Applications and Mechanisms of Action of Plant-Derived Antioxidants: Postprint

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Abstract

Plant-derived antioxidants are a class of substances originating from plants that possess antioxidant functions. Applied as feed additives in animal husbandry, they are characterized by wide availability, high efficiency, safety, and absence of residues. This review primarily summarizes the commonly used types of such antioxidants in livestock production, their application effects, and the research progress on their mechanisms of action, thereby providing a reference for future more extensive and in-depth research and application of plant-derived antioxidants and further elucidation of their underlying mechanisms.

Full Text

Application of Phytogenic Antioxidants and Their Mechanisms of Action

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Abstract: Phytogenic antioxidants are a class of substances derived from plants with antioxidant functions. When applied as feed additives in animal production, they offer advantages including wide availability, high efficiency, safety, and no residues. This paper reviews the commonly used types of these antioxidants in livestock production and their application effects, and summarizes research progress on their mechanisms of action, providing a reference for future extensive and in-depth research and application of phytogenic antioxidants and further elucidation of their underlying mechanisms.

Keywords: phytogenic antioxidants; oxidative stress; mechanisms of action
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Oxidative stress occurs when peroxides accumulate excessively in animal bodies, exceeding the capacity of the antioxidant defense system and disrupting the oxidation-antioxidation balance, thereby harming certain tissues, organs, or physiological functions and reducing production performance. Numerous factors can cause oxidative stress, and current research suggests that adverse internal and external environments, peroxidized substances in feed, diseases, and foreign substance metabolism can all trigger oxidative stress. Reduced immunity, enteritis, pneumonia, postpartum sepsis, mastitis in dairy cows, and various other livestock diseases are directly or indirectly related to oxidative stress. Particularly under current intensive farming conditions, factors such as high-density housing, poor ventilation, lack of exercise, and high-energy diets make oxidative stress ubiquitous in animal production, severely impacting immune function and production performance. Synthetic antioxidants are commonly added to alleviate oxidative stress and prevent oxidation of feed components, but since the degree of oxidative stress is difficult to estimate precisely, antioxidants are often added in excess. These excess antioxidants frequently accumulate in animal tissues and animal products, creating food safety and environmental hazards. Therefore, finding safe, efficient, and residue-free antioxidants has become a research priority.

Phytogenic antioxidants are bioactive substances derived from plants with special functional groups that offer efficient and safe antioxidant effects. Their categories include polyphenols, plant polysaccharides, and alkaloids, with commonly used examples including resveratrol, proanthocyanidins, and *Paris polyphylla* polysaccharides. Due to structural differences, their antioxidant mechanisms vary. This paper summarizes the main causes of oxidative stress in current animal production and reviews the types, characteristics, and mechanisms of common phytogenic antioxidants to provide references for future research and development.

1.1 Causes of Oxidative Stress

Various stressors in the internal and external environment of animal growth, including feed composition (excessive unsaturated fatty acids, trace element and vitamin deficiencies), diseases, certain chemicals in feed (such as herbicides or pesticide residues), and physiological and psychological changes in animals, can cause peroxide accumulation and oxidative damage. Meanwhile, aerobic metabolism is an oxidation reaction process in which electrons "leak" during electron chain transfer, leading to free radical accumulation. If these accumulated free radicals cannot be cleared promptly and exceed the scavenging capacity of the antioxidant defense system, the oxidation-antioxidation balance is disrupted, resulting in oxidative stress.

1.2 Main Hazards and Mechanisms

In livestock production, animals frequently suffer from various oxidative stresses that reduce productivity, affect product quality, and can trigger large-scale disease and death under chronic stress. Research shows that accumulated peroxides contain many active electrons and exist in unstable chemical states that can induce cell senescence and apoptosis in animal tissues and organs through multiple pathways, cause DNA damage, and inhibit cell cycle progression. They also affect enzymatic metabolism, accelerate fat and protein decomposition, promote gluconeogenesis, and reduce glucose oxidation for energy supply, thereby decreasing resistance and immunity and triggering various diseases. Studies have found that oxidative stress can cause peroxidation of polyunsaturated fatty acids in eggs, affecting egg quality and reducing nutritional value, and can impair digestion and absorption in early-weaned young animals, leading to diarrhea.

1.2.1 Induction of Cell Senescence Oxidative stress is a major factor causing cell senescence. Known pathways include: (1) DNA damage pathway: Oxidative stress causes DNA damage, which is unwound into single strands by a protein complex, activating ataxia telangiectasia mutated kinase and triggering phosphorylation of histone H2AX near the damaged DNA, which induces cell senescence through the p53-p21-Cip1-pRB pathway. (2) Activation of p38 mitogen-activated protein kinase (MAPK) pathway: The MAPK family is a highly conserved serine/threonine protein kinase and important signal transduction molecule. This pathway consists of a three-level kinase chain, and reactive oxygen species (ROS) can activate p38 through this pathway, upregulating p16 and p19 ARF expression and triggering cell senescence. (3) Activation of nuclear factor B (NF- B) pathway: Under normal conditions, NF- B binds to NF- B inhibitor in the cytoplasm and remains inactive. ROS generated by oxidative stress can activate NF- B inhibitor kinase (IKK), causing phosphorylation of NF- B inhibitor α and activating NF- B. Activated NF- B translocates to the nucleus, binds to corresponding DNA sequences, and upregulates interleukin (IL)-8 expression, accelerating cell senescence. (4) Activation of miRNA pathway: miRNA is an endogenous non-transcribed small RNA that moves to the cytoplasm during DNA transcription and directly binds to target mRNA, altering its secondary structure and hindering translation. Oxidative stress can accelerate cell senescence by regulating miRNA levels.

1.2.2 Effects on Digestion and Absorption Oxidative stress affects animal digestion and absorption mainly through two pathways. On one hand, animals under oxidative stress show increased intestinal crypt depth and reduced villus length, with excessive nitric oxide (NO) production causing dysfunction of intestinal epithelial cells and affecting digestive absorption. On the other hand, oxidative stress alters intestinal mucosal morphology and structure, damaging mucosal function, reducing nutrient absorption rates, allowing toxic and harmful substances to enter the body, destroying the intestinal mucosal immune barrier, decreasing resistance, and increasing disease susceptibility. Oxidative stress induced by acidosis damages rumen intestinal cells, and oxidative metabolites deplete ATP, leading to dysfunction of the intestinal epithelial cell barrier.

1.2.3 Interference with Nutrient Metabolism Oxidative stress affects carbohydrate, lipid, and protein metabolism. It reduces insulin secretion and, by activating silent information regulator 2 homolog 1 (SIRT1), indirectly decreases forkhead box protein O1 (FoxO1) acetylation levels, increasing expression of gluconeogenesis key enzymes phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G-6-pase), promoting hepatic gluconeogenesis and inhibiting glucose oxidation for energy supply. Protein carbonylation level is an important indicator of protein oxidative damage. Oxidative stress causes activated carbonyl groups to undergo carbonylation reactions with amino acid side chains such as lysine, cysteine, and histidine, damaging receptors, enzymes, transport proteins, and structural proteins. Meanwhile, free radicals generated by oxidative stress upregulate muscle atrophy protein Fbox-1 expression through the p38 MAPK pathway, causing muscle cell-specific E3 ubiquitin protein ligase to present target proteins to ubiquitin, and ubiquitinated Atrogin-1 protein is recognized and degraded by the 26S proteasome. Fatty acids are important components of cell phospholipid bilayers, and free radicals generated by oxidative stress can oxidize unsaturated fatty acids, triggering lipid peroxidation and producing the stable end product malondialdehyde (MDA), damaging biomembrane structure, disrupting physiological functions, and triggering pathological processes.

2. Body' s Response Mechanisms to Oxidative Stress and Common Antioxidant Types

Animals respond to oxidative stress mainly through endogenous antioxidant enzyme systems and non-enzyme systems. Antioxidant enzymes include superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase (CAT), and phase II detoxification enzymes. Research shows that the antioxidant enzyme system can dismutate superoxide anion (·O2-) into hydrogen peroxide (H2O2), eliminating the toxic effects of ·O2- and ultimately generating harmless alcohols and water. The non-enzyme system, also called exogenous antioxidants, includes vitamins (vitamins A, C, and E), trace elements (selenium, zinc), ethoxyquin (EMQ), butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), and phytogenic antioxidants. These antioxidant additives can directly or indirectly scavenge free radicals to achieve antioxidant stress effects, providing electrons to reduce free radicals.

Under oxidative stress conditions, besides ensuring adequate supply of substances required for normal synthesis of antioxidant enzymes and antioxidants (essential amino acids, metal ions, and ATP), exogenous supplementation of bioactive substances or antioxidants that intervene in antioxidant enzyme synthesis pathways or mediate oxidative stress damage to tissues and organs are effective approaches to alleviate oxidative stress. However, due to environmental changes, feed factors, and diseases, relying solely on animals' own resistance cannot completely solve oxidative stress problems. With deepening research, understanding of the causes, hazards, and mechanisms of oxidative stress in livestock production is increasing, and studies on prevention, repair, and treatment methods are gradually expanding. Adding antioxidant additives to feed is considered the most widely used method to prevent animal oxidative stress, improving animal production performance by reducing oxidative stress from various causes.

3. Application and Mechanisms of Phytogenic Antioxidants

Phytogenic antioxidants are the main natural antioxidants that have attracted extensive research attention due to their wide availability, efficient antioxidant performance, and low toxicity. Currently, they mainly come from herbs, spices, and fruits and vegetables, and can be classified by molecular structure into polyphenols, polysaccharides, alkaloids, and saponins. Research suggests that phytogenic antioxidants work through several mechanisms: (1) directly binding to free radicals by providing protons and electrons to scavenge or inhibit them; (2) regulating related pathways to inhibit free radical-related oxidase activity or promote antioxidant enzyme activity to alleviate oxidative damage; (3) chelating metal ions required for free radical generation to block their production; and (4) synergistic enhancement of antioxidant capacity among antioxidant components.

The Kelch-like ECH-associated protein 1-nuclear factor E2-related factor 2-antioxidant response element (Keap1-Nrf2-ARE) pathway is a recently well-studied antioxidant pathway. Nrf2 is an important antioxidant stress-regulating transcription factor that normally binds to cytoplasmic protein partner Keap1 for antioxidant regulation, while ARE is a cis-acting element encoding phase II detoxification enzyme and antioxidant enzyme genes. Keap1-Nrf2-ARE is a defense signal transduction pathway that responds to ROS-induced oxidative stress in animals, regulating the expression of phase II detoxification enzyme genes in the nucleus to enhance antioxidant capacity.

3.1 Polyphenols Most plant polyphenolic compounds have antioxidant effects that reduce oxidative stress damage in animals by scavenging free radicals and improving immune function. Common plant polyphenols are mostly phenol-based with polyhydroxy substitution on benzene rings, and can be divided into monomers (flavonoids, chlorogenic acid, gallic acid, ellagic acid, etc.) and polymers (proanthocyanidins, gallotannins, ellagitannins) based on polymerization degree. Resveratrol, the main polyphenol in grape skin, has antioxidant effects, protects blood vessels by activating SIRT1, and significantly inhibits proliferation of Hepalc1c7 cancer cells. Data show that adding 500 mg/kg plant polyphenols to yellow-feathered broiler diets enhances CAT, SOD, and GSH-Px activities while reducing meat water loss and drip loss, improving meat quality.

Polyphenols function as hydrogen proton or electron donors that scavenge free radicals and terminate chain reactions. Flavonoids interrupt chain reactions by reacting with free radicals through phenolic hydroxyl groups to form semiquinone radicals. Additionally, polyphenols can promote Keap1 protein degradation, facilitate Nrf2 nuclear translocation, enhance ARE binding capacity, activate the Keap1-Nrf2-ARE signaling pathway, and regulate downstream antioxidant enzyme expression (Figure 1 [Figure 1: see original paper]). Curcumin, an acidic polyphenol, inhibits nitric oxide synthase activity during ischemia-reperfusion injury to exert antioxidant effects. Ferrous ions (Fe2+) can cause kidney cell damage and affect antioxidant enzyme activity, while quercetin, a polyphenol, can restore antioxidant enzyme activity in animals.

3.2 Polysaccharides Plant polysaccharides are functional polysaccharides connected by α-1,4, α-1,6, β-1,3, and β-1,4 glycosidic bonds that enhance cellular immunity, provide antibacterial and antiviral effects, and have antioxidant and anti-aging functions. *Acanthopanax senticosus* polysaccharides can scavenge ·O2- and the organic radical 1,1-diphenyl-2-picrylhydrazyl (DPPH), and improve antioxidant capacity by upregulating Nrf2 gene expression and increasing secretion of antioxidant enzymes such as SOD, CAT, and GSH-Px. Esterified polysaccharides extracted from red algae can scavenge hydroxyl radicals and H2O2, reducing oxidative stress damage. *Ganoderma* polysaccharides can scavenge accumulated DPPH and hydroxyl radicals and chelate Fe2+ for antioxidant purposes. Adding apple pectin oligosaccharides to rat diets can scavenge excess free radicals, reduce lipid peroxide production, and improve antioxidant capacity.

The antioxidant mechanisms of plant polysaccharides include: (1) reacting with OH·and ·O2- to scavenge ROS; (2) indirectly increasing activities of antioxidant enzymes such as SOD, CAT, and GSH-Px; (3) chelating metal ions such as Fe2+ and copper ions (Cu2+) required for ROS generation through alcohol hydroxyl groups in polysaccharide molecules; and (4) promoting SOD release from cell surfaces to scavenge ROS.

3.3 Saponins Saponins are complex compounds composed of sapogenins, sugar groups, and organic acids, differing in sugar group position, number, and connection mode, including triterpenoid saponins and steroid saponins. Saponins can improve immune function, regulate lipid metabolism, and provide antioxidant, antibacterial, antiviral, and anti-inflammatory effects.

The antioxidant mechanism of saponins involves increasing activities of antioxidant enzymes such as SOD and CAT, inhibiting oxidase activity, and enhancing antioxidant capacity, though saponins have minimal direct effect on free radicals. Studies show that treating induced diabetic rat models with *Gynostemma pentaphyllum* saponins reduces renal tissue xanthine oxidase and myeloperoxidase activities while increasing SOD activity and enhancing the antioxidant system.

3.4 Alkaloids Alkaloids are complex organic compounds containing nitrogen ring structures with significant antioxidant activity, mainly found in dicotyledonous plants such as Solanaceae, Leguminosae, Papaveraceae, and Rutaceae, though research and application in animal production remain limited.

The antioxidant mechanism of alkaloids mainly involves scavenging free radicals by binding oxygen free radicals with exposed nitrogen atoms in heterocycles to improve antioxidant capacity. Electron-donating groups or factors that enrich nitrogen atoms can enhance alkaloid antioxidant activity. Additionally, studies have found that sinapine in humans can inhibit lipase and lipoxygenase activity, thereby reducing lipid peroxidation.

4. Other Antioxidant Substances and Their Mechanisms

Besides commonly used phytogenic antioxidants, certain vitamins and trace elements are frequently applied as antioxidants in production practice. Vitamins C and E have strong antioxidant capacity and can directly bind to oxygen free radicals in the body by serving as proton and electron donors. Vitamin C scavenges free radicals by sequentially providing electrons to become semi-dehydroascorbic acid and dehydroascorbic acid, while vitamin E can bind to cell membranes to protect cells from free radical damage and increase antioxidant enzyme activity. Additionally, vitamins C and E have synergistic effects with other antioxidants. Studies report that adding 13.59–23.59 mg/kg vitamin E can improve antioxidant capacity in mice. Injecting 15 mg vitamin C in 21-day-old broilers significantly increases plasma total antioxidant capacity, and at this level, 42-day-old broilers show significantly higher plasma SOD and GSH-Px than other groups. Adding 200 IU/kg vitamin E to broiler diets can improve antioxidant capacity and significantly increase feed conversion efficiency and body weight gain.

Trace elements such as selenium and zinc are also frequently added to animal diets to alleviate oxidative stress damage. Studies show that adding 0.5–0.7 mg selenium to diets can improve antioxidant capacity in Taihe silky fowls to alleviate heat stress effects on production performance and melanin synthesis. Trace elements can directly scavenge free radicals and increase antioxidant enzyme activity. Additionally, selenium' s antioxidant effects can be achieved through glutathione peroxidase, and selenium has synergistic effects with vitamin E.

5. Other Biological Effects and Mechanisms of Antioxidants

Certain substances with significant antioxidant effects can also promote secretion of immune factors and improve immune function. Resveratrol can both improve antioxidant capacity and has anti-inflammatory properties that alleviate inflammatory responses. Willow bark extract can increase antioxidant enzyme activity, activate the Nrf2 pathway to reduce oxidative stress damage, inhibit tumor necrosis factor-α and cyclooxygenase-2 expression, reduce NO release, and improve immunity.

Studies show that inflammatory responses can cause free radical accumulation and oxidative stress in animals. Terra et al. found that in macrophages treated with endotoxin lipopolysaccharide, proanthocyanidin B2 can block P65 subunit translocation into the nucleus and reduce cyclooxygenase-2 expression by activating the NF- B signaling pathway (Figure 1).

Figure 1. Signaling pathways of regulating the expression of related enzymes by phytogenic antioxidants [31, 55]

Legend: Extracellular; Cytoplasm; Nucleus; RV: resveratrol; Procyanidins; TLRs: Toll like receptors; Nrf2: nuclear factor E2-related factor 2; Keap1: Kelch-like epichlorohydrin associated protein 1; ROS: reactive oxygen species; ASK-1: apoptosis signaling kinase-1; MEK: mitogen-activated extracellular signal-regulated kinase; MKK: mitogen-activated protein kinase kinase; MAPK: mitogen-activated protein kinase; JNK: c-Jun N-terminal kinase; ERK: extracellular signal-regulated kinase; MyD88: myeloid differentiation factor 88; IRAK1: interleukin-1 receptor associated kinase; TRAF6: tumor necrosis factor receptor-associated factor 6; IKKs: inhibitor of nuclear factor kappa-B kinases; I Bα: inhibitor of nuclear factor kappa-B α; NF- B: nuclear factor kappa-B; Gene Regulation; Phase II detoxification enzymes and GSH-Px; GSH-Px: glutathione peroxidase; CAT: catalase; SOD: superoxide dismutase; COX-2: cyclooxygenase-2.

Due to their green, safe, and efficient characteristics, phytogenic antioxidants have gained widespread recognition, and research on their effects is increasing. However, several issues remain in phytogenic antioxidant research. First, extraction and purification processes need improvement, and applying these processes to various plant extracts in production practice requires substantial work. Second, research on appropriate dosages for different livestock species and growth stages is insufficient, and dosage standards for production applications remain uncertain, requiring more in-depth studies to determine optimal amounts for different animals. Third, besides antioxidant effects, phytogenic antioxidants also affect the immune system, inflammatory responses, and apoptosis, involving internal signaling pathways and multiple biological processes with extremely complex signal transduction that requires further exploration of the relationship between antioxidant mechanisms and other biological effects.

China has abundant plant resources and a long history of developing and utilizing biologically active phytogenic substances. With increasing research in this field, extraction and purification processes for phytogenic antioxidants will gradually improve, and pathway mechanisms will become clearer. Applying phytogenic antioxidants in animal production is important for improving livestock production and reproductive performance, ensuring animal product safety, improving product quality, and promoting the development of a sustainable, safe, and efficient modern animal husbandry industry.

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