiting good drug-loading capacity. For example, proanthocyanidins delivery systems based on complex coacervates can effectively encapsulate proanthocyanidins and protect them from degradation. Stability: Complex delivery systems can remain stable under specific conditions (e.g., pH) and release the drug in response to environmental changes upon reaching the target site. This intelligent release mechanism contributes to enhanced therapeutic efficacy.	Targeting capability: Compared to nanoparticles and liposomes, the targeting capability of complex delivery systems may be relatively weak, and further research and improvement are needed to achieve precise delivery. Complexity of Preparation: The preparation process for complex delivery systems may be relatively complicated, requiring precise control over various conditions to ensure their stability and drug-loading performance.

Based on the physicochemical properties of proanthocyanidins as polyphenols and the core requirements for clinical tumor therapy (targeted enrichment, low toxicity and safety, controlled drug release, and clinical feasibility), combined with key indicators such as drug-loading capacity, stability, targeting ability, and toxicity of delivery carriers, it is determined that targeted modified liposomes represent the optimal carrier for the clinical translation of proanthocyanidins in oncology, with biodegradable polymer nanoparticles serving as alternative carriers in specific scenarios. With their natural structure composed of phospholipids/cholesterol, targeted modified liposomes exhibit excellent biocompatibility, extremely low immunogenicity, and complete biodegradability. They can achieve passive tumor enrichment through the enhanced permeability and retention effect, and realize active targeted delivery and site-specific release of proanthocyanidins by combining surface ligand modification and microenvironment-responsive design.

Furthermore, their mature manufacturing processes, quality control, and safety evaluation systems are highly compatible with the long-term, low-toxicity requirements of proanthocyanidins in tumor therapy, making them the carrier with the greatest potential for clinical translation at present. Biodegradable polymer nanoparticles (such as PLGA and gelatin), due to their enhanced circulatory stability and higher drug-loading capacity, are suitable only for tumor maintenance therapy requiring high doses, long-term sustained release, and combination therapy. Their clinical translation maturity is lower than that of liposomes, and further improvement in safety evaluation is required to reduce the risk of *in vivo* accumulation. In summary, the selection of carriers for the clinical translation of proanthocyanidins in oncology should be based on the specific therapeutic regimen, with targeted modified liposomes as the priority and biodegradable polymer nanoparticles as an option for special applications. This provides both a theoretical and practical basis for carrier selection in the clinical application of proanthocyanidins in tumor therapy.

8. Challenges and future prospects

8.1 Challenges

Despite the promising anti-cancer properties of proanthocyanidins, several challenges hinder their translation from laboratory research to clinical application as shown in **Figure 3**. For example, there are few clinical trials and gaps in clinical translation, lack of standardized dosing, low bioavailability, and limited researches on evaluating the safety and efficacy of long-term consumption. Additionally, interindividual variability in factors such as genetics, diet, and lifestyle may influence treatment response.

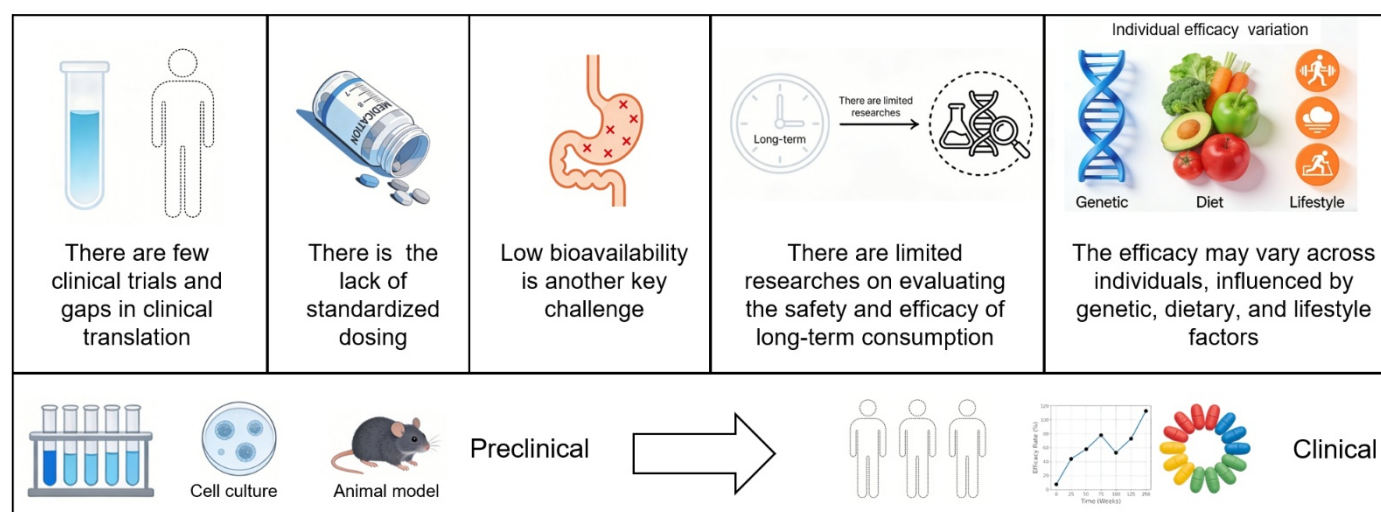


Figure 3 Several challenges hinder proanthocyanidins translation from laboratory research to clinical application.

(1) There are few clinical trials and gaps in clinical translation. The majority of supporting evidence is derived from cell models and CDX models, while preclinical experiments are still in early stages. Existing clinical trials are small in scale, short-term, and exploratory. The preclinical PDO model may help improve the predictive value. It will be essential to conduct large-scale Phase III clinical trials and to systematically optimize dosing regimens.

(2) One of the major challenges in phytochemical research is the lack of standardized dosing. Bioactive components in plant extracts may be influenced by various factors, such as geographical origin, plant source,

harvest time, and the extraction method. This variability hinders direct comparison of results across different studies and complicates the determination of optimal therapeutic doses. The concentration of proanthocyanidin compounds in commercial products can vary widely, leading to inconsistent results in studies and clinical applications [108].

(3) Bioavailability of phytochemicals is another key challenge. Proanthocyanidins have low bioavailability due to poor absorption, and rapid metabolism and excretion. This limits its effectiveness *in vivo* and complicates the assessment of its therapeutic potential. It is necessary to explore suitable delivery systems to improve bioavailability. Therefore, understanding how it is metabolized and how to improve its bioavailability remains a major challenge.

(4) There are limited researches on evaluating the safety and efficacy of long-term phytochemical consumption. Most clinical trials on proanthocyanidins are short-term, typically ranging from several weeks to a few months. Further studies are needed to investigate their long-term effects, potential toxicity, and interactions with other medications to ensure safe use in the general population [109].

(5) The efficacy of phytochemicals may vary across individuals, influenced by genetic, dietary, and lifestyle factors. However, these variables are often not adequately controlled in current study designs, resulting in generalized conclusions that may not be applicable to diverse populations [110]. A personalized approach is needed in phytochemistry research, considering factors such as genetics, microbiome composition, and individual health status.

8.2 Future prospects

Future research aimed at integrating proanthocyanidins into cancer therapy and chemoprevention should consider the following directions as shown in **Figure 4**, which emerge from the challenges discussed above.

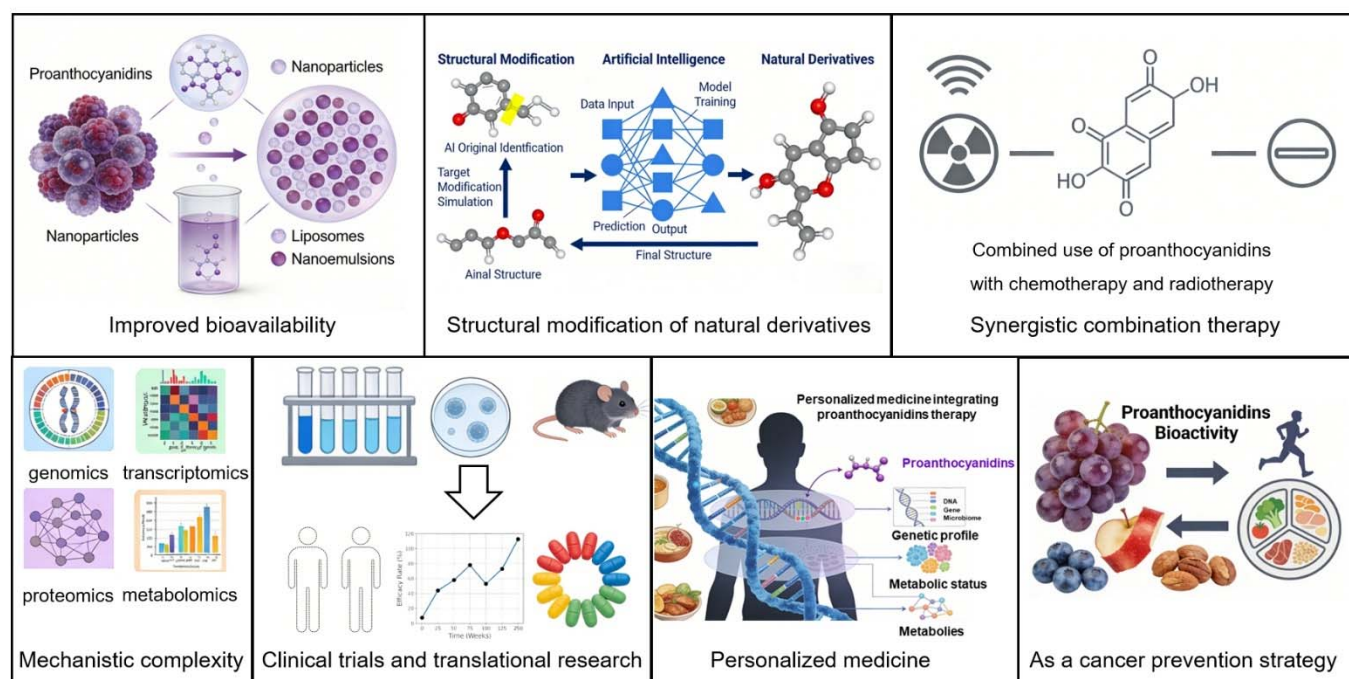


Figure 4 Future research aimed at integrating proanthocyanidins into cancer therapy and chemoprevention.

(1) Improved bioavailability: Nanocarrier systems such as nanoparticles, liposomes, or nanoemulsions can enhance the solubility and stability of proanthocyanidins. Furthermore, conjugating proanthocyanidins with targeting ligands that recognize receptors overexpressed on cancer cells may allow for the selective delivery of higher compounds concentration to tumor sites. This strategy could improve anti-tumor efficacy while minimizing systemic toxicity.

(2) Structural modification of natural derivatives: The biological activity and pharmacokinetic profile of proanthocyanidins can be optimized through chemical modifications such as acylation and hydroxylation. The structural design and formulation development of proanthocyanidin derivatives are optimized by combining with artificial intelligence.

(3) Synergistic combination therapy: Proanthocyanidins could enhance the sensitivity of cancer cells to standard treatments, potentially improving therapeutic efficacy while allowing for reduced doses and mitigating associated side effects ^[111]. Future research should focus on combining phytochemicals with traditional therapies to improve efficacy and target multiple pathways in cancer progression ^[112, 113]. Some cancer cells become resistant to chemotherapeutic agents by activating survival pathways. Proanthocyanidins may help overcome this resistance by regulating key signaling pathways.

(4) Mechanistic complexity: The multi-target anti-tumor effect of proanthocyanidins leads to unclear analysis of key pathways. Future studies could employ multi-omics approaches, including genomics, transcriptomics, and metabolomics to elucidate their precise molecular targets.

(5) Clinical trials and translational research: Rigorous clinical trials are required to evaluate the long-term effects of proanthocyanidins in cancer prevention and adjuvant therapy. Advancing this translational research will depend on multidisciplinary collaboration to bridge the gap between preclinical findings and clinical application.

(6) Personalized medicine: Due to interindividual variability driven by genetic and dietary factors, integrating proanthocyanidin therapy with personalized medicine could enable treatments tailored to an individual's genetic profile, microbiome composition, and metabolic status. Such personalization may optimize dosing regimens and improve therapeutic outcomes ^[63]. Furthermore, drug sensitivity testing using PDOs could help predict individual responses and advance the implementation of precision oncology.

(7) As a cancer prevention strategy: Future work should explore how dietary patterns and lifestyle factors modulate the bioactivity of proanthocyanidins, and investigate the potential of incorporating proanthocyanidin-rich foods or supplements into daily diets for cancer prevention.

9. Conclusions

In summary, proanthocyanidins, as a widely available and well-tolerated dietary polyphenol, show great potential in both cancer prevention and treatment. Their broad mechanisms include inhibiting proliferation, inducing cell apoptosis and cell cycle arrest, improving the tumor immune microenvironment, regulating tumor-related signaling pathways, inhibiting angiogenesis, and suppressing invasion and metastasis, highlighting their potential as multi-target drugs. Although preclinical studies conducted on various models

have provided strong mechanistic insights, and advancements in novel delivery systems have offered solutions to the bioavailability challenges, there still exists a significant translational gap.

To bridge these gaps, future efforts should prioritize the elucidation of precise molecular targets, the establishment of standardized extraction processes, the optimization of targeted delivery systems, and systematical evaluation its long-term safety and effectiveness through rigorous clinical trials. In addition, it is also crucial to integrate proanthocyanidins into combination therapies and adopt personalized approaches based on individual genetic and metabolic profiles. Ultimately, advancing research in these areas is essential to translate the preclinical potential of proanthocyanidins into practical clinical strategies, potentially improving cancer treatment outcomes and enriching public health dietary interventions.

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Conflicts of Interest

The authors declare no conflict of interest.

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