Research and Application of Proanthocyanidins in Livestock and Poultry Production: Postprint

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Abstract

Proanthocyanidins are a collective term for a large class of polyphenolic compounds widely distributed in plants, possessing exceptional antioxidant capacity and recognized internationally as the most effective natural antioxidant for scavenging free radicals in the organism. Existing in vivo and in vitro studies have demonstrated that proanthocyanidins hold broad application prospects in improving physiological functions, such as reducing inflammation, ameliorating oxidative stress, exerting anticancer effects, and modulating immunity. This article reviews the chemical structure, raw material sources, isolation and extraction methods, biological functions of proanthocyanidins, and their current application status in livestock and poultry production.

Full Text

Preamble

Research and Application of Proanthocyanidins in Livestock Production

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Abstract: Proanthocyanidins are a class of polyphenolic compounds widely distributed in plants, renowned for their exceptional antioxidant capacity and recognized internationally as the most effective natural antioxidants for scavenging free radicals in the body. Numerous in vitro and in vivo studies have demonstrated that proanthocyanidins hold promising applications for improving physiological functions, such as reducing inflammation, ameliorating oxidative stress, exerting anti-cancer effects, and modulating immune responses. This review summarizes the chemical structure, raw material sources, extraction and isolation methods, biological functions, and current applications of proanthocyanidins in livestock production.

Keywords: proanthocyanidins; biological function; antioxidant; immune; livestock production
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Introduction

Oxidative stress represents one of the primary challenges in livestock production, causing structural and functional alterations in biomacromolecules such as proteins, nucleic acids, and lipids. This leads to metabolic disorders, impaired growth and development, weakened disease resistance, and ultimately reduced production performance and product quality. Therefore, effective antioxidant strategies are crucial for improving animal health and enhancing production efficiency.

Proanthocyanidins are widely distributed in fruits, vegetables, nuts, seeds, flowers, and the bark of certain plants. They constitute a class of phenolic compounds present as oligomeric or polymeric forms of polyhydroxyflavan-3-ols (such as catechin and epicatechin) [1]. The phenolic hydroxyl structure of proanthocyanidins, particularly the ortho-hydroxyl groups in catechol or pyrogallol moieties, can be readily oxidized to quinone structures, thereby consuming oxygen. This confers strong scavenging capacity against oxygen free radicals including superoxide anions, reactive oxygen species, and hydroxyl radicals, making proanthocyanidins excellent free radical scavengers and lipid peroxidation inhibitors. They are internationally recognized as the most effective natural antioxidants for eliminating free radicals in the body [2]. As early as 1997, studies demonstrated that proanthocyanidins are more potent free radical scavengers than vitamins C and E, with antioxidant capacities 50 times greater than vitamin E and 20 times greater than vitamin C [3]. Recent research has revealed that proanthocyanidins function not only as effective antioxidants but also possess immunomodulatory [4], anti-inflammatory [5], and melatonin level- and hypothalamic clock gene expression-modulating properties [6], offering broad prospects for improving human and animal health. Consequently, they have attracted increasing attention in nutrition and medical healthcare fields.

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1.1 Chemical Structure of Proanthocyanidins

Proanthocyanidins are among the most abundant polyphenolic compounds in plants and belong to the flavonoid family. Structurally, proanthocyanidins are composed of varying numbers of (+)-catechin or (-)-epicatechin units. For example, the chemical structure of grape seed proanthocyanidins is shown in Figure 1 [Figure 1: see original paper] [7]. The simplest forms are catechin and epicatechin monomers, or dimers formed from catechin and/or epicatechin, with more complex polymeric forms also existing. Based on degree of polymerization (DP), dimers to pentamers are typically classified as oligomeric proanthocyanidins (OPC), while those with DP greater than five are termed polymeric proanthocyanidins (PPC). Generally, the average DP of proanthocyanidins ranges from 3 to 11 [8]; however, liquid chromatography-mass spectrometry analysis has revealed that proanthocyanidins in cider apple extracts can have DP values as high as 17 [9].

[Figure 1: see original paper] The chemical structure of grape seed proanthocyanidins [7]

1.2 Influence of Polymerization Degree on Proanthocyanidin Bioactivity

Studies have shown that proanthocyanidin-rich foods or proanthocyanidin monomers exhibit preventive effects against cardiovascular diseases and cancer, with efficacy dependent on intestinal absorption of proanthocyanidins [8]. Absorption is determined by the degree of polymerization (DP). In vitro studies have demonstrated that only proanthocyanidin dimers and trimers can be absorbed by intestinal epithelial cells, whereas polymeric proanthocyanidins with an average DP of 7 cannot be absorbed [10]. Comparative studies on the antioxidant properties of catechins and proanthocyanidins revealed that antioxidant capacity in oil phase decreases with increasing DP, while in aqueous phase it initially increases then decreases, with trimers showing the strongest antioxidant activity [11]. Furthermore, polymeric proanthocyanidins can be degraded by colonic microorganisms into low-molecular-weight compounds that are subsequently absorbed. For instance, proanthocyanidin dimers and epicatechin can be metabolized into phenolic acids and non-phenolic aldehyde aromatic compounds [12-13].

2.1 Raw Material Sources of Proanthocyanidins

Proanthocyanidins represent a broad class of polyphenolic compounds found in plants, with diverse sources including fruits, vegetables, seeds, nuts, flowers, and bark that can be used for extraction and isolation. Among these, grape seed proanthocyanidins have been most extensively studied.

Grape seeds, a byproduct of grape juice and wine production, contain 60%-70% polyphenolic substances, including abundant proanthocyanidins in the form of dimers, trimers, and oligomers composed of catechin and epicatechin monomers [14-15]. These grape seed proanthocyanidins have been demonstrated to possess antioxidant, anti-mutagenic, anti-inflammatory, and anti-cancer properties [7,16-19]. Additionally, pine bark serves as an excellent raw material for proanthocyanidin extraction. Wu et al. [20] compared the active compound content in bark from six pine species: *Pinus massoniana*, *Pinus elliottii*, *Pinus kwangtungensis*, *Pinus taiwanensis*, *Pseudolarix amabilis*, and *Pinus caribaea*. Although significant differences existed among species, all contained proanthocyanidins, with *Pinus massoniana* bark showing the highest content of total polyphenols, total flavonoids, and proanthocyanidins. The proanthocyanidin content reached 34.8 mg/kg, accounting for over 30% of total polyphenols.

2.2 Extraction and Isolation Methods for Proanthocyanidins

Numerous methods exist for the extraction and isolation of proanthocyanidins, commonly including organic solvent extraction, membrane filtration, chromatography, aqueous two-phase extraction, macroporous resin adsorption, and high-performance liquid chromatography [21-22]. Organic solvent extraction typically employs ethanol, methanol, acetone, or mixed solvent systems. While efficient, this method generates environmentally hazardous waste, and the toxicity of methanol and acetone limits its application. Membrane filtration utilizes selective membranes for separation, purification, or concentration without requiring heating, thereby minimizing loss of active compounds. However, prolonged operation causes membrane fouling and clogging, necessitating regular cleaning or multiple membrane systems in series. Aqueous two-phase extraction simultaneously extracts and preliminarily purifies proanthocyanidins under mild conditions with minimal activity loss, but suffers from long separation times and low single-run efficiency, restricting industrial application. Chromatography and high-performance liquid chromatography offer high separation efficiency, good selectivity, and automated operation, but involve high equipment costs and maintenance expenses. Macroporous resin adsorption provides advantages including good selectivity, high adsorption capacity, easy regeneration, rapid desorption, and convenient operation [23], making it widely applicable for natural product isolation.

3.1 Antioxidant Effects

The diverse biological functions of proanthocyanidins can be attributed to their potent antioxidant activity, which manifests primarily in four aspects: (1) Direct scavenging of reactive oxygen and nitrogen species, increasing mitochondrial membrane potential and cellular oxygen consumption, reducing oxygen free radical generation, and terminating oxidation reactions [24]. Studies have reported that Pycnogenol (a water extract from French maritime pine bark) exhibits exceptionally high free radical scavenging capacity, primarily due to its proanthocyanidin content of up to 85% [25]. Numerous investigations on proanthocyanidin scavenging of 1,1-diphenyl-2-picrylhydrazyl (DPPH·), 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) cation radicals (ABTS+·), superoxide anion radicals, and hydroxyl radicals have shown that introducing gallic acid at the 3-position of the proanthocyanidin benzene ring significantly enhances free radical scavenging ability, whereas glycosylation at this position reduces it [11]. The free radical scavenging capacity of proanthocyanidins is closely related to their DP; research indicates that DP of 3 increases radical scavenging activity, while further DP increases conversely reduce activity [11,25].

(2) Antioxidant effects through metal ion chelation. Studies show that most polyphenols in tea and red wine can inhibit non-heme iron absorption [8]. However, mouse models have demonstrated that tea consumption does not affect iron absorption unless tea and iron are ingested simultaneously [26]. Therefore, questions remain regarding whether proanthocyanidins first chelate iron to inhibit Fenton reactions and protect intestinal tissue from oxidative damage, and whether proanthocyanidin intake negatively impacts systemic iron reserves. These interactions between proanthocyanidins and iron in vivo require further investigation.

(3) Enhancement of endogenous antioxidant enzyme activities, such as superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase. Qin Shengli [27] reported that proanthocyanidins significantly increased superoxide dismutase and glutathione peroxidase activities in rat brain tissue, thereby enhancing antioxidant capacity.

(4) Regeneration of other endogenous antioxidants, including vitamin C, glutathione, coenzyme Q (ubiquinone), and vitamin E [28].

3.2 Anti-Cancer Effects

Cancer development is associated with chronic inflammation resulting from persistent oxidative stress, making potent antioxidant compounds a focal point in anti-cancer drug development. As early as 1998, Joshi [29] demonstrated that 25 mg/L of grape seed proanthocyanidins could induce apoptosis in human breast tumor MCF-7 cells, human lung cancer A-427 cells, human gastric adenocarcinoma CRL1739 cells, and chronic myeloid leukemia K562 cells.

Recently, Zhu et al. [30] found that sorghum proanthocyanidins significantly prevented HepG2 cancer cell diffusion and inhibited their growth. Analysis of intracellular signaling pathways revealed that proanthocyanidins upregulated phosphorylated 5' -adenosine monophosphate-activated protein kinase α while downregulating phosphorylated extracellular regulated protein kinases 1/2 (ERK1/2) and p38 mitogen-activated protein kinase (p38 MAPK). Liu et al. [31] similarly reported that *Pinus massoniana* bark proanthocyanidins significantly inhibited ovarian cancer cell growth in a dose-dependent manner. The underlying mechanism may involve loss of mitochondrial membrane potential, downregulation of the anti-apoptotic protein B-cell lymphoma-2 (bcl-2), and activation of cysteinyl aspartate-specific proteinase 3/9 (Caspase 3/9), indicating that *Pinus massoniana* bark proanthocyanidins trigger cancer cell apoptosis via mitochondrial-associated apoptotic signaling pathways. Additionally, *Pinus massoniana* bark proanthocyanidins inhibited ovarian cancer cell migration and invasion by significantly suppressing matrix metallopeptidase-9 (MMP-9) activity and expression, and blocking nuclear factor- B (NF- B) activity as well as ERK1/2 and p38 MAPK activation [31].

Furthermore, proanthocyanidins can prevent carcinogen-induced pre-cancerous lesions. For instance, they effectively block nitrosamine synthesis and scavenge nitrates, thereby preventing tissue carcinogenesis caused by ammonium nitrite [32]. Proanthocyanidins can also act as interleukin-6 (IL-6) antagonists, avoiding the pro-carcinogenic effects of IL-6 induced by various stimuli [33]. They effectively inhibit the tumor-promoting effects of the inducers diglyceride and terephthalic acid in vitro [34], and share mechanisms with protein kinase C, which plays important roles in suppressing tumor initiation, progression, and metastasis [35]. These findings demonstrate that proanthocyanidins can inhibit cancer development and progression, highlighting their potential for development as anti-cancer agents.

3.3 Immunomodulatory Effects

Proanthocyanidins possess immunomodulatory functions in animals, such as effectively preventing UV radiation-induced immunosuppression. Studies have shown that dietary proanthocyanidin supplementation in mice increases interleukin-12 (IL-12) content [36] and stimulates CD8+ effector T cell differentiation [37], thereby suppressing UV radiation-induced immunosuppression. Although the underlying mechanisms are not fully elucidated, reports indicate that DNA damage contributes to UV-induced dendritic cell tolerance [38], suggesting that proanthocyanidin-mediated repair of DNA damage in UV-exposed dendritic cells may play an important role in ameliorating UV-induced immunosuppression. Additionally, in a rat model of recurrent colitis, oral administration of varying doses of proanthocyanidins significantly reduced colonic tissue levels of interleukin-1β (IL-1β) and IL-6 while increasing interleukin-4 (IL-4) and interleukin-10 (IL-10) levels [5]. These findings indicate that proanthocyanidins can decrease pro-inflammatory cytokine expression while enhancing anti-inflammatory cytokine expression. Recent research from our team has demonstrated that proanthocyanidins and other polyphenols can dynamically modulate the inflammatory cytokine network, thereby controlling systemic inflammation levels and regulating animal immune function [39-40].

4 Research and Application of Proanthocyanidins in Livestock Production

In livestock production, particularly intensive farming systems, animals are constantly exposed to oxidative stress. Numerous studies have shown that various factors including environmental cold and heat stress, chemical drugs, pathogenic bacteria, unbalanced feed nutrients, spoiled feed, and radiation can induce free radical production and trigger oxidative reactions in livestock [41-43]. Under normal conditions, animals possess certain antioxidant capacities. However, when the balance between oxidation and antioxidant defense is disrupted, lipid peroxidation occurs with excessive oxygen free radicals that damage cells, tissues, and organs, severely compromising animal health, growth performance, and product quality. For example, Gao et al. [44] demonstrated that dexamethasone injection in broiler chickens caused muscle lipid peroxidation and significantly increased fatty acid saturation, resulting in decreased meat quality. As effective natural antioxidants that scavenge free radicals, proanthocyanidins show significant potential in alleviating oxidative stress and improving production performance in livestock.

4.1.1 Research and Application in Enhancing Antioxidant Capacity and Reducing Diarrhea

Numerous studies on proanthocyanidins in swine production have been reported in recent years, as detailed in Table 1 . Zhao Jiao [45] found that dietary supplementation with 100 mg/kg grape seed proanthocyanidins significantly improved serum and hepatic antioxidant capacity in piglets, alleviating Diquat-induced oxidative stress and damage comparable to the effect of 50 mg/kg vitamin E. Further signaling pathway analysis revealed that grape seed proanthocyanidins significantly reduced hepatocyte apoptosis rates by inhibiting mitochondrial and endoplasmic reticulum-mediated apoptotic pathways, thereby decreasing liver injury. Hao Ruirong et al. [46] also reported that sorghum proanthocyanidins significantly increased serum antioxidant enzyme activities in weaned piglets, enhancing their antioxidant capacity and consequently reducing diarrhea incidence.

Recent main research and applications of proanthocyanidins in pig production

No.	Stage	Added level (mg/kg)	Sources	Effects
1	Not specified	50 or 100	Grape seed	Significantly improved antioxidant capacity under oxidative stress, alleviated liver oxidative damage, reduced hepatocyte apoptosis rate; 100 mg/kg was optimal
2	28-day weaned piglets	50, 100 or 150	Not specified	Significantly reduced diarrhea rate without affecting daily gain, feed intake, or feed conversion ratio; increased serum IgG, IgM, complement 3, complement 4, and IL-2 expression; enhanced SOD and GSH-Px activities; decreased MDA content

No.	Stage	Added level (mg/kg)	Sources	Effects
3	28-day weaned piglets	Not specified	Grape seed	Improved daily gain, reduced feed conversion ratio and diarrhea rate (comparable to antibiotics); improved small intestinal villus morphology; increased serum IL-1β, IL-2 expression
4	28-day weaned piglets	40, 70 or 100	Grape seed	Improved intestinal digestive enzyme activity and increased white blood cell and red blood cell counts at 3 weeks post-trial; 70 mg/kg was optimal

No.	Stage	Added level (mg/kg)	Sources	Effects
5	13 kg piglets	200 or 400	Grape seed	In LPS inflammation model, 400 mg/kg reduced pro-inflammatory cytokines IL-1β, IL-6 and TNF-α expression, alleviating inflammation
6	19 kg piglets	100 or 200	Grape seed	Under normal physiological conditions, improved feed conversion efficiency

4.1.2 Research and Application in Improving Growth Performance

Song Peixia [47] conducted a comparative study between grape seed proanthocyanidins and antibiotics, finding that dietary supplementation with 250 mg/kg grape seed proanthocyanidins reduced intestinal mucosal permeability, enhanced mucosal antioxidant capacity, and alleviated weaning stress-induced diarrhea, thereby significantly improving daily gain and feed conversion ratio and enhancing growth performance in weaned piglets, with effects comparable to antibiotics. Park et al. [48] reported that under normal physiological conditions, dietary supplementation with 100 or 200 mg/kg proanthocyanidins significantly improved feed conversion efficiency and reduced serum creatinine levels in piglets. In an LPS-induced nursery pig model, dietary supplementation with 400 mg/kg proanthocyanidins significantly decreased platelet counts and suppressed LPS-induced elevation of blood IL-1β, IL-6, and tumor necrosis factor-α (TNF-α) levels. These results indicate that dietary proanthocyanidins can improve feed conversion efficiency and reduce inflammation in pigs. In a study examining different proanthocyanidin supplementation levels in weaned piglets, 70 mg/kg grape seed proanthocyanidins significantly increased intestinal trypsin, lipase, and amylase activities, facilitating nutrient absorption and utilization, while also elevating blood white blood cell counts, red blood cell counts, and hemoglobin content, though visceral organ indices were not significantly affected [49].

Additionally, research has indicated that grape seed proanthocyanidins can serve as immunomodulators for weaned piglets to significantly improve growth performance [50], though mechanistic studies and subsequent promotion and application are still lacking.

4.1.3 Absorption and Metabolism in Pigs

Previous studies have demonstrated that proanthocyanidins (research has focused primarily on grape seed proanthocyanidins) exert positive effects on growth performance, diarrhea prevention, oxidative damage alleviation, inflammation reduction, and immune modulation in pigs. Due to variations in proanthocyanidin purity, the effective supplementation range in pig diets is 70-400 mg/kg [47-50]. Bittner et al. [51] investigated proanthocyanidin absorption and metabolism in pigs by oral administration of 100 mg/kg BW proanthocyanidin B4 (dimer) with subsequent measurement of urine and plasma over 48 hours. The results showed intact proanthocyanidin B4 molecules were detected in both urine and plasma, with a maximum plasma concentration of 2.13 ng/mL and urinary excretion of 0.008% as intact molecules. In addition to catechin and epicatechin monomers, methylated and conjugated monomeric metabolites were also detected. This indicates that proanthocyanidin dimers can be absorbed as intact molecules in pigs and excreted in urine, with primary degradation products being catechin and epicatechin monomers that are further metabolized into methylated and glucuronidated compounds.

4.2.1 Research and Application in Broiler Production

Research on proanthocyanidins in poultry production has primarily focused on improving growth performance, regulating lipid metabolism, antioxidant effects, and immune modulation. Yang Guoyu et al. [52] confirmed that compound preparations containing grape seed proanthocyanidins could alleviate heat stress in broilers, improve carcass composition, and reduce body fat deposition. Yang Jinyu [53] investigated the regulatory effects and mechanisms of grape seed proanthocyanidins on broiler chickens. In vitro results showed that grape seed proanthocyanidins significantly promoted broiler lymphocyte proliferation and exhibited good efficacy in free radical scavenging and lipid oxidation inhibition. In vivo experiments demonstrated that dietary supplementation with 7.5-15.0 mg/kg grape seed proanthocyanidins significantly improved growth performance and intestinal villus morphology, increased T and B lymphocyte transformation rates, and enhanced blood lysozyme activity, thereby improving immune function. However, when the dosage reached 30.0 mg/kg, adverse effects on blood metabolism were observed. In addition to grape seed proanthocyanidins, extracts from other plant sources have been studied in broilers. Park et al. [54] found that oral administration of 5, 10, and 20 mg/kg BW pine bark proanthocyanidins for 5 weeks significantly promoted spleen cell, bursa cell, and thymocyte proliferation, increased type I helper T cell cytokine (interferon-γ) expression, and decreased type II helper T cell cytokine (IL-6) expression, thereby enhancing immune function in broilers.

4.2.2 Research and Application in Layer Production

In layer hens, studies have shown that dietary grape seed proanthocyanidin supplementation improved laying rate in late-phase hens, increased eggshell thickness, enhanced total superoxide dismutase activity in egg yolk and plasma, and reduced malondialdehyde content in plasma and liver, thereby improving antioxidant capacity. The optimal dosage was 50 mg/kg, which outperformed 200 mg/kg of the antioxidant tert-butylhydroquinone [55]. Zhang Yu [56] compared five different antioxidants in layer hens: tert-butylhydroquinone, tea polyphenols, vitamin E, pyrroloquinoline quinone, and grape seed proanthocyanidins. The results showed that tea polyphenols possessed the strongest total antioxidant capacity and free radical scavenging ability, followed by grape seed proanthocyanidins. Dietary supplementation with 100 or 200 mg/kg tert-butylhydroquinone and 400 mg/kg tea polyphenols showed the strongest inhibition of auto-oxidation in soybean and rapeseed oils, while 400 mg/kg tea polyphenols and 85 mg/kg vitamin E provided the best antioxidant effects in egg yolk, liver, and plasma of late-phase laying hens.

4.3 Research and Application in Other Livestock Species

Beyond swine and poultry, limited reports exist on proanthocyanidin applications in ruminants and rabbits. In dairy cows (particularly early lactation cows) with ketosis, intense oxidative reactions occur, marked by significantly elevated blood malondialdehyde and nitric oxide levels and decreased activities of glutathione peroxidase, superoxide dismutase, and catalase, resulting in substantially reduced antioxidant capacity. Therefore, enhancing antioxidant capacity in early lactation cows is essential. Early lactation supplementation with proanthocyanidins significantly increased plasma antioxidant enzyme activities, reduced oxidative metabolites and ketone bodies, and effectively improved systemic antioxidant capacity [57]. However, Huang Yunfei et al. [58] found that oral administration of 20-80 mg/(kg $\cdot$ d) grape seed proanthocyanidins to early lactation cows had no significant effects on liver enzyme activities (aspartate aminotransferase, alanine aminotransferase, and γ-glutamyl transpeptidase), plasma protein content (albumin, total protein, and globulin), or kidney function indicators (uric acid and urea nitrogen). Niu Caiqin et al. [59] reported that intravenous injection of 64 mg/kg BW proanthocyanidins significantly reduced arterial blood pressure in rabbits with a dose-effect relationship, while L-nitroarginine and methylene blue markedly attenuated this hypotensive effect. This suggests that the blood pressure-lowering mechanism of proanthocyanidins in rabbits may be related to nitric oxide release from endothelial cells.

5 Conclusion

Proanthocyanidins are internationally recognized as the most effective natural antioxidants for scavenging free radicals in the body, possessing potent antioxidant, anti-cancer, anti-radiation, and immune-modulating biological functions. With advantages including natural origin, no residues, non-toxicity, and no resistance development, proanthocyanidins can serve as a novel feed additive to enhance antioxidant capacity and immune function in swine, poultry, and ruminants, thereby improving livestock performance, preventing diarrhea, and enhancing product quality.

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Note: Figure translations are in progress. See original paper for figures.