DOI 10.24425/pjvs.2026.158513

Review paper

Advances in the application of natural bioactive compounds for the prevention and control of porcine epidemic diarrhea virus via the oxidative stress pathway

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Abstract

The porcine epidemic diarrhea virus (PEDV) represents a critical challenge to the global swine industry due to its profound adverse effects on pig health and production efficiency. A key pathological outcome of PEDV infection is the induction of oxidative stress, which significantly exacerbates intestinal injury and accelerates disease progression. Natural bioactive compounds, sourced from plants, animals, and microorganisms, have been extensively studied for their diverse biological properties, including potent antioxidant, anti-inflammatory, and antiviral activities. These compounds demonstrate significant potential in alleviating oxidative stress and playing a pivotal role in the prevention and management of PEDV infections. This review provides a comprehensive analysis of the mechanisms by which natural bioactive compounds enhance the antioxidant defence system and suppress PEDV replication. Current evidence indicates that these compounds alleviate oxidative stress primarily through the modulation of antioxidant enzyme systems, such as superoxide dismutase (SOD) and glutathione peroxidase (GPx), and the activation of key signalling pathways, including the Nrf2/ARE axis. These actions collectively contribute to reduced viral loads and improved health outcomes in PEDV-infected pigs. Although these findings underscore the potential of natural bioactive compounds, several critical challenges persist, particularly the incomplete elucidation of their mechanisms of action and the substantial costs associated with large-scale applications. Addressing these challenges necessitates further research aimed at uncovering the precise molecular pathways underlying their effects and developing cost-effective strategies to facilitate their practical implementation in the swine industry.

Keywords: porcine epidemic diarrhea virus, natural bioactive compounds, oxidative stress

Introduction

Porcine epidemic diarrhea (PED) is an intestinal infectious disease caused by porcine epidemic diarrhea virus (PEDV) (Zou et al. 2025). Since its first report in Europe in the 1970s, PED has spread rapidly worldwide, especially after 2010, when the emergence of variant strains has made the epidemic more severe (Li et al. 2025). Epidemics frequently break out in major pig-raising regions such as Asia and North America, leading to a large number of piglet deaths and posing enormous challenges to the sustainable development and economic benefits of the pig farming industry (Zhang et al. 2023). The main clinical manifestations of PEDV infection include acute enteritis, vomiting, watery diarrhea, and dehydration (Liu et al. 2025). Neonatal piglets are highly susceptible to PEDV, with mortality rates after infection reaching up to 80%-100%, which severely affects the survival rate of piglets and production efficiency in pig farms (Koonpaew et al. 2019). PEDV infection triggers the body's immune response while leading to the massive production of reactive oxygen species (ROS) (Sun et al. 2025a). Under normal conditions, the body maintains the balance between ROS production and elimination through the antioxidant defence system. However, during PEDV infection, this balance is disrupted. Excessive ROS triggers oxidative stress, damaging intracellular biological macromolecules such as lipids, proteins, and DNA. This leads to pathological changes, including altered cell membrane fluidity and permeability, loss of protein function, and gene mutations (Zhou et al. 2023). For instance, ROS induces lipid peroxidation, affecting the normal functions of cell membranes. Meanwhile, its oxidative modification of proteins reduces enzyme activity and disrupts cellular metabolic processes (Zeng et al. 2022). In infected piglets, oxidative stress further causes intestinal damage, disrupts the function of the intestinal mucosal barrier, facilitates viral invasion, impairs nutrient absorption, and hinders the normal growth and development of piglets (Sun et al. 2021a). At present, the main prevention and control measures for PEDV infection include vaccination and biosecurity management (Wei et al. 2024). However, due to the high mutability of PEDV, the protective efficacy of existing vaccines is limited, making it difficult to cope with the continuously emerging variant strains. Meanwhile, biosecurity measures have certain limitations in practical operation. Therefore, the development of new prevention and control strategies has become an urgent issue to be addressed (Liang et al. 2024). In recent years, natural bioactive compounds have received extensive attention in the field of animal nutrition and health due to their advantages of wide sources, high safety, and low side effects (Fonseca et al. 2025). These compounds possess multiple biological activities such as antioxidant, anti-inflammatory, and antibacterial properties, enhancing animal immunity and disease resistance by regulating physiological functions of the body (Duan et al. 2022). For example, polyphenols and flavonoids rich in plant extracts can scavenge excessive ROS in the body, reducing the damage caused by oxidative stress to the body (Song et al. 2011). Meanwhile, these components can also regulate the activity of immune cells and enhance immune responses, thereby improving animals' resistance to pathogens. The application of natural bioactive compounds in pig farming is expected to alleviate oxidative stress induced by PEDV infection, improve pig health, enhance their antiviral ability, and provide new ideas for the prevention and control of PEDV (Tong et al. 2020). Based on this, this study aims to systematically explore the action mechanisms and application effects of natural bioactive compounds in addressing PEDV infection. Through in-depth research on the performance of these compounds in regulating oxidative stress and improving the body's immune function, it provides theoretical support for the development of safe and effective PED prevention and control strategies, and contributes to the green and healthy development of the pig farming industry.

Overview of PEDV and oxidative stress virus morphology and genomic characteristics

PEDV is a virus belonging to the order *Nidovirales*, family *Coronaviridae*, and genus *Coronavirus* (Wang et al. 2016). Under the electron microscope, the viral particles are slightly spherical with a diameter of approximately 130 nm, but they often exhibit pleomorphism in feces (Lin et al. 2016). PEDV particles are enveloped, with petal-shaped spikes distributed on the surface of the envelope. The spikes are 12-24 nm in length, regularly arranged, and exhibit a typical crown morphology (Li et al. 2025). PEDV has a linear single-stranded positive-sense RNA genome, which is infectious. The full-length genome is approximately 28 kb and contains seven open reading frames (ORFs) (Guo et al. 2019), encoding replicase polyproteins (pp1ab and pp1a), spike protein (S), ORF3 protein, envelope protein (E), membrane glycoprotein (M), and nucleocapsid protein (N), respectively (Fig 1) (Zhuang et al. 2025). These genes collectively participate in the processes of viral replication, assembly, and host cell infection (Li et al. 2024).

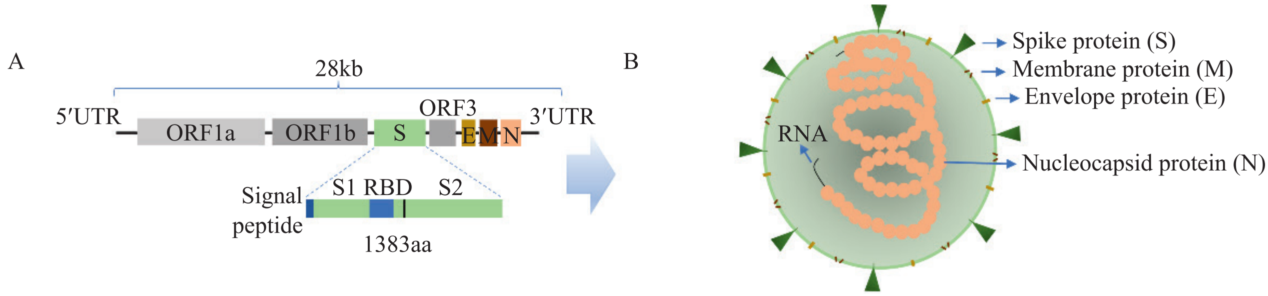

Fig 1. Schematic diagram of the porcine epidemic diarrhea virus (PEDV) genome and virion.

Oxidative stress induced by PEDV infection

ROS are a class of oxygen metabolites with high chemical reactivity, mainly including superoxide anion, hydrogen peroxide, and hydroxyl radical (Shen et al. 2025). Under normal physiological conditions, intracellular redox reactions maintain a dynamic balance, with the production and scavenging of ROS in a steady state, playing important roles in processes such as cell signalling and immune defence (Yuan et al. 2025). However, factors such as infection, inflammation, environmental stress, or drugs can significantly increase ROS production, exceeding the scavenging capacity of the antioxidant defence system, thus triggering oxidative stress (Wang et al. 2025). ROS are mainly derived from multiple metabolic pathways within cells, with mitochondria being the most important site of production (Narayanan 2025). During aerobic respiration in the electron transport chain, some electrons leak from the respiratory chain and directly react with oxygen to generate superoxide anion (Zambrano et al. 2025). Additionally, the NADPH oxidase (NOX) family, located on the cell membrane, can catalyze the oxidation of NADPH under stimulatory conditions, transferring electrons to oxygen to generate O_2^-, which is also an important mechanism for ROS production (Xu et al. 2025). When ROS levels increase, they cause significant damage to biological macromolecules within cells (Sharma and Ismail 2025). First, lipids, as important components of cell membranes, are vulnerable to ROS attack, leading to lipid peroxidation (Soni et al. 2025). Oxidation of unsaturated fatty acids produces lipid peroxides, which in turn reduce membrane fluidity and increase membrane permeability (Méndez-García et al. 2025). This not only affects material transport and signal transduction but also generates cytotoxic substances that further damage cells (Mukhopadhyay and Weiner 2007). Second, ROS-induced oxidative modification of proteins alters their structure and function, leading to loss of biological activity or misfolding (Yigit and Chien 2025). Finally, ROS attack on DNA molecules can cause damage such as base oxidation and DNA strand breaks, thereby interfering with genomic stability and affecting normal cellular functions (Mo et al. 2025).

When PEDV invades pigs, the virus primarily infects small intestinal epithelial cells and replicates abundantly within them, triggering the host's immune response (Xie et al. 2025). During viral phagocytosis, immune cells release a large amount of ROS through respiratory burst to kill the virus (Wang et al. 2019). However, excessive immune responses often lead to uncontrolled ROS production, inducing oxidative stress. Meanwhile, PEDV infection directly disrupts intracellular redox balance and significantly inhibits the activity of antioxidant enzymes (Wang et al. 2024), which are crucial for maintaining cellular antioxidant defence. By reducing the activity of these enzymes, PEDV infection impairs the cell's ability to scavenge ROS, further exacerbating oxidative stress (Liu et al. 2022). Oxidative stress not only aggravates damage to small intestinal epithelial cells but also exerts critical effects on disease progression and pathological changes. First, excessive ROS damages the membranes and organelles of small intestinal epithelial cells, leading to impaired cellular functions. This further disrupts intestinal digestion and absorption, exacerbating symptoms such as diarrhea and dehydration (Aviello and Knaus 2017). Second, ROS activate inflammation-related signalling pathways, promoting the expression and release of proinflammatory cytokines (e.g., TNF-α and IL-1β), thereby intensifying intestinal inflammatory responses (Bao et al. 2024). Inflammation-induced mucosal barrier dysfunction facilitates viral invasion, forming a vicious cycle that significantly affects pig health and growth (Liu 2015). Notably, ROS can both kill the virus via immune cells and exacerbate lesions through excessive production, highlighting the complexity of oxidative stress in PEDV infection (Dickson and Zhou 2020).

Types and sources of natural bioactive compounds from plant sources

Plants serve as a vital source of natural bioactive compounds, harbouring abundant active components (Huang et al. 2025). These components not only play crucial roles in plant growth, development, and response to environmental stresses but also provide valuable resources for animal nutrition and health (Yuan et al. 2024). Flavonoids, as important polyphenolic compounds in plant secondary metabolites, are widely distributed in plants such as fruits, vegetables, cereals, tea, and Chinese herbal medicines (Huang et al. 2025). Their basic structure consists of two benzene rings (ring A and ring B) connected by a central three-carbon chain to form a C6-C3-C6 skeleton. Depending on the oxidation degree and linkage pattern of the three-carbon chain, they can be further classified into flavones, flavonols, flavanones, isoflavones, anthocyanins, etc. (Lu et al. 2024, Farooq and Ngaini 2025). Flavonoids exhibit remarkable antioxidant activities. They can directly scavenge free radicals, as phenolic hydroxyl groups donate hydrogen atoms to combine with free radicals, converting them into stable substances and terminating chain reactions (Shen et al. 2022). Additionally, they can chelate metal ions, forming complexes with iron or copper ions to reduce metal-catalyzed free radical generation (Zhang et al. 2023). Flavonoids also upregulate antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), enhancing intracellular defence capabilities (Yang et al. 2023).

Polyphenolic compounds represent another class of plant secondary metabolites, including phenolic acids, lignans, tannins, etc. (Dai and Mumper 2010). Phenolic acids can be further divided into hydroxybenzoic acids (such as gallic acid, protocatechuic acid) and hydroxycinnamic acids (such as caffeic acid, ferulic acid) (Cione et al. 2019). Lignans are commonly found in seeds, fruits, and tree barks (Suleria et al. 2020), while tannins mainly exist in plant leaves, barks, and fruits (Xia et al. 2023). The antioxidant mechanisms of phenolic compounds are similar to those of flavonoids, primarily involving the scavenging of free radicals by phenolic hydroxyl groups donating hydrogen atoms, enhancing antioxidant enzyme activity by upregulating antioxidant enzyme gene expression, and indirectly alleviating oxidative stress damage by inhibiting the release of inflammatory factors (Kwaśny et al. 2025).

Alkaloids are a class of nitrogen – containing natural organic compounds widely present in medicinal plants (Liu et al. 2025). They have diverse structures, and common types include pyridine, quinoline, isoquinoline, and indole (Rosales et al. 2020). Alkaloids exhibit antioxidant effects, capable of scavenging hydroxyl radicals and DPPH radicals, inhibiting lipid peroxidation, and protecting cells from oxidative damage (Macáková et al. 2019). Their antioxidant mechanism may be related to the conjugate system and nitrogen atoms in the molecular structure (Li et al. 2025). In addition, some alkaloids indirectly improve the cellular redox status by regulating signalling pathways (Wibowo et al. 2021). However, it should be noted that some alkaloids are toxic, and the dosage must be strictly controlled to ensure safety during application (Akinboye et al. 2023).

Bioactive compounds from animal sources

Animal-derived bioactive compounds possess unique structures and functions, demonstrating significant application value in the field of animal nutrition. They are primarily derived from animal tissues, secretions, and metabolites, and are extracted through specific technologies to improve animal health and production performance (Šimat et al. 2022). Chitosan, a linear polysaccharide produced by deacetylation of chitin, is mainly derived from crustaceans such as shrimp and crabs. Due to its excellent biocompatibility and adsorbability, chitosan is widely used as a drug delivery system (Varshosaz 2007). In animal nutrition, chitosan plays an important role by prolonging hydration time, reducing mildew, and decreasing water pollution. It can protect DNA vaccines and enhance the durability of immune responses (Senel and McClure 2004). Adding chitosan to the diet of weaned piglets can increase daily weight gain and feed conversion rate while reducing diarrhea rates. It also lowers serum cholesterol and triglyceride levels, contributing to the prevention of cardiovascular diseases (Xu et al. 2018).

Active peptides are small-molecule peptides produced by protein hydrolysis, which can be classified into milk-derived, soybean-derived, and marine-derived active peptides according to their sources (Zaky et al. 2021). They have various biological activities such as antioxidant, antibacterial, and immunomodulatory activities (Hajfathalian et al. 2018). In animal nutrition, active peptides can improve feed utilization, balance intestinal flora, and alleviate oxidative stress by scavenging free radicals (Bechaux et al. 2019).

Mechanisms of natural bioactive compounds in enhancing antioxidant defence in pigs regulation of the antioxidant enzyme system

The antioxidant enzyme system serves as a key defence line against oxidative stress in pigs, primarily relying on oxidoreductases, including SOD, catalase (CAT), and GSH-Px (Tang et al. 2024). Natural bioactive compounds can effectively enhance the antioxidant capacity of pigs by boosting the activity of these enzymes (Wan et al. 2024). SOD is responsible for scavenging superoxide anion radicals by catalyzing their disproportionation into hydrogen peroxide and oxygen, maintaining intracellular redox balance (Wang et al. 2018). Studies have shown that quercetin can interact with specific amino acid residues of SOD to stabilize its active center, thereby improving catalytic efficiency (Ghasemi et al. 2025). CAT degrades hydrogen peroxide into water and oxygen, preventing its conversion to the more toxic hydroxyl radical (Gebicka and Krych-Madej 2019). For instance, microbial-derived polysaccharides such as yeast extract significantly enhance CAT activity in pigs, reduce hydrogen peroxide content in intestinal tissues, and alleviate oxidative stress-induced damage to intestinal mucosa (Li et al. 2024). Additionally, carvacrol and thymol in oregano essential oil activate CAT by regulating cellular redox status, significantly increasing CAT activity in the liver and serum to enhance the antioxidant capacity of pigs (Hall et al. 2021). GSH-Px plays an equally important role in scavenging lipid hydroperoxides and hydrogen peroxide, with its activity dependent on reduced glutathione (GSH) (Forman et al. 2009). The specific amino acid sequences of marine bioactive peptides can interact with GSH-Px molecules to enhance their activity and reduce lipid peroxidation (Jia et al. 2024). Furthermore, astragalus polysaccharides promote selenium metabolism, thereby indirectly increasing GSH-Px activity and enhancing the body's antioxidant capacity (Rao et al. 2022).

Scavenging of free radicals

Natural bioactive compounds directly scavenge free radicals, significantly reducing the accumulation of ROS, thereby alleviating oxidative stress-induced damage to the porcine body (Tang et al. 2024). Among them, flavonoids exhibit excellent free radical scavenging capacity due to the phenolic hydroxyl groups in their molecular structure (Vo et al. 2019). As a typical representative, quercetin's phenolic hydroxyl groups can donate hydrogen atoms, undergoing conversion reactions with superoxide anion radicals to H_2O_2, while forming stable radical intermediates themselves (Podder et al. 2023). In vitro experiments have confirmed the excellent antioxidant properties of quercetin through its scavenging capacity against O_2^- (Chen et al. 2016). In addition to the significant scavenging effect on O_2^-, flavonoids also demonstrate remarkable scavenging effects on hydroxyl radicals (Treml and Šmejkal 2016). For example, rutin effectively protects the integrity of cell membranes by inhibiting ·OH-induced lipid peroxidation. This action not only reduces ROS-induced oxidative damage to lipids but also further enhances the cell's antioxidant defence capacity (Zhou et al. 2016).

Activation of antioxidant signalling pathways

Activating antioxidant signaling pathways represents a crucial mechanism by which natural bioactive compounds enhance antioxidant defense in pigs. The Nrf2-ARE signaling pathway serves as the core pathway regulating cellular redox homeostasis (Tang et al. 2024). Under normal conditions, nuclear factor E2-related factor 2 (Nrf2) binds to Kelch-like ECH-associated protein 1 (Keap1) and remains in an inhibited state. When cells are exposed to oxidative stress, structural changes in Keap1 lead to the release of Nrf2, which then translocates to the nucleus to activate the expression of antioxidant genes (Matsumaru and Motohashi 2021). For instance, quercetin interacts with the thiol groups of Keap1, altering its conformation and promoting the release and nuclear translocation of Nrf2 (Luo et al. 2022). Epigallocatechin-3-gallate (EGCG) in tea polyphenols activates upstream molecules such as protein kinase C (PKC), indirectly promoting the activation of the Nrf2-ARE pathway (Zhang et al. 2021). Upon entering the nucleus, Nrf2 binds to antioxidant response elements (ARE) to initiate the transcription of antioxidant genes, such as heme oxygenase-1 (HO-1), NAD(P)H quinone dehydrogenase 1 (NQO1), and glutathione synthetase. HO-1 catalyzes the decomposition of heme to produce biliverdin and bilirubin, which exhibit antioxidant properties (Vomhof-Dekrey and Picklo 2012). NQO1 reduces free radical generation from quinoid compounds (Ross and Siegel 2021), while glutathione synthetase promotes the GSH, enhancing cellular antioxidant capacity (Yu et al. 2024). Additionally, natural bioactive compounds can activate the PI3K/Akt signaling pathway. For example, sea cucumber collagen peptides alleviate oxidative damage through the PI3K/AKT/Nrf2 pathway, reducing ROS levels and mitigating oxidative stress-induced cellular damage (Fig. 2) (Gao et al. 2025).

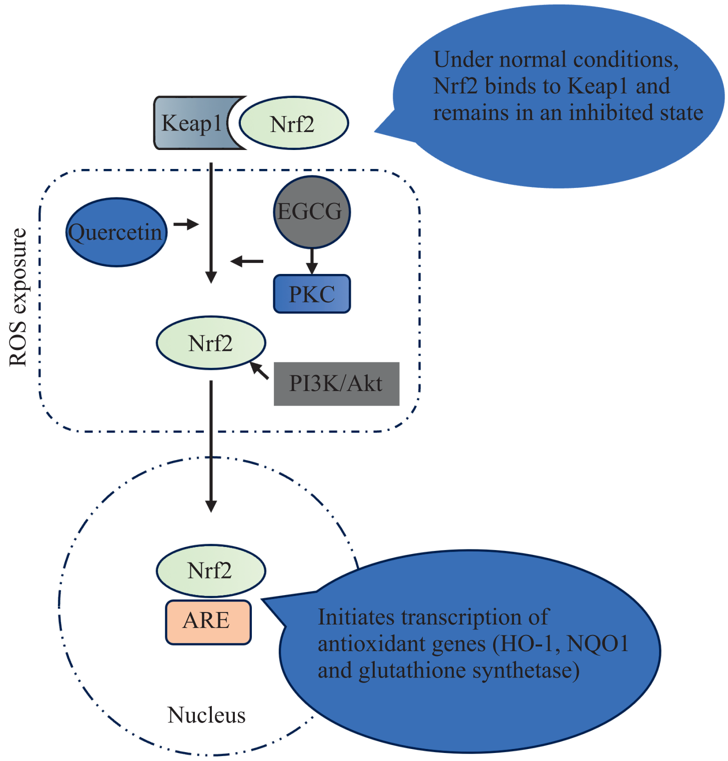

Fig 2. Schematic diagram of antioxidant signaling pathway activation.
EGCG – epigallocatechin-3-gallate; PKC – protein kinase C; ARE – antioxidant response elements.

Effects of natural bioactive compounds on resistance to PEDV infection

Studies have shown that various natural bioactive compounds can significantly inhibit PEDV infection and exert antiviral effects through multiple unique mechanisms. The antiviral mechanisms of some compounds are closely related to the regulation of reactive oxygen species (ROS) generation and endoplasmic reticulum (ER) stress (Zou et al. 2024). For instance, natural products such as Levistolide A (LA) (Zeng et al. 2022), docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) (Suo et al. 2023), and the alkaloid 1-deoxynojirimycin (DNJ) (Sun et al. 2025b) have all demonstrated the ability to alleviate PEDV-induced ER stress and ROS production. These compounds effectively reduce viral replication and inflammatory responses by enhancing the antioxidant capacity of host cells. However, the related mechanisms are not yet fully understood, and the specific regulatory processes still require further exploration (Zhou et al. 2023). The aqueous leaf extract of *Camellia oleifera* (MOE) exhibits significant antiviral activity during PEDV infection. Studies have shown that MOE exerts its effects through multiple mechanisms, including significant inhibition of reactive oxygen species (ROS) and malondialdehyde (MDA) production, restoration of glutathione peroxidase (GSH-Px) activity, and alleviation of oxidative stress and inflammatory cytokine expression. These combined effects reduce cell apoptosis during infection (Cao et al. 2022). The antiviral properties of MOE provide an important research basis for its development as a natural antiviral agent. PEDV infection-induced ROS generation is associated with the activation of multiple key signalling pathways. Among them, activation of p53 is closely linked to elevated ROS levels and plays a critical role in virus-induced cell apoptosis (Xu et al. 2019). Yi Liu et al. demonstrated that ergosterol peroxide (EP) extracted from the fruiting bodies of the mushroom *Cryptoporus volvatus* exhibits significant antiviral activity in vitro. EP not only directly inactivates PEDV but also significantly inhibits virus-induced cell apoptosis by interfering with virus-induced ROS generation and p53 activation (Liu et al. 2022). These findings reveal the potential of EP as an antiviral agent and highlight its important role in regulating ROS and p53 signalling pathways. PEDV infection not only induces ROS production but also triggers endoplasmic reticulum (ER) stress responses through the activation of PERK and IRE1 pathways. Studies have shown that the PERK pathway promotes cellular autophagic responses by regulating the phosphorylation level of eIF2α, while the IRE1 pathway further enhances this process by regulating the unfolded protein response (UPR) (Sun et al. 2021b). These mechanisms collectively induce autophagy through ROS-dependent ER stress, thereby inhibiting viral replication to a certain extent. Studies have shown that the early stage of PEDV infection triggers a DNA damage response (DDR) by activating the ATM-Chk2 signalling pathway. Further research has revealed that PEDV-induced H2AX phosphorylation does not directly depend on ATM-Chk2, but is achieved through the activation of caspase-7 and caspase-activated DNase (CAD) (Ming et al. 2022). These results suggest that during the initial infection, the host promotes DDR generation via activation of the ROS-ATM and caspase7-CAD-γH2AX signalling pathways, providing conditions for early viral replication. However, as the host's antiviral strategies are gradually activated, viral replication is further inhibited. Chen Yuan *et al.* found that salinomycin significantly inhibits PEDV replication in Vero cells in a dose-dependent manner. The compound suppresses virus-related processes by interfering with the activation of Erk1/2, JNK, and p38 MAPK signalling pathways. Additionally, salinomycin does not directly interact with or inactivate viral particles but induces ROS production through an independent pathway to exert antiviral effects, revealing its potential application value in signalling pathway regulation (Yuan et al. 2021).

Some key issues to be addressed currently

In summary, natural bioactive compounds have demonstrated significant potential in regulating oxidative stress and preventing PEDV infection, but their research still faces several challenges. First, the binding patterns of activated signalling pathways with upstream/downstream regulatory factors or key proteins lack in-depth analysis (Zhu et al. 2023). Additionally, the PEDV infection process involves multiple stages, including viral adsorption, entry, replication, and release, but the specific mechanisms of action of compounds at each stage remain unclear (Zou et al. 2025). On the other hand, although natural bioactive compounds may exhibit synergistic or antagonistic effects, related research is still in its infancy. This limitation not only hinders the development of composite formulations but also poses new challenges for the optimized configuration of multi-component natural products (Li et al. 2024).

The low bioavailability of natural bioactive compounds is a major obstacle to their application in PEDV control. Orally administered compounds are susceptible to degradation by gastric acid and digestive enzymes, making it difficult for active ingredients to enter the bloodstream in their intact active form. Furthermore, the physicochemical properties of compounds often limit their transmembrane absorption, hindering their passage through intestinal epithelial cells. Even if a small amount of the compound is successfully absorbed into the bloodstream, it may be largely decomposed by the first-pass metabolism in the liver, significantly reducing the effective concentration at the infection site (Zhang et al. 2024). In recent years, novel delivery systems such as nanotechnology have shown potential in improving solubility and stability, but their high cost and limited large-scale production capacity make them difficult to meet the practical needs of the aquaculture industry. Many highly effective bioactive compounds are mainly derived from rare plants or marine organisms, making it difficult to meet the needs of industrial production and widespread application (Suo et al. 2023).

Conclusion

Natural bioactive compounds show great potential in preventing porcine epidemic diarrhea virus (PEDV) infection and improving pig farming health through oxidative stress pathways. However, current research faces challenges, including unclear action mechanisms, poor bioavailability of natural bioactive compounds, and high production/application costs, which urgently require interdisciplinary collaborative research for solutions.

Acknowledgements

This research was funded by "Three Gorges Talent" Modern Animal Husbandry Faculty Innovation Team, Chongqing Three Gorges Vocational College, grant number sxyc202410. This work was supported by scientific research project of chongqing municipal education commission, grant number KJQN202503510.

Author Declarations

Ethics approval

This article is a review, and ethical approval is not required.

Use of generative artificial intelligence

This manuscript was prepared without the use of AI tools.

Conflict of interest

The authors declare no conflicts of interest.

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