

REVIEW

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Houttuynia cordata Thunb. extract in pig production: a multifaceted alternative to antibiotics with antimicrobial, antioxidant, and health-promoting properties

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Abstract

This review explores the feasibility of *Houttuynia cordata* Thunberg extract as a viable substitute for antibiotics in swine husbandry, emphasizing its multifaceted activities against microbial infections, oxidative stress, and inflammatory responses. The extract improves intestinal health, boosts immune responses, and enhances reproductive performance in pigs, tackling key challenges such as antibiotic resistance and oxidative stress. Key bioactive compounds, including flavonoids (quercetin, hyperoside) and volatile oils (2-undecanone), exhibit dose-dependent efficacy against pathogens such as *Salmonella*, PRRSV, and *Staphylococcus aureus*. This work underscores the dual role of the extract in improving pig productivity and reducing reliance on conventional antibiotics, suggesting a paradigm shift in sustainable livestock management.

Keywords *Houttuynia cordata* Thunberg extract, Antimicrobial, Antioxidant, Anti-inflammatory, Immune regulation, Pig production

Graphical abstract

Houttuynia cordata extract exhibits core bioactivities, including antimicrobial, antioxidant, anti-inflammatory, and immunomodulatory through specific molecular mechanisms. These actions synergistically enhance disease resistance, reduce oxidative stress and inflammation, and promote immune balance, ultimately improving overall pig health, growth performance, and reproductive efficiency, which positions *Houttuynia cordata* extract as a natural, sustainable alternative to antibiotics in swine husbandry.

Handling editor: Zhixin Lei

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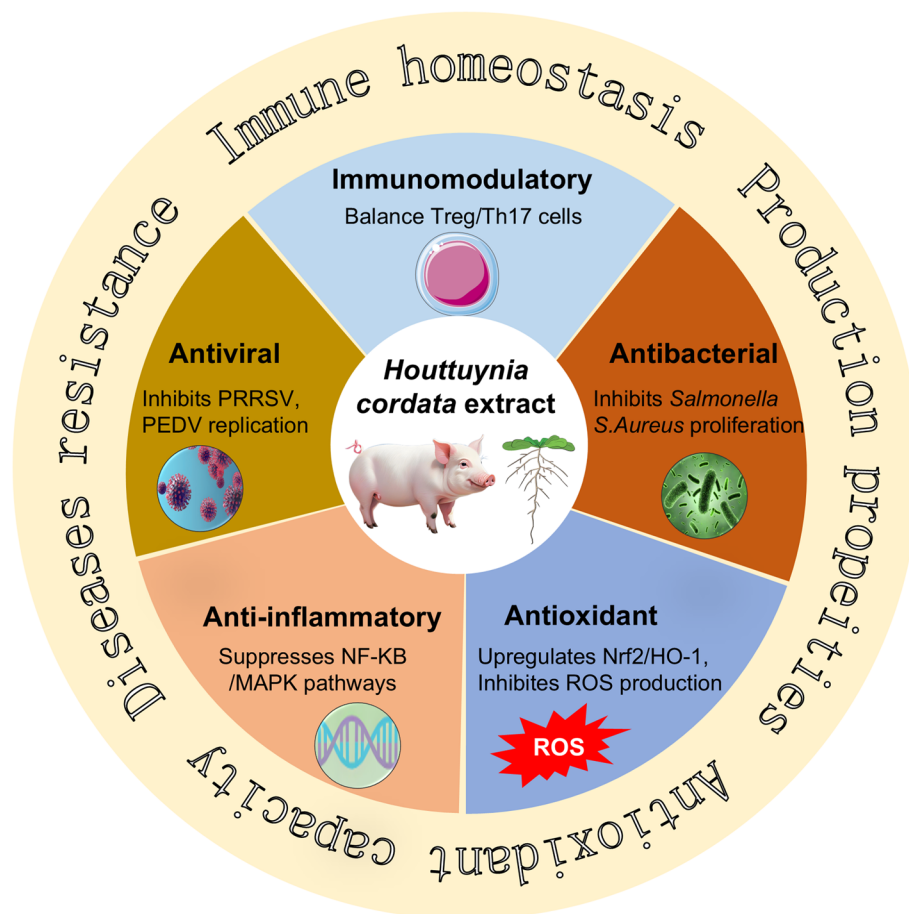
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Introduction

The excessive use of antimicrobials in animal nutrition promotes residue accumulation and resistance development in bacteria, critically endangering food safety and community health. Hence, plant extracts have emerged as promising alternatives (Li L et al. 2021; Seidavi et al. 2021). Unlike single-target antibiotics, *H. cordata* offers multitarget efficacy against pathogens while enhancing host immunity—a dual advantage documented in subsequent sections. However, the occurrence of major animal epidemics has led to a series of problems in pig production. The health and immunity of pigs, production efficiency, and economic benefits are also threatened by viruses, bacteria and parasites; insufficient feed; nutrition; stress; and mycotoxins. While antibiotics are vital in controlling infectious diseases, the threat of antibiotic resistance in treating both human and animal infections is substantial (Yirgu et al. 2023). If antibiotic resistance is allowed to continue unabated, it could kill an estimated 10 million people by 2050 and cost an estimated \$100 trillion

annually (Odongo et al. 2023). Furthermore, drug residues in milk can cause allergic reactions in consumers, disrupt the intestinal flora, and contribute to resistant bacteria (Arbab et al. 2022). Certain commercial anti-inflammatory medications cause adverse side effects. Therefore, the discovery of new drugs is increasingly urgent (Campos et al. 2023). Plant extracts offer promising solutions as antibiotic substitutes to overcome these harmful factors. Throughout millennia, botanicals have served as foundational reservoirs of therapeutics and remain integral to this practice (Yadav et al. 2011). With the ongoing advancement of research techniques, identifying natural product molecules with high safety for safeguarding pig intestines as veterinary drugs or feed additives is highly important. Thus, there is a critical demand to explore alternatives such as botanical agents, which are readily available and have reduced adverse effects, for the development of safe clinical drugs (Woranam et al. 2020).

A traditional medicinal plant belonging to the Saururaceae family, *Houttuynia cordata* Thunberg (*H. cordata*),

is employed for treating inflammation-related conditions (Ahn et al. 2017). *H. cordata*, known in Chinese as “Yu-xing-cao”, is not only a perennial flowering herb with a distinctive odor (Sekita et al. 2016) but also a wild vegetable crop that grows in moist and shaded areas and is widely cultivated or harvested in Asian countries (Chen et al. 2013; Yadav and Temjenmongla 2011). In China, it is found mainly in central, southeastern, and southwestern provinces, particularly in regions such as Sichuan, Hubei, Hunan, and Jiangsu (Yu et al. 2022). As a botanical remedy in traditional Chinese medicine (TCM), *H. cordata* has historically been used to treat conditions such as ulcers, skin lesions, heat stroke, diarrheal diseases, and dysentery (Woranam et al. 2020). Owing to its anti-inflammatory characteristics, this herb was selected among eight TCM agents with unique therapeutic effects on severe acute respiratory syndrome (Li et al. 2013). Unlike synthetic drugs, *H. cordata* offers a multitarget approach to combat pathogens while enhancing host immunity, making it ideal for pig production. This review bridges traditional knowledge and modern science by systematically analyzing its bioactive components, mechanisms, and practical applications, positioning it as a transformative solution for sustainable farming.

Bioactive compounds of *H. cordata* extract

Given its therapeutic potential, we first characterized its key bioactive constituents. *H. cordata* consists of aerial portions (leaves and stems) and subterranean components (roots), each containing a variety of bioactive components. HS-SPME/GC-MS analysis revealed that the root part contained the maximum amount of vitamin C, whereas the leaf part contained the highest total flavonoid, soluble sugar, and total protein contents (Qi et al. 2022). Compared with the roots and leaves, the stems of *H. cordata* have lower nutrient contents (Qi et al. 2022). Ultrasonic extraction analysis revealed varying chemical profiles in the *H. cordata* parts. Roots and stems contain low levels of polyphenols with weak antioxidant capacity. Conversely, flowers and leaves have high total phenol contents and strong antioxidant capacity (Song et al. 2022). These findings indicate that distinct pharmacological and food effects occur across plant parts. Traditional Chinese medicine commonly uses dried aerial parts or whole fresh *H. cordata* plants, whereas the tender leaves and root structures of *H. cordata* are utilized as culinary vegetables (Song et al. 2022). Notably, the underground parts of *H. cordata* are the primary reservoir for 2-undecanone, a pivotal medicinal constituent, which can be readily extracted (Qi et al. 2022). The bioactive components in the vapor extract of *H. cordata*, which include 4-terpineol, α -terpineol, l-bornyl acetate, and methyl-nonyl ketone, have been found to suppress LPS-induced

RPF (rapid pulmonary fibrosis) via the upregulation of IFN- γ and blockade of the TGF- β 1/Smad pathway (Du et al. 2012). Notably, MNK (2-methyl nonyl ketone), within the volatile oil of *H. cordata*, stands out as the predominant and most stable constituent (Wang et al. 2021). Furthermore, research findings suggest that the chemical makeup of *H. cordata* comprises volatile substances, flavonoid compounds, alkaloid components, fatty acid molecules, organic acid entities, sterol compounds, trace element contents, and polyphenolic acid derivatives (Oh 2015; Sekita et al. 2016). Moreover, it is frequently utilized for alleviating fever, purifying toxins, resolving boils, and promoting pus drainage (Li et al. 2017).

Flavonoids are strong natural antioxidants (Capcarova et al. 2015). In most plants (fruits, vegetables, and wild herbs), quercetin (3,3',4',5,7-pentahydroxyflavone) and its sugar conjugates are the most abundant and most active flavonoids (Ader et al. 2000; Sirotkin et al. 2019a). Flavonoids from *H. cordata* (HCF) contain 78.5% flavonoid glycosides (Ling et al. 2020). The primary active compounds in *H. cordata* are quercetin, kaempferol, hyperoside, and rutin (Lai et al. 2022). Among these, HCF contains 8.8% rutin, 26.7% hyperin, 9.9% isoquercitrin, and 31.7% quercitrin (Ling et al. 2020). HCFs exhibit diverse bioactive properties, including microbe-fighting, inflammation-reducing, free-radical-scavenging, allergy-relieving, mutation-preventing, cancer-inhibiting, and chromosome damage-protecting properties (Capcarova et al. 2015). Notably, these beneficial effects are dose dependent, with a study reporting cytotoxic effects at higher concentrations (> 250 mg/mL) that induce apoptosis (Ren et al. 2011). HCF suppresses the proliferation and viral activity of influenza virus H1N1 by downregulating TLR3/4/7 expression, NF- κ B p65 phosphorylation, and cytokine secretion and reducing nuclear translocation (Ling et al. 2020). Among the four main flavonoid glycosides present in HCF, hyperin and quercitrin stand out as crucial elements driving the therapeutic benefits of HCF (Ling et al. 2020). The major flavonoids extracted from *H. cordata* in 70% ethanol, including afzelin, hyperoside, and quercitrin, significantly inhibited the pneumonia response in an LPS-induced acute lung injury mouse model. In particular, 100 mg/kg quercetin has the most potent effect on LPS-induced pneumonia in mice by suppressing interleukin-6 (IL-6) expression and NO production (Lee et al. 2015). Quercetin, classified as a phytoestrogen, is a nonsteroidal compound sourced from plants (Capcarova et al. 2015). *H. cordata* comprises a variety of medicinal components distributed across different chemical categories, such as alkaloids, essential oils, and flavonoids, with further details provided in Table 1 and Fig. 1.

Mechanisms of action

These bioactive compounds in *H. cordata* extracts exert their effects through multiple interconnected pathways.

Antimicrobial activity

The current treatment of bacterial infectious diseases faces a significant threat from antibiotic resistance. Therefore, there is a need to find new, effective and affordable drugs to treat microbial infections to overcome resistance. The antibacterial compounds found in natural plant extracts, such as *H. cordata* extracts, strongly suppress the proliferation of pathogenic bacteria and have garnered considerable attention. As per earlier research, the liquid phase of *H. cordata* essential oils (at concentrations ranging from 128–1024 µg/mL in broth and 1024 µg/mL in agar) shows inhibitory activity against a range of Gram[−] and Gram⁺ bacteria, such as *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Streptococcus pyogenes*, *Klebsiella pneumoniae*, *Chromatin*, *B. subtilis*, *B. cereus*, and *V. cholerae*, in addition to acid-fast bacilli and fungi (Rebickova et al. 2020; Song et al. 2022). eHCPs derived from the ethanol extract of *H. cordata* show remarkable antibacterial efficacy against *Staphylococcus aureus*, particularly methicillin-resistant strains (MRSA), while preventing MRSA biofilm formation and inhibiting IL-8 and CCL20 production induced by *S. aureus* LTA in human keratinocytes (Sekita et al. 2016). In terms of the selection of environmentally friendly antimicrobials for food packaging, the *H. cordata* ethanol extract is encapsulated in the hollow cavities of β -cyclodextrins to form capsules. After the addition of capsules, researchers noted marked inhibitory effects on *B. subtilis* growth and proliferation (Kong et al. 2022). Furthermore, dHC shows antibiofilm activities against methicillin-resistant *Staphylococcus aureus*, *Fusobacterium nucleatum* (which contributes to dental plaque), and *Candida albicans*. Additionally, this agent inhibits the generation of IL-8, CCL20, IP-10, and GRO α within *P. gingivalis* LPS-stimulated human oral keratinocytes, a key etiological factor in periodontitis, while maintaining noncytotoxic conditions (Sekita et al. 2017).

In addition to addressing the issue of bacterial diseases, humans and animals must also ward off viral infections. For example, influenza viruses can induce mild to severe respiratory conditions in both humans and animals. Annually, influenza viruses, including types A (H1N1 and H3N2) and B, result in 3–5 million severe illness cases and 250,000–500,000 deaths. Influenza viruses have high mutability. Therefore, current vaccines often fail against new strains and need annual updates (Makau et al. 2018). Additionally, emerging virulent diseases such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

require urgent solutions. Therefore, on the basis of the diversity of natural plant extracts, they are of interest as potential sources of antiviral drugs. Research has demonstrated that *H. cordata* is among eight traditional Chinese medicines with distinctive effects on severe acute respiratory syndrome (SARS) because of its capacity to reduce inflammation (Li et al. 2011). Like other RNA viruses, SARS-CoV-2 produces the RdRp (RNA-dependent RNA polymerase) enzyme, which enables the transcription and replication of viral genes. The persistent affinity binding of *H. cordata* compounds to the RdRp enzyme persists through hydrogen bonds with residues Arg553, Cys622, and Asp623, in parallel with hydrophobic interactions involving other residues (Bahadur Gurung et al. 2021). Consequently, these findings highlight the promise of bioactive compounds from *H. cordata* as prospective anti-SARS-CoV-2 drug candidates directed at this enzyme. The development of these compounds as viable therapeutic agents for SARS-CoV-2 infection is feasible. Moreover, extracts of *H. cordata*, containing afzelin, apigenin, kaempferol, and quercetin, engage in the PI3K-Akt, Jak-STAT, MAPK, and NF- κ B signaling pathways through stable binding to SARS-CoV-2 targets, namely, DPP4, ELANE, HSP90AA1, IL6, MAPK1, SERPINE1, ACE2, and 3CLpro, respectively (Liu J et al. 2022). *H. cordata* is commonly used to relieve oral inflammation associated with "shanghuo" (a traditional Chinese medicine concept describing symptoms of excessive internal heat such as mouth ulcers and sore throat) and contains quercetin, a flavonoid documented to suppress multiple viruses (Choi et al. 2009a). A hot water extract of quercetin effectively reduced the severity of herpes simplex virus (HSV) infection, potentially through inhibiting the NF- κ B pathway (Wu et al. 2021). Four newly identified compounds in *H. cordata*, showing the ability to inhibit HSV-1, are flavonoid derivatives linked to houttuynin (3-oxododecanal), and the IC₅₀ values for these compounds are 38.46 µM, 14.10 µM, 62.00 µM, and 70.76 µM (Chen et al. 2013). A novel type of flavonoid, houttuynoids, comprising a flavonoid core and a houttuynin chain, has been discovered in *H. cordata* for the first time and exhibits anti-herpes simplex virus activity (Li et al. 2017). This will help people pay more attention to the discovery of new structural compounds of *H. cordata* and their specific biological activities. A coronavirus known as avian IBV (infectious bronchitis virus) is responsible for causing infectious bronchitis in poultry. *H. cordata*, particularly its essential oil component, inhibits IBV infection in both Vero cells and chicken embryo kidney cells, with an efficacy exceeding 90%, and reduces IBV-induced apoptotic cells by over 90%. *H. cordata* protects SPF embryos from IBV challenge, with a success rate of over 50% in SPF chickens (Yin et al. 2011). *H. cordata*

Table 1 Main biological functions of *H. cordata* extracts

Category	Compound	Dosage	Supplementation method	Test subject	Duration	Functions	Reference
Volatile oil	2-methyl nonyl ketone	10 µg/mL	Dissolved in dimethyl sulfoxide	MAC-T cells	28 h	Increase cell viability, inhibit ROS and inflammation	Wang et al. 2021
Ethyl acetate fraction	Chlorogenic acid, hyperoside, and quercitrin	25, 50, 100, or 200 µg/mL	Dissolved in ethyl acetate	RAW 264.7 cells	2 h	Inhibit inflammation	Chun et al. 2014
Fermentation product	HCFP aqueous extract; methanolic extract	50–750 µg/mL, 4–12 µg/mL		RAW 264.7 cells	2 h	Anti-inflammatory	Woranam et al. 2020
Ethanol extract	eHCP	0.1, 0.5, 1.0%	Ethanol	<i>S. aureus</i> LTA,	24 h	Antibacterial, anti-inflammatory	Sekita et al. 2016
Flavonoids	Quercetin	0, 4, 8, 16, 32 µg/mL or 100 mg/kg BW	Dissolved in DMSO	SS2 ZY05719, J774 cells, mice	5, 6, 96 h	Antimicrobial activity- <i>Streptococcus Suis</i>	Li et al. 2019
<i>H. cordata</i> water extract	HCWE	25 to 100 mg/mL		<i>S. typhimurium</i> , RAW 264.7 cells BALB/c mice	8 h	Antibacterial activity, activate macrophages	Kim et al. 2008
Flavonoids	Quercetin	5 µM	Dissolved in DMSO	IPEC-1 cells	24 h	Protective effect on oxidative damage	Jia et al. 2021
Flavonoids	Quercetin	0–50 µM	Dissolved in DMSO	Porcine neutrophil, PMNs/PBMCs	24 h	Anti-inflammatory	Jo et al. 2021
<i>H. cordata</i> water extract		25–200 µg/mL	Prepared in sterile water	VECs	6, 18 h	Immunomodulatory effects on the vaginal mucosa	Sattthakarn et al. 2015
Flavonoids	Quercetin	12.5, 25, 50 µM	Dissolved in DMSO	Vero cells	0–48 h	Anti-PRV	Sun et al. 2021
Flavonoids	Quercetin	25, 50, 100 µM	Dissolved in DMSO	Pig sperm	7 d	Antioxidant	Bang et al. 2022
Flavonoids	Quercetin	0.25, 0.50, 0.75 mM	Added to the IVF medium	Pig sperm	0, 2, 4, 6, 8, 10, 48, 144 h	Antioxidant	Winn and Whittaker 2020
Flavonoids	Quercetin	0.01, 0.1, 1, 10, 100 mmol/L	Dissolved in DMSO	Porcine ovarian granulosa cell	24 h	Influence ovarian functions	Kolesarova et al. 2019
Flavonoids	Quercetin	0, 1, 10, 100 ng/mL	Dissolved in culture medium	Granulosa cells of pigs	2 d	Proliferation, apoptosis, and hormones release	Sirotkin et al. 2019a
Flavonoids	Quercetin	0, 1.25, 2.5, 5 µg/mL	Dissolved in DMSO	IPEC-J2 cell	2, 20, 24, 3 h	Promote cell proliferation, inhibit apoptosis	Chen et al. 2018
<i>H. cordata</i> methanol extract		1 g/kg	Supplemented in the diet	Weaning pigs	5 weeks	Reduce the fecal <i>E. coli</i> concentration	Yan et al. 2012
Flavonoids	Quercetin	2 g/kg	Supplemented in the diet	Growing pigs	7 weeks	Improve feed conversion	Burdeos et al. 2020
Flavonoids	Quercetin	25 mg/kg	Supplemented in the diet	Finishing pigs	4 weeks	Regulate oxidative status and inflammation	Zou et al. 2016
Flavonoids	Quercetin	10 ⁻¹³ –10 ¹ M	Dissolved in ethanol and diluted with deionized water	Myometrium strips of uterine horns	60–90 min	Cause relaxation of the uterine smooth muscle	Zygmuntowicz et al. 2021
Flavonoids	Quercetin	0, 1, 10, 100 ng/mL	Dissolved in culture medium	Porcine ovarian granulosa cells and ovarian follicles		Regulate proliferation, apoptosis, hormone release	Sirotkin et al. 2019b

Table 1 (continued)

Category	Compound	Dosage	Supplementation method	Test subject	Duration	Functions	Reference
Flavonoids	Quercetin	1, 10, 100 ng/mL	Dissolved in DMSO	porcine granulosa cells from Slovakian White gilts	24 h	Antioxidant, detoxification activity of T-2	Capcarova et al. 2015
Flavonoids	Quercetin	20, 50, 75, 100 mmol/L	Diluted in acetone-trile	IPEC-J2 cells	24 h	Antioxidant, detoxification activity of DON	Pomothy et al. 2021

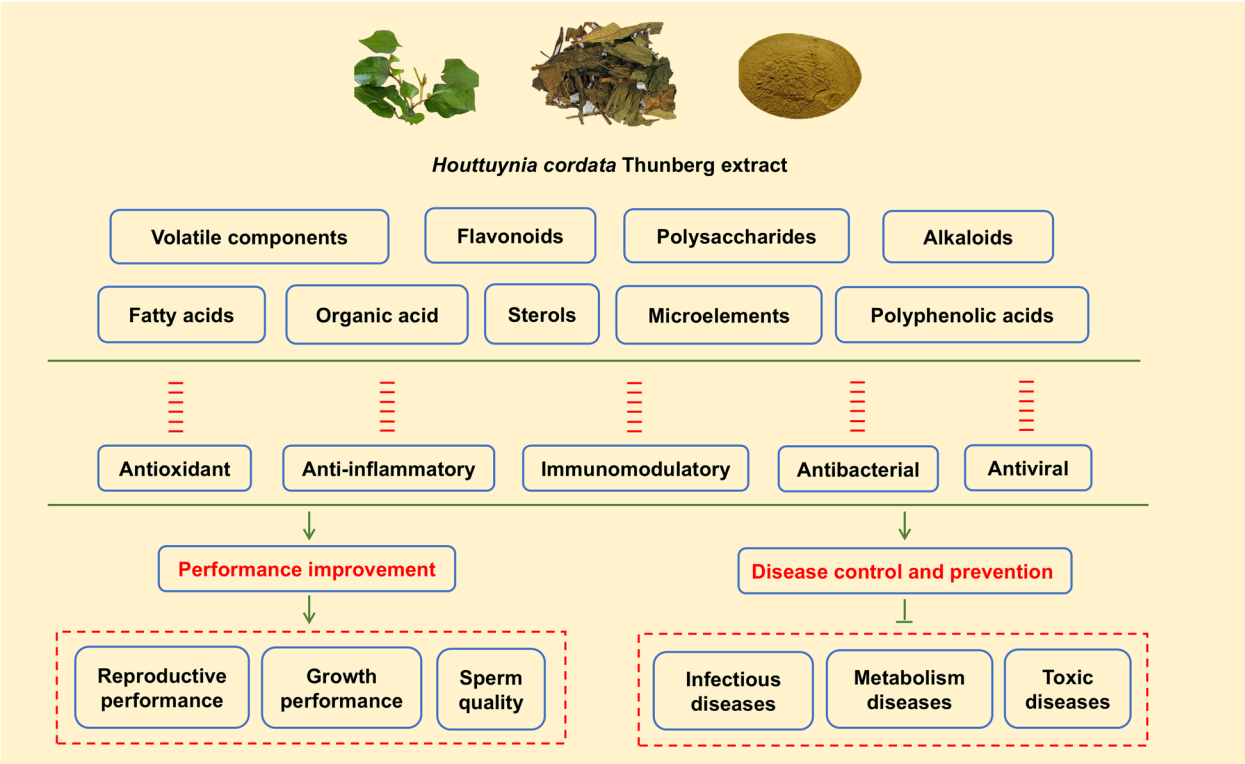


Fig. 1 Main components and functions of *H. cordata* extracts. The chemical components of *H. cordata* extract include volatiles, flavonoids, polysaccharides, alkaloids, fatty acids, organic acids, sterols, microelements, and polyphenolic acids. *H. cordata* extract exerts antioxidant, anti-inflammatory, antiviral, and antibacterial effects, enhancing animal health and production performance

exerts potent anti-influenza activity through direct neuraminidase inhibition. At a concentration of 250 mg/mL, the extract achieves complete blockade of viral neuraminidase activity, preventing viral release from infected cells. The active compound quercetin-3-rhamnoside (Q3R), which is isolated from *H. cordata*, dose-dependently suppresses influenza A/WS/33 virus replication in cytopathic effect reduction assays. This specific targeting of neuraminidase, a key viral surface glycoprotein, disrupts the final step of the viral replication cycle, as validated through functional enzymatic inhibition studies (Choi et al. 2009b; Han et al. 2016). Overall, flavonoids

in *H. cordata* employ a multipronged targeting strategy against diverse viruses. This includes enzymatic inhibition of neuraminidase in influenza and 3C-like proteases in coronaviruses, structural disruption of glycoprotein D in PRV, and catalytic interference with RdRp in SARS-CoV-2. These molecular interactions specifically disrupt critical infection stages: viral entry through receptor blockade in PRV, replication suppression via polymerase inhibition in influenza and PEDV, and viral release prevention through neuraminidase inactivation, demonstrating broad-spectrum antiviral efficacy through distinct yet complementary pathways. Furthermore,

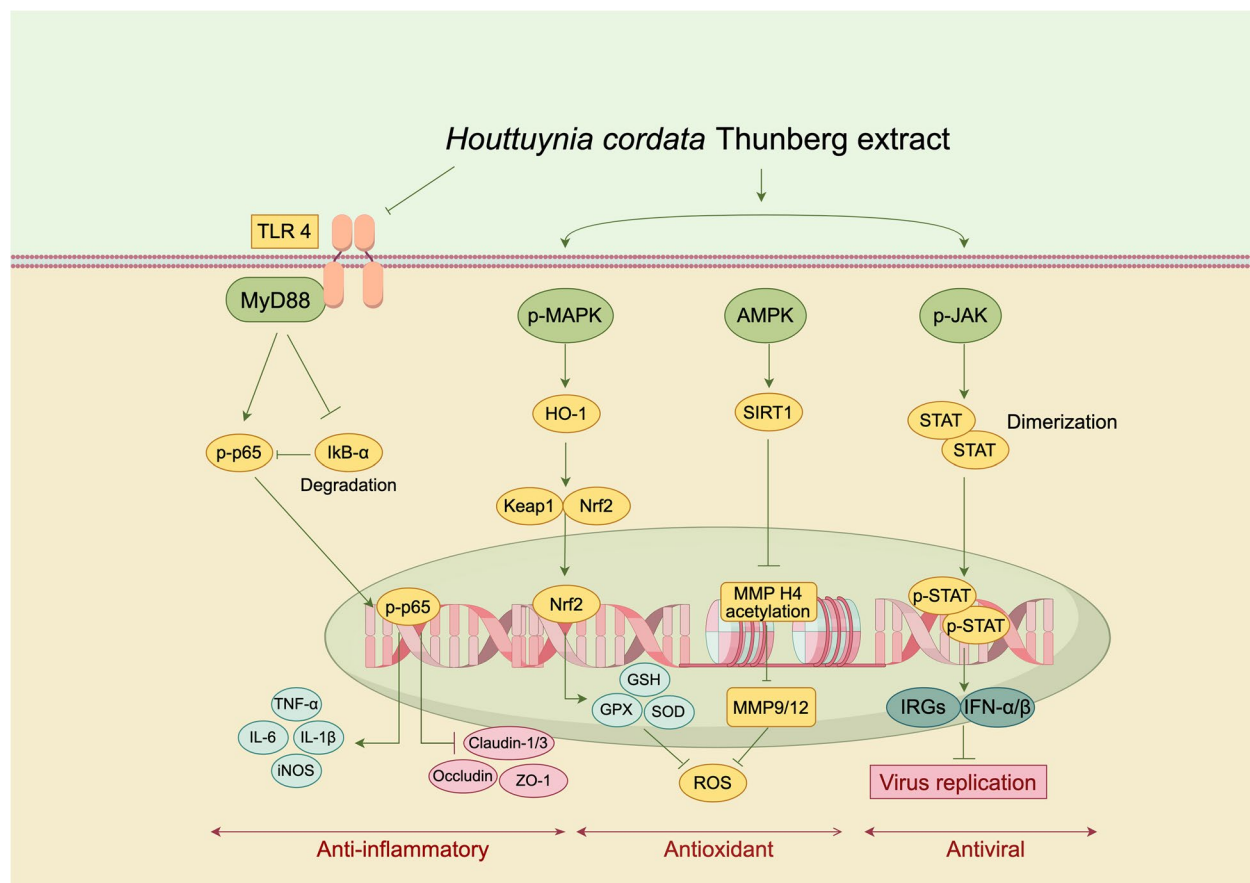


Fig. 2 Proposed mechanism of the antioxidant, anti-inflammatory, and antiviral effects of *H. cordata* extract. The extract exerts its regulatory functions through the modulation of multiple signaling pathways: (1) its antioxidant activity is mediated by reducing ROS production; (2) its anti-inflammatory effects are achieved through the regulation of inflammatory factor expression; and (3) its antiviral properties arise from the inhibition of viral replication. This integrated action highlights the multitarget therapeutic potential of *H. cordata* extract. (By Figdraw, ID: OUYUA2c862)

H1N1-induced viral pneumonia in mice was alleviated by a mixture of flavonoids and polysaccharides from *H. cordata* through the multimodal regulation of lung and gut homeostasis (Ling et al. 2023). In Fig. 2, the possible mechanism of the antiviral properties of the *H. cordata* extract is depicted.

Antioxidant properties

While pathogen control is essential, managing the resulting oxidative stress is equally critical for systemic health. In general, the balance of reactive oxygen species (ROS) is essential for the growth and survival of normal cells. Oxidative stress occurs when an imbalance causes the generation of ROS to exceed the body's antioxidant defense mechanisms. An overabundance of ROS can harm the lipids, proteins, and DNA of normal cells, as well as compromise mitochondrial function and cause protein misfolding, consequently disturbing normal cellular functions and resulting in apoptosis, mutation, and

cancer. Oxidative stress is linked to multiple human conditions. These include pathological pregnancy outcomes such as abortion and preeclampsia (Chaurasia et al. 2019; Li M et al. 2021). In animals, it is associated with disorders such as weaning stress syndrome and immunosuppression. As previously noted, the primary chemical constituents of *H. cordata* extract are flavonoids. Among flavonoids, quercetin shows potent antioxidant activity through scavenging free radicals, inhibiting lipid peroxidation and metal ions, and modulating cellular antioxidant defenses (Jia et al. 2021; Paleco et al. 2014). Its polyphenol structure enables efficient neutralization of free radicals, while upregulation of Nrf2 and glutathione (GSH) enhances cellular protection against oxidative damage (Jia et al. 2021). Additionally, quercetin mitigates apoptosis induced by ROS overproduction and mitochondrial dysfunction (Jia et al. 2021). Following 48 h of treatment, the *H. cordata* water extract restored C2C12 cell viability, which was reduced by TNF-α, concurrently

increasing SOD activity and reducing ROS levels (Ju et al. 2021). The ethyl acetate fraction of *H. cordata* (HC-EA), along with quercitrin and hyperoside, shields keratinocytes against UVB-triggered oxidative stress and inflammatory responses. HC-EA exerts this protective effect by modulating caspase-9 and caspase-3 activation; inhibiting UVB-induced apoptosis in HaCaT cells; reducing IL-6, IL-8, COX-2, and iNOS expression; scavenging intracellular ROS; and increasing heme oxygenase-1 and superoxide dismutase levels. These effects are mediated by diminished phosphorylation of UVB-stimulated p38 and JNK coupled with increased phosphorylation of ERK and Akt (Charachit et al. 2022). HC-EA, by removing alkyl and hydroxyl radicals and exhibiting strong antioxidant activity, significantly reduces carbon tetrachloride in mice, with elevated serum levels adjusted after the change in serum cholesterol levels, reversing the morphological changes in the liver cell structure of carbon tetrachloride-induced liver toxicity to protect the mouse liver (Kang et al. 2014). HC-AE (the aqueous extract of *H. cordata*) offers hepatoprotection in mice suffering from acetaminophen-induced acute liver injury by preserving the hepatic GSH content, sustaining GPX (glutathione peroxidase) and SOD activities, inhibiting CYP2E1 activity, and reducing IL-6 and MCP-1 production (Chen et al. 2014). In Fig. 2, the possible mechanism of the antioxidant capacity of the *H. cordata* extract is depicted.

Anti-inflammatory effects

Inflammation is the innate immune system's natural defense. It responds to infection, foreign threats, and tissue injury (Li et al. 2011). While essential for immunity, uncontrolled inflammation causes tissue damage. Acute inflammation represents a normal defensive reaction, in contrast to chronic inflammation, which arises as a complex process following the activation of inflammatory or immune cells. The inflammatory response involves the activation of diverse cell types, which subsequently release multiple inflammatory-promoting factors, such as IL-1 β , TNF- α , IL-6, NO, and PGE2 (Woranam et al. 2020). In mouse resident peritoneal macrophages exposed to LPS in vitro, NO and TNF- α production was inhibited by *H. cordata* volatile oil at concentrations of 1, 10, 100, and 1000 mg/mL in a dose-dependent manner (Li et al. 2013). An investigation of *H. cordata* compounds revealed their inhibitory effects on NO generation in LPS-stimulated RAW 264.7 cells, with compound 15 (perlolyrine) exhibiting the highest potency (IC₅₀=8.7 μ M) among the anti-inflammatory agents tested (Ahn et al. 2017). When HSE (the supercritical extract of *H. cordata*) is orally administered at 200 mg/kg, it suppresses inflammation in male ICR mice. The mechanism involves the suppression of

the TNF- α -NO and cyclooxygenase II-PGE2 pathways, leading to the inhibition of carrageenan-induced fluid exudation, albumin extravasation, and inflammatory cell infiltration. Suppression of NO and PGE2 generation by HSE (final concentration of 0.001-1%) was likewise observed in RAW 264.7 cells (Shin et al. 2010). Compared with aqueous extracts (IC₅₀ $\approx$ 0.1%), HSE (IC₅₀<0.001%) demonstrated significantly greater efficacy in suppressing macrophage NO generation. Consequently, HSE is a more promising therapeutic candidate or adjunct than aqueous extracts are (Shin et al. 2010). Key anti-inflammatory phenolic compounds in HCFP (*H. cordata* fermentation products), specifically syringic, vanillic, p-hydroxybenzoic, and ferulic acids, were identified and quantified via quantitative HPLC. In RAW264.7 cells, extracts of HCFP prepared with either water or methanol diminished nitric oxide (NO) production and inhibited the LPS-stimulated expression of PGE2, iNOS, IL-1 β , TNF- α , and IL-6 in a concentration-dependent manner, as reported by Woranam et al. (Woranam et al. 2020). HCFP also increases neutrophil phagocytic activity and antibody production in immunosuppressed rats (Utaiwat et al. 2021). In inflammatory allergic diseases, HCWE (*H. cordata* water extract) exerts therapeutic effects through the inhibition of multiple stages of cytokine- and Fc ϵ RI-dependent signaling pathways. In IgE-sensitized RBL-2H3 cells, HCWE diminishes the antigen (DNP-BSA)-triggered release of β -hexosaminidase, histamine, and ROS. Furthermore, it decreases both the production and expression of IL-4 and TNF- α . These effects are mediated via the suppression of antigen-induced NF- κ B activation, I κ B- α degradation, and phosphorylation involving Syk, Lyn, LAT, Gab2, PLC gamma2, Akt, ERK1/2, and JNK1/2 (Han et al. 2009; Lai et al. 2022). HC-EA (the ethyl acetate fraction derived from *H. cordata* extract), which includes chlorogenic acid, hyperoside, and quercitrin, displays anti-inflammatory characteristics. This anti-inflammatory activity likely stems from its capacity to inhibit the expression of NO, PGE2, TNF- α , IL-6, iNOS, and COX-2 in RAW 264.7 cells. HC-EA achieves this by blocking NF- κ B p65 nuclear translocation and I κ B- α phosphorylation, as well as by suppressing MAPK (p38 and JNK) signaling cascades (Chun et al. 2014; Li et al. 2011). When HMC-1 cells were treated with PMA and A23187, the ethanol extract (HCT) reduced TNF- α and IL-6 secretion and decreased TNF- α , IL-6, and IL-8 mRNA levels. This suppression occurs through the inhibition of NF- κ B activity, its nuclear translocation, and I κ B- α phosphorylation (Lee et al. 2013). The aqueous extract (traditional decoction) elevates the expression of ZO-1, occludin, and IL-10, concurrently reducing IL-1 β , IL-6, and EGFR levels. This modulation has anti-inflammatory effects both in Caco-2

cells and in an in vivo colitis model and is mediated by an EGFR-dependent MAPK/ERK1/2 signaling cascade (Wang J et al. 2022).

Inflammation is recognized as a key pathophysiological mechanism in numerous chronic diseases (Chun et al. 2014). Mastitis, a widespread inflammatory disorder triggered by bacterial infection of the mammary gland, compromises the well-being of both humans and livestock while resulting in significant financial implications (Liu Y et al. 2022). Using murine mastitis models, researchers reported that *H. cordata* essential oil (HEO) and its self-microemulsion (SME-HEO) suppress the proinflammatory factors TNF- α and IL-1 β while increasing the anti-inflammatory cytokine IL-10. These treatments also curtail MPO expression, increase the levels of junction proteins (ZO-1, claudin-1, claudin-3, and occludin), and decrease histopathological injury in mammary gland tissue. Consequently, the integrity of the blood–milk barrier is maintained. Blockade of the MAPK signaling pathway and a reduction in iNOS expression underlie the anti-inflammatory actions of HEO and SME-HEO (Liu Y et al. 2022). In bovine mammary epithelial cells (MAC-T), methyl nonyl ketone (MNK), identified as the main volatile constituent in *H. cordata* aqueous vapor extract, diminishes the secretion of proinflammatory cytokines (e.g., interleukins, TNF- α). This occurs through the inhibition of LPS-triggered activation of the TLR4-NF- κ B signaling cascade. Furthermore, MNK stimulates the expression of the antioxidant enzyme HO-1 (heme oxygenase-1) through the Nrf2 pathway, which involves AKT and ERK signaling, subsequently lowering LPS-induced ROS (reactive oxygen species) generation and mitigating oxidative stress in MAC-T cells (Wang et al. 2021). Another key component, 2-undecanone, promotes the expression of HO-1 in the mouse myocardium by activating Nrf2. This activation leads to suppression of the NF- κ B pathway and attenuation of inflammatory injury resulting from PM2.5 exposure (Jiao et al. 2022). Houttuynin (synonymous with 2-undecanone), a bioactive compound in *H. cordata* essential oil, interacts with the IP3 binding site of the inositol trisphosphate receptor (IP3R). This interaction specifically targets dysregulated calcium (Ca²⁺) signaling, offering a mechanism to alleviate asthma progression and inhibit airway constriction (Huang et al. 2023). Matrix metalloproteinases (MMPs), which are secreted by inflammatory and epithelial cells, amplify proteolytic activity within the lungs. Their action degrades alveolar walls, contributing to alveolar space enlargement and the pathogenesis of emphysema (Ganesan et al. 2010). Quercetin exerts anti-inflammatory effects by inhibiting kinases (e.g., lipids, protein tyrosine, serine/threonine kinases) via competition with ATP at nucleotide-binding sites (Ganesan et al. 2010). It

suppresses NF- κ B activation (Al-Shalmani et al. 2011) and reduces the expression of inflammatory mediators such as MMPs in pulmonary disease (Ganesan et al. 2010). Vascular endothelial cell (EC) senescence can contribute to human atherosclerosis development. Treatment with *H. cordata* (40 μ g/mL) increases both high glucose (HG)-induced endothelial cell (EC) migration and NO production and activates the sirtuin 1 (SIRT-1)/endothelial nitric oxide synthase (eNOS) pathway in a dose-dependent manner (Kim 2020). Moreover, *H. cordata* reduces the number of senescence-associated galactosidase (an aging biomarker)-positive cells, indicating its potential to protect ECs from HG-induced aging (Kim 2020). Thus, the extract of *H. cordata* can modulate the expression of proinflammatory and anti-inflammatory factors by regulating various signaling pathways, thereby exerting anti-inflammatory effects and demonstrating potential therapeutic value in treating inflammatory diseases. Figure 2 shows the possible mechanism by which *H. cordata* extract regulates inflammation.

Immunomodulatory effects

In combination with these anti-inflammatory actions, broader immune regulation further enhances host defense. Immunomodulators enhance host defense through specific cellular and molecular pathways (Abbas et al. 2023; Utaiwat et al. 2021). A primary cellular defense within the innate immune system is formed by neutrophils against invading microorganisms. Neutrophil extracellular traps (NETs) are a recently discovered immune response. They consist of dense chromatin and antimicrobial substances such as NE and MPO. NETs capture bacteria, fungi, and parasites. While beneficial for host defense, they also contribute to autoimmune and inflammatory diseases. For example, quercetin suppresses NET formation in PMNs (polymorphonuclear cells) by reducing TNF- α production in LPS-stimulated PBMCs (peripheral blood mononuclear cells) (Jo et al. 2021), demonstrating its anti-inflammatory and immunomodulatory effects.

H. cordata fractions (HcFs) inhibit Th2-mediated allergic inflammation by increasing IL-4/5 in Jurkat T and HMC-1 mast cells, blocking IL-4/TNF- α -induced TARC (thymus and activation-regulated chemokine) production in fibroblasts and promoting TARC-mediated Jurkat T-cell migration (Lee et al. 2008). In vaginal epithelial cells, *H. cordata* extract (25–200 μ g/mL) enhances mucosal immunity by upregulating hBD2 (human β -defensin 2), SLPI (secretory leukocyte protease inhibitor), and IL-2/IL-6 while decreasing CCL5 (Satthakarn et al. 2015). *H. cordata* corrects the Treg/Th17 imbalance by increasing CD4⁺CD25⁺FoxP3⁺ Treg cells and IL-10 and decreasing Th17 cells and IL-17A (Wang C et al.

2022). Mechanistically, its polysaccharide (HCP) inhibits Th17 differentiation via reduced p-STAT3 while promoting Treg differentiation through p-STAT5 upregulation (Shi et al. 2020).

Flavonoids from *H. cordata* (quercetin, quercitrin, afzelin, and isoquercitrin) regulate complement system activation. The anticomplementary effects of these compounds correlate with C-3 hydroxyl/glycoside groups, preventing dysregulation-induced pathologies (Jiang et al. 2014). The pectic polysaccharide HCP-2 (linear 1,4-linked α -D-galacturonic acid chain with methyl/acetyl groups) enhances cytokine/chemokine production (IL-1 β , TNF- α , MIP-1a/b, and RANTES) in PBMCs postabsorption, modulating innate immunity (Cheng B H et al. 2014b; Zhu et al. 2018). This immunostimulation may exacerbate autoimmune conditions, as NET formation, while antimicrobial activity, contributes to inflammatory diseases (Jo et al. 2021). In summary, *H. cordata* extract is crucial for activating immune responses and modulating the host defense system.

Cross-mechanism synergistic network:

antioxidant-anti-inflammatory-immunomodulation

The bioactivities of *H. cordata* extract (HCE) operate within a highly interconnected network, where its antimicrobial, antioxidant, anti-inflammatory, and immunomodulatory effects synergize to enhance overall host defense. The antioxidant and anti-inflammatory properties are interconnected. The potent antioxidant activity of HCE flavonoids (e.g., quercetin) directly reduces oxidative stress by scavenging ROS and upregulating endogenous defenses such as Nrf2 (Charachit et al. 2022; Jia et al. 2021). This suppression of ROS is critical, as ROS are key activators of the proinflammatory NF- κ B and MAPK pathways. By quenching ROS, HCE indirectly inhibits these pathways, leading to reduced production of inflammatory cytokines (TNF- α , IL-6) and mediators (NO, PGE2) (Chun et al. 2014; Li et al. 2013). Concurrently, its compounds directly inhibit these same inflammatory pathways, establishing a reinforcing loop where antioxidant effects mitigate inflammation and vice versa. Anti-inflammatory-immunomodulatory synergy: Anti-inflammatory action directly promotes immune homeostasis. HCE rectifies immune imbalances by increasing anti-inflammatory Treg cells and IL-10 while decreasing proinflammatory Th17 cells and IL-17A (Wang C et al. 2022). This calibrated response prevents collateral tissue damage while maintaining effective pathogen clearance. Additionally, antimicrobial and immunomodulatory activities collaborate. Direct pathogen inhibition by HCE components (e.g., quercetin against viruses and volatile oils against bacteria) reduces the infectious load that would otherwise trigger massive inflammatory

and oxidative responses (Kim et al. 2008; Li et al. 2020; Sun et al. 2021). This proactive containment underpins its systemic protective effects. These mechanisms are exemplified by HCE polysaccharides, which alleviate lung inflammation and concurrent intestinal injury by modulating the gut microbiota, strengthening the intestinal barrier, and suppressing systemic inflammatory signaling (Chen et al. 2019; Shi et al. 2022; Zhu et al. 2018). This finding demonstrates multiorgan protection through integrated mechanisms. In conclusion, the efficacy of HCE stems from the synergy of its bioactivities. It simultaneously eliminates pathogens, reduces oxidative stress, resolves inflammation, and calibrates immunity, providing comprehensive, multitargeted health benefits. In Fig. 3, a multitarget regulatory network of *H. cordata* extract is depicted.

Applications in pig production

The multitarget mechanistic actions of *H. cordata* extract, including antimicrobial, antioxidant, anti-inflammatory, and immunomodulatory activities, directly translate into tangible benefits for swine health and productivity. The antimicrobial and antiviral properties, which are effective against key pathogens such as *Salmonella*, *S. suis*, PRRSV, and PEDV, provide a frontline defense that reduces disease incidence and the need for conventional antibiotics (Kim et al. 2008; Li et al. 2019; Sun et al. 2021). Concurrently, the potent antioxidant capacity, primarily mediated by flavonoids such as quercetin, mitigates oxidative stress induced by common production challenges such as weaning, transport, and high-density housing (Jia et al. 2021; Zou et al. 2016). This reduction in oxidative damage preserves intestinal epithelial integrity, enhances nutrient absorption, and increases growth performance (Zou et al. 2016). Furthermore, the extract has anti-inflammatory and immunomodulatory effects, including regulating the Treg/Th17 balance and suppressing proinflammatory cytokines (e.g., TNF- α and IL-6), preventing systemic inflammation and promoting a balanced immune response (Shi et al. 2020; Wang C et al. 2022). This is crucial for maintaining overall health in intensive farming systems. Ultimately, the synergy of these mechanisms underpins the role of the extract in enhancing disease resistance, improving gut health, and supporting reproductive performance, positioning HCE as a comprehensive, natural alternative for sustainable pig production.

Disease resistance enhancement

Owing to its comparative advantages, *H. cordata* specifically addresses key swine disease challenges. Inflammatory responses and oxidative stress jeopardize the integrity of the intestinal epithelium. This allows

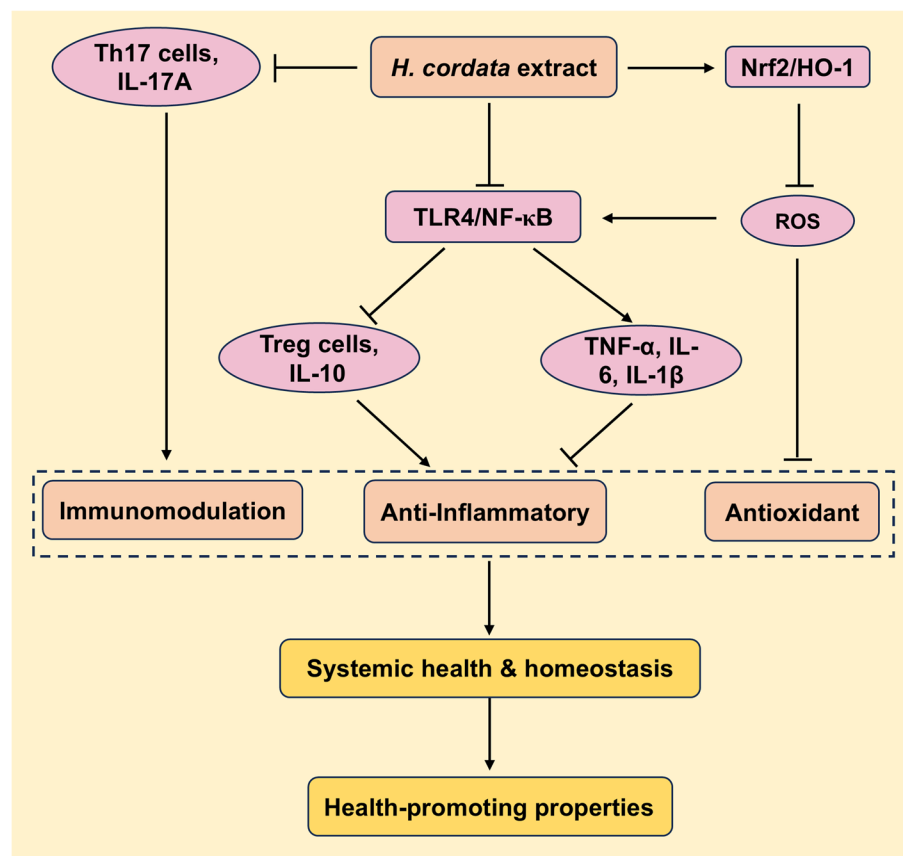


Fig. 3 Multitargeted regulatory network of *H. cordata* extracts. The diagram illustrates the interconnected mechanisms by which *H. cordata* extract exerts its health-promoting effects, including antioxidant effects (by upregulating Nrf2/HO-1 and scavenging ROS), anti-inflammatory effects (via inhibition of the TLR4/NF-κB pathway and reduction in the proinflammatory cytokines TNF-α, IL-6, and IL-1β), and immunomodulatory effects (by balancing Treg cells and IL-10 against Th17 cells and IL-17A). These actions synergize to achieve systemic health and homeostasis

pathogens such as *Salmonella*, *Streptococcus suis*, and *E. coli* to invade the porcine gut. Consequently, intestinal disorders develop, causing significant economic losses. Consequently, the necessity for alternatives to antibiotics has increased. These alternatives should possess the ability to preserve gastrointestinal well-being and mitigate the emergence of antibiotic resistance in swine populations. Salmonellosis stands out as a predominant bacterial zoonotic disease that is responsible for a diverse spectrum of disease manifestations (Kim et al. 2008). Within the confines of a *Salmonella typhimurium* infection model, the aqueous extract of *H. cordata* (HCWE) exhibited dose-responsive antibacterial efficacy (25–100 mg/mL) throughout an 8-h incubation period. Notably, this was achieved without any discernible cytotoxic effects. RAW 264.7 cells are influenced by HCWE, resulting in morphological changes and facilitating bacterial uptake. When RAW 264.7 cells were contaminated with *S. typhimurium*, upregulated NO production and iNOS mRNA expression were detected in HCWE-treated cells during the 8-h incubation period. After

receiving the *S. typhimurium* lethal dose, all untreated mice died by day 7. Conversely, BALB/c mice administered HCWE (25, 50, or 100 mg/mL) survived for 11, 17, or 23 d, respectively (Kim et al. 2008). Notably, even the highest dose (100 mg/mL) only delayed mortality rather than preventing it, underscoring therapeutic limitations against established infections. The increase in the level of intracellular ROS caused by LPS treatment was reduced by the addition of flavonoid compounds (quercetin, its methylated derivative 3-o-methylquercetin, and rhamnazin) at 50 μM. The increased IL-6 production in enterocytes induced by *S. Typhimurium* LPS can be alleviated by flavonoid compounds. Moreover, there was no alteration in the permeability of the cell layer treated with either *S. enterica* ser. Typhimurium LPS and flavonoid compounds (quercetin, 3-O-methylquercetin, and rhamnazin) compared with those in untreated cells (Karancsi et al. 2022). *S. suis* is a pathogen of zoonotic importance that is responsible for severe conditions, such as streptococcal toxic shock syndrome (STSS), meningitis, and

arthritis, and inflicts considerable economic damage to the pig industry. Suliyisin (SLY), a cytotoxic toxin primarily secreted by pathogenic *S. suis* strains, generates pores in cell membranes containing cholesterol, leading to cell lysis. When applied at concentrations of 0, 4, 8, 16, and 32 µg/mL, quercetin directly blocks the capacity of SLY for pore formation, reduces the release of inflammation-promoting cytokines (IL-1 β , IL-6, and TNF- α) following bacterial stimulation, and markedly diminishes the degree of cytotoxicity resulting from *S. suis* challenge. Quercetin also significantly reduces mortality in mice contaminated with *S. suis* (Li et al. 2019). Therefore, *H. cordata* extract has good antibacterial activity against infections and diseases caused by *Staphylococcus*, *Streptococcus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Salmonella*, etc., indicating that it can be used as a supplement or substitute for modern medical treatment.

Globally, swine viral infections such as PRV (pseudorabies virus), PRRSV (porcine reproductive and respiratory syndrome virus), and PEDV (porcine epidemic diarrhea virus) cause significant economic damage. To prevent latent infection, compensate for the deficiency of effective protection against some circulating strains, and reduce pathogenicity, the development of novel antiviral agents is necessary for prophylaxis against viral pathogens (Sun et al. 2023). In contrast to pseudorabies virus, quercetin targets the viral envelope glycoprotein gD with high specificity. Molecular interactions occur at the ligand-binding cleft of gD, where quercetin forms hydrogen bonds with residues in the N-ring and α 3 helix domains. This binding competitively occupies receptor-binding sites at concentrations of 12.5–50 µM, effectively blocking viral adsorption to Vero cell surfaces. The mechanism prevents PRV entry across multiple strains, including HNX, Fa, Ea, and Bartha, as confirmed through viral adsorption inhibition assays and structural binding analysis (Sun et al. 2021). Furthermore, in mouse models, quercetin has anti-PRV effects, decreases mortality and decreases PRV replication in mouse brain tissue (Sun et al. 2021). A low dose (10 mg/mL) of *H. cordata* injection (essential oil) directly inhibited PRV in both Vero cells and swine testis cells. Considering that a high dose (250 mg/mL) of *H. cordata* alone can induce apoptosis, it is imperative to consider the optimal administration dosage of *H. cordata* in future applications (Ren et al. 2011). In breeding swine, PRRSV induces reproductive failure. Additionally, this pathogen induces pulmonary disorders, growth retardation, and potential mortality in juvenile swine. However, coinfections involving PRRSV-1 and PRRSV-2, coupled with strain variations, lead to restricted cross-protection conferred by vaccines, thereby resulting in clinical losses. Various efforts have been undertaken to increase the cross-protective efficacy of vaccines. As an effective

oral immunomodulator, quercetin elevates IRG and IFN α mRNA expression but reduces TGF β mRNA levels. This increase in cross-protection potentially reduces both viremic swine incidence and HP-PRRSV viremia incidence, surpassing the protective capacity of the PRRSV-1-modified live virus vaccine (Ruansit et al. 2020). Over the past decade, various strains of PEDV have caused severe damage to the global pig industry. PEDV is the primary etiological agent of severe enteropathogenic diarrhea in swine and is currently associated with a lack of effective therapeutic interventions. A study revealed that Q7R (quercetin 7-rhamnoside) neither directly interacts with nor inactivates PEDV particles. Rather, it targets the early phase of PEDV infection, inhibiting viral replication at an IC₅₀ of 0.014 µg/mL (Choi et al. 2009a). Additionally, Q7R structural analogs such as quercetin, apigenin, luteolin and catechin also exhibit modest PEDV-inhibitory efficacy (Choi et al. 2009a). Specifically, quercetin inhibited PEDV replication without causing cytotoxicity at the tested concentrations. This inhibition occurs by binding to both the active site and the binding pocket of the PEDV 3CLpro (3C-like protease), leading to its suppressive action (Li et al. 2020). However, its structural analogs like, such as apigenin and luteolin, show only modest efficacy (Choi et al. 2009a), indicating compound-specific antiviral activity limitations. Therefore, *H. cordata* extract inhibits viral replication and thus can be used to control viral infection.

Gut health and growth performance

Concurrently with pathogen control, maintaining intestinal homeostasis is fundamental to productivity. The intestinal tract's most populous cellular component, intestinal epithelial cells, establish a mucosal barrier via intercellular tight junctions. This barrier serves to prevent detrimental intestinal contents, permits the selective uptake of nutrients by the intestinal tract, and safeguards the intestinal well-being of both humans and animals (Jia et al. 2021). Conversely, dysfunction of the intestinal epithelial barrier, increased intestinal permeability, and intestinal apoptosis can precipitate intestinal injury, diarrhea, gastrointestinal disturbances, growth stagnation, and an array of intestinal pathologies, with oxidative stress posited as a key instigator (Jia et al. 2021). Maintaining equilibrium in the gut's redox state is therefore crucial for intestinal health. Under normal physiological conditions, ROS production is maintained at stable levels via endogenous antioxidant defense mechanisms, including SOD (superoxide dismutase), CAT (catalase), GSH-PX (glutathione peroxidase), and TPX (thioredoxin peroxidase). Conversely, excessive generation of ROS or a decline in antioxidant capacity results in ROS accumulation within the intestinal mucosa or cells. This, in turn,

induces oxidative stress and macromolecular damage, manifested as DNA damage, protein adduction, lipid peroxidation, intestinal epithelial apoptosis, and disruption of the intestinal mucosal barrier (Jia et al. 2021). Factors such as weaning, transportation, herd rotation, and temperature changes can cause stress in pigs, resulting in oxidative damage, intestinal dysfunction, and decreased immune function, thereby reducing growth performance. Premature weaning, while being a principal strategy for enhancing the efficiency of contemporary pig farming systems, can subject piglets to weaning stress. This stress may result in temporary anorexia, imbalance of the gut microbiota, severe intestinal injury, infection, and diarrhea, thereby undermining the disease resistance of piglets. After the regulation of feed resistance, sustainable antibiotic substitutes with good antioxidant activity to relieve weaning stress in piglets are urgently needed.

Oxidative stress is associated with weanling stress and toxicosis, both of which are capable of impairing porcine intestinal health. Plant polyphenols, which are abundant in fruits, vegetables, and seeds, demonstrate potent antioxidant and antibacterial properties (Xu et al. 2022b). *H. cordata*, in either pharmaceutical or dietary form, exhibits therapeutic potential for treating oxidative stress-related diseases (Ju et al. 2021). Nontumorigenic intestinal columnar epithelial cells, IPEC-J2 (intestinal porcine enterocyte cells), originate from newborn piglets midjejunum. While IPEC-J2 cells provide useful in vitro models for oxidative stress studies (Pomothey et al. 2021), they cannot replicate complex host-microbiome interactions occurring in intact porcine intestines, particularly under commercial production stresses. Quercetin enhances IPEC-J2 cell proliferation by regulating cell cycle progression (G1 to S phase) and suppressing P21/P27 expression (Chen et al. 2018). It reduces H₂O₂-induced apoptosis, ROS levels, and mitochondrial dysfunction while improving tight junction integrity (Chen et al. 2018). In finishing pigs, dietary quercetin (25 mg/kg) alleviates transport stress-induced intestinal injury by suppressing oxidative stress (ROS, MDA) and proinflammatory cytokines (Zou et al. 2016). Quercetin also diminishes the elevated levels of malondialdehyde (MDA), the product of lipid peroxidation, and the activity of superoxide dismutase (SOD) in cells with minor damage. Moreover, quercetin slightly increased claudin-1 and occludin levels. As a feed additive, quercetin is promising for enhancing swine intestinal health and mitigating oxidative damage and apoptotic cell death triggered by pathogens (Chen et al. 2018). Following dietary quercetin and fecal microbiota transplantation (FMT), elevated intestinal antioxidant capacity enhances anaerobic traits and carbohydrate metabolic activity in the intestinal

microbiota, consequently increasing the synthesis of short-chain fatty acids (SCFAs).

Transport often causes stress in pigs, and transport stress is associated with impaired intestinal barrier function. ROS levels increase as a result of emergency transportation. Oxidative stress may arise from the engagement of ROS with cellular membrane targets, inducing lipid peroxidation, disintegration of membranes, and endothelial damage. Furthermore, transport stress increases microbial translocation risk, potentially leading to increased morbidity, diminished meat quality, and carcass deterioration (Zou et al. 2016). Additionally, it increases the height of the jejunal villus and increases the mRNA levels of occludin and ZO-1 in this gut region. These effects are correlated with suppressed MAPK (ERK1/2, JNK), Akt, and NF- κ B pathway activity (Zou et al. 2016).

The balance of the intestinal microflora is crucial for maintaining intestinal health. *H. cordata* can regulate the intestinal microbiota. In male C57BL/6 mice with DSS-induced ulcerative colitis (UC), *Houttuynia cordata* polysaccharides (HCPs) increase *Firmicutes* and *Bacteroides* populations but reduce *Proteobacteria* within the gut microbiota (Cen et al. 2022). These polysaccharides significantly suppress HIF-1 α (hypoxia-inducible factor-1 α) expression and diminish goblet cell mucosubstances, whereas they increase sIgA and ZO-1 levels in intestinal tissue. Such modulation alleviates H1N1-induced compromise of the intestinal physical and immune barriers (Chen et al. 2019; Zhu et al. 2018). Furthermore, HCP decreases *Vibrio* and *Bacillus* pathogen abundance, contributing to partial restoration of gut homeostasis in H1N1-challenged mice (Chen et al. 2019; Zhu et al. 2018). Moreover, HCP can suppress inflammation, which is associated with reduced levels of Toll-like receptors (TLRs), p-NF κ B p65, and IL-1 β in the intestine, along with increased IL-10 production (Chen et al. 2019; Zhu et al. 2018). During pathological states, HCP-gut microbiota interplay modulates the Th17/Treg equilibrium along the gut-lung axis, offering therapeutic benefits for murine H1N1-triggered pulmonary damage (Shi et al. 2022). Furthermore, the combination of HCPs and *Lactiplantibacillus plantarum* P101 elevates beneficial bacterial populations, including *Alloprevotella*, *Roseburia*, and *Akkermansia*, but reduces inflammation-promoting genera, including *Alistipes*, *Enterorhabdus*, *Anaerotruncus*, and *Escherichia-Shigella* (Xu et al. 2022a). Moreover, this coadministration alleviates oxidative stress and inflammatory liver damage through the gut-liver axis, attenuating carbon tetrachloride-induced ALI (acute liver injury) via Nrf2 pathway activation and TLR4/NF- κ B suppression in mice (Xu et al. 2022a). *H. cordata*, when used in conjunction with metformin, has been shown to

alleviate endotoxemia by modulating the gut microbiota, especially *Roseburia*, *Akkermansia*, and gram-negative bacteria (Wang et al. 2017). Derived from *H. cordata*, sodium houttuynfonate (SH) modulates microbiota composition and diversity, increasing the abundance of beneficial bacterial taxa such as SCFA-producing genera (*Lachnospiraceae_NK4A136_group*, *Intestinimonas*) and probiotic species (*Lactobacillus*, *Alloprevotella*) (Cheng et al. 2023). In *C. albicans*-infected ulcerative colitis (UC) model mice, SH treatment ameliorated pathological manifestations, attenuated oxidative stress and inflammation, and reinforced intestinal mucosal integrity. Compared with the control, *H. cordata* methanol extract (1 g/kg) reduces fecal *E. coli* levels in weaned swine without altering *Lactobacillus* concentrations (Yan et al. 2012). Thus, *H. cordata* extract promotes intestinal health via mechanisms including oxidative stress alleviation, permeability reduction, tight junction protein regulation, barrier restoration, and microbiota equilibrium maintenance.

Reproductive health

While gut health supports growth, reproductive efficiency determines herd sustainability. On pig farms, various factors, such as stress and viral infections, can trigger reproductive disorders in sows. Chronic stress (CS) is notorious for inducing neurological and vital organ dysfunction, leading to infertility across species, including animals and humans. Stress has the potential to disrupt the HPA (hypothalamic–pituitary–adrenal) axis, triggering a substantial increase in serum cortisol levels (Lapyuneyong et al. 2022). As a prominent livestock nutrition flavonoid, quercetin is categorized under phytoestrogens, nonsteroidal plant compounds. It has a dual nature of estrogenic and antiestrogenic effects in vitro, implying a complex influence on reproductive function. This necessitates a cautious approach to the role of flavonoids in animal nutrition. Quercetin concentration-dependently suppresses progesterone synthesis, disrupts angiogenesis *via* VEGF inhibition, and alters redox balance in granulosa cells (Santini et al. 2009). It inhibits FSH-induced effects (e.g., reduces PCNA and cyclin B1) while promoting the expression of apoptosis markers (BAX) and modulating hormone secretion (P4, leptin, and testosterone) (Sirotkin et al. 2019b). Given the critical roles of hormonal regulation and angiogenesis in follicular maturation, such actions may detrimentally influence ovarian function (Santini et al. 2009). FSH (follicle-stimulating hormone) and IGF-I (insulin-like growth factor I) stimulate granulosa cell proliferation while suppressing apoptosis. Specifically, FSH elevates PCNA (proliferating cell nuclear antigen), decreases BAX levels, and enhances the secretion of P4 (progesterone), T (testosterone), and

L (leptin). Quercetin, a key flavonoid in livestock nutrition and a type of phytoestrogen, has both estrogenic and antiestrogenic activities in vitro, indicating its potential to differentially affect reproductive function (Santini et al. 2009). Ovarian follicles exhibit reduced P4 and T levels under quercetin exposure. Additionally, quercetin concentration-dependently (0.01–100 $\mu\text{mol/L}$) regulates ovarian activity via progesterone, cyclin B1, and p53 modulation (Kolesarova et al. 2019). Treatments at 0–100 ng/mL also diminish PCNA and BAX accumulation, reduce T output, and decrease P4 and IGF-I release in these cells (Sirotkin et al. 2019a). During IVM (in vitro maturation), immature porcine oocytes are treated with quercetin (1–10 $\mu\text{g/mL}$). Although it fails to promote nuclear maturation or increase blastocyst cell counts, quercetin decreases ROS, enhances blastocyst formation rates, and facilitates subsequent embryonic development (Kang et al. 2013). Paradoxically, it concurrently suppresses progesterone synthesis (Santini et al. 2009) and disrupts angiogenesis, revealing complex dualistic impacts on reproductive physiology. These in vitro findings require validation in gestating sows, where metabolic and endocrine dynamics differ substantially from those in culture systems. Quercetin also impacts reproductive tract function. After 60–90 min of preincubation, quercetin (10^{-13} to 10^{-1} M) induces relaxation of uterine smooth muscle in both cyclic and early pregnant gilts (7–8 months old, 120–130 kg) under progesterone dominance (Zygmuntowicz et al. 2021). Intrauterine growth restriction (IUGR) commonly presents as low birth weight. It is a leading cause of neonatal piglet mortality on commercial farms. In sows, uterine congestion and placental dysfunction are the primary causes. These factors lead to oxidative stress during parturition and severe oxidative stress in newborn piglets due to their underdeveloped antioxidant systems. This results in impaired fetal and postnatal growth. Maternal nutrition is crucial for enhancing neonatal antioxidant capacity. According to (Liu C et al. 2022), dietary interventions involving nanoselenium and *Macleaya cordata* extracts enhance the antioxidant status and immune function while reducing oxidative stress in IUGR offspring.

The reduction in postthaw sperm quality is significantly influenced by oxidative stress, which plays a key role. Owing to their high polyunsaturated fatty acid content, spermatozoa are particularly susceptible to lipid peroxidation caused by ROS. This process is considered the primary mechanism of infertility caused by sperm damage. Antioxidants can mitigate this damage by disrupting lipid peroxidation chains. Critical sperm structures such as lipids, proteins, carbohydrates, and nucleic acids are highly vulnerable to damage from ROS produced during freezing and thawing cycles, which compromises

fertility (Bang et al. 2022; Winn et al. 2020). Supplementation with 50 μ M quercetin has been demonstrated to improve thawed sperm quality by enhancing plasma and acrosomal membrane integrity as well as mitochondrial function. It also improves sperm motility and viability, reduces hydroperoxide levels, and decreases the incidence of polyspermy. According to (Bang et al. 2022; Winn and Whitaker 2020), quercetin enhances the proportion of embryos that achieve the blastocyst stage during in vitro culture. Nevertheless, Winn and Whitaker (Winn and Whitaker 2020) emphasized that additional studies must be conducted to verify this impact on porcine in vitro fertilization and subsequent pregnancy outcomes. *H. cordata* extract can inhibit ROS production by regulating signaling pathways, thereby alleviating oxidative stress and restoring normal physiological functions.

Therefore, as mentioned above, *H. cordata* mediates oxidative status, inflammation, immune regulation, intestinal homeostasis, metabolism, reproduction, and antiviral and antibacterial functions in humans and animals to prevent harmful pathogens from invading the body and causing damage. Large-scale farming challenges, such as weaning stress, antinutritional feed components, mycotoxins, and diseases, induce oxidative damage and inflammation in pig intestines. This disrupts the intestinal structure, impairs immune function, and reduces nutrient absorption and growth performance. The normal development of the intestinal mucosa and villi depends critically on the proliferation of epithelial cells within the intestine. Increasing villus height can increase the absorption capacity of the small intestine, suggesting a strategy to improve pig intestinal health (Chen et al. 2018). To increase pork production, litter sizes have increased, but this increase in low-birth-weight piglets results in intestinal health and immune challenges. These piglets face increased preweaning morbidity and mortality, delayed growth, and increased economic losses. Animal welfare and ethical concerns also emerge. To address these issues, interventions are usually carried out in three dimensions: sows (adequate reproductive nutrition during gestation), piglets (foster care, artificial colostrum), and pig farms (providing a comfortable delivery environment and in-depth monitoring of delivery). Newborn piglets, especially those with low birth weights, struggle to balance ROS production and clearance, causing cellular damage to nucleic acids, proteins, and lipids. Oxidative stress compromises the intestinal barrier, disrupts development, increases pathogen and toxin permeability, and hinders nutrient absorption (Van Tichelen et al. 2021). Dietary supplementation with antioxidants seems to be a viable solution. On the basis of the biological function of the *H. cordata* extract described above, it is expected to be used in pig production.

Safety and future prospects

Given these complex physiological impacts, rigorous safety assessment becomes imperative before field application. *H. cordata* extract has diverse biological functions and benefits in disease treatment (Fig. 4). However, given recent concerns regarding the genotoxic and carcinogenic potential of certain traditional medicinal plants, preclinical genotoxicity testing is recommended prior to their application (Kang et al. 2012). Some extract components carry toxic risks. For example, cis-lines in *H. cordata* oil may cause allergic reactions and skin irritation (Rebickova et al. 2020). Thus, balancing beneficial antibacterial compounds with potentially toxic compounds is critical. Critical unresolved questions include the following: 1) antagonistic interactions with common feed additives; 2) long-term impacts of aristolochic acid analogs at subtoxic doses; and 3) optimal dosing protocols avoiding the apoptosis-inducing threshold observed at >250 mg/mL (Ren et al. 2011). The genotoxicity of the *H. cordata* methanol extract was assessed via the *S. typhimurium* reverse mutation assay, the mammalian cell chromosome aberration test, and the mouse micronucleus test. These tests demonstrated no harmful genetic effects in bacterial, mammalian, or mouse bone marrow cells. These findings suggest that *H. cordata* extract may be safe for human health promotion and disease treatment (Kang et al. 2012). Aristolochic acids and their metabolites are known to be nephrotoxic, carcinogenic, and mutagenic. *H. cordata* contains several alkaloids, including aristolactams, which resemble aristolochic acids and aristolactam I in structure (Yu et al. 2022). Researchers have established a new method using UHPLC-Q/TOF-MS (ultrahigh-performance liquid chromatography-quadrupole/time-of-flight mass spectrometry) to simultaneously quantify aristolochic acid analogs in *H. cordata* samples collected from various regions across China. The established approach is anticipated to improve the safety assessment of *H. cordata* (Yu et al. 2022). In addition to the cytotoxicity and safety of *H. cordata* extract, several key problems still need to be further explored. First, the in vivo metabolic pathways of key bioactive components such as quercetin and kaempferol have not been fully elucidated (Li et al. 2024). Although methyl nonyl ketone shows rapid absorption and broad tissue distribution without accumulation in rats (Shi 2014), its detailed metabolic fate and interactions with the gut microbiota require further investigation. Second, the long-term safety and potential impacts of chronic drug administration, especially with respect to reproductive health and residue depletion, need validation under realistic conditions. Additionally, the structural complexity of natural products poses challenges for chemical modification and multitarget mechanism analysis (Zhang et al. 2025).

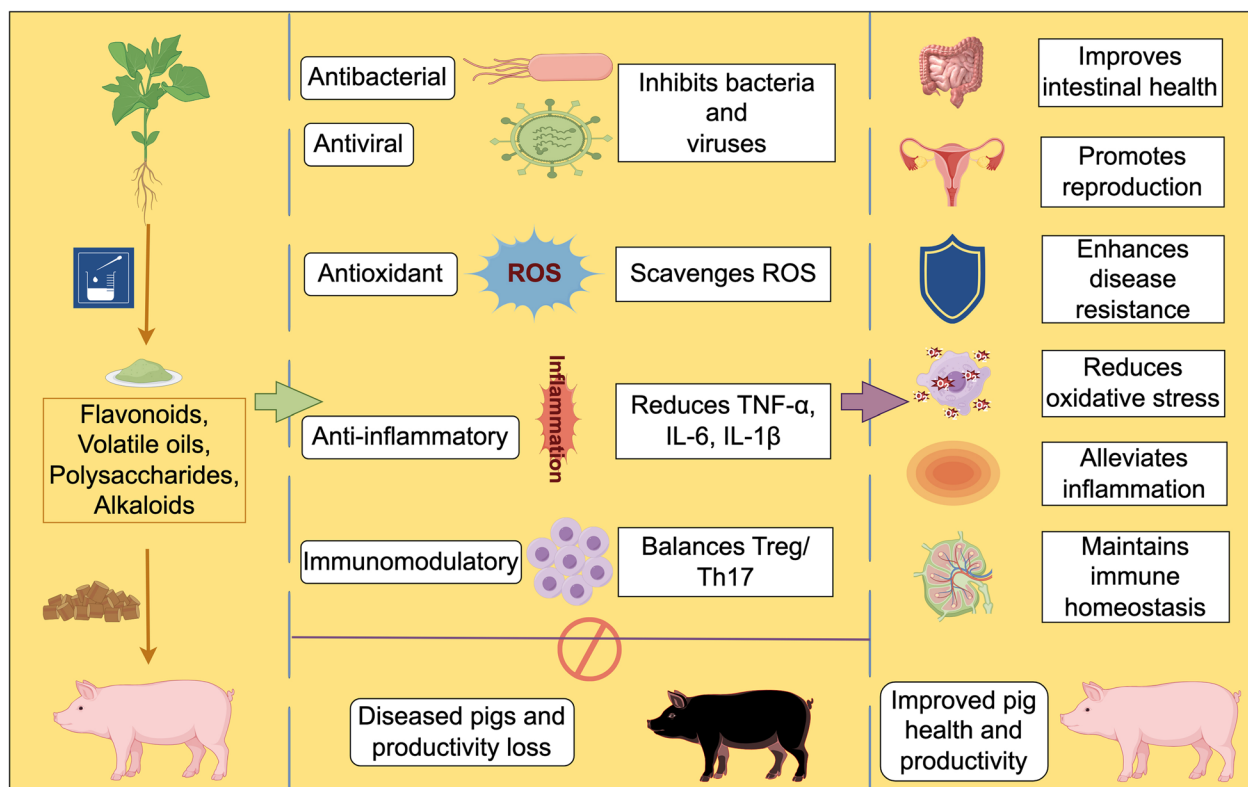


Fig. 4 Multifaceted benefits of *H. cordata* extract in pig health. The bioactive compounds of *H. cordata* extract, including flavonoids, volatile oils, polysaccharides, and alkaloids, exert antibacterial, antiviral, antioxidant, anti-inflammatory, and immunomodulatory effects. These functions inhibit pathogens, reduce ROS, alleviate inflammation, and balance immune responses, enhancing intestinal health, reproductive performance, disease resistance, and overall productivity in pigs. (By Figdraw, ID: IWIP045e7c)

Future research should also explore the potential endocrine effects of flavonoid phytoestrogens (e.g., quercetin) and the impact of aristolochic acid analogs at trace levels (Yu et al. 2022). Combining systems biology with AI-based data integration, such as leveraging large language models (LLMs) for molecular generation, optimization, and target identification, will accelerate the development of *H. cordata*-derived precision therapeutics and functional feed additives (Yang et al. 2025). Furthermore, the application of autonomous AI-driven experimental platforms (e.g., Coscientist, ChemCrow) could streamline compound validation and translation from bench to field (Boiko et al. 2023; Bran et al. 2024).

In addition to identifying active ingredients and assessing genotoxicity in traditional Chinese medicine, compatibility issues must also be considered. Because low-birth-weight piglets often have poor viability or cannot compete for functional teats, quercetin administered during the first 7 d after birth has no positive effect on their survival rate. This highlights the complex, multifactorial origins of preweaning mortality (Van Tichelen et al. 2021). As recently reviewed, the reduced uniformity of litters is due to

uterine capacity limitations and placental insufficiency (Van Tichelen et al. 2021). Given the complex nature of preweaning piglet mortality, researching different doses and compound combinations may help address production challenges. The fermentation of medicinal plants is now broadly acknowledged for its capacity to improve health and disease management. This process can increase flavonoid levels in *H. cordata* preparations and exerts beneficial anti-inflammatory effects on lipopolysaccharide (LPS)-stimulated cells (Utaiwat et al. 2021; Woranam et al. 2020). The extract of *H. cordata* has multiple biological properties, including antioxidant, anti-inflammatory, and antibacterial activities, accompanied by negligible adverse effects. Importantly, a critical advantage over antibiotics is that *H. cordata* extracts do not accumulate residues in milk and cause allergic reactions (Arbab et al. 2022). Nonetheless, the clinical use of *H. cordata* extract faces substantial obstacles, including its limited bioavailability, inadequate stability, and undesirable taste. Notably, most current studies are preclinical (in vitro or rodent models), with limited validation in swine under commercial farming conditions. Additionally, variations in

Table 2 Comparative analysis of *H. cordata* extract with conventional antibiotics and other antibiotic alternatives in pig production

Alternative	Mechanism of action	Key advantages	Key limitations	References
<i>H. cordata</i> Extract	Multitarget: Antimicrobial, antioxidant, anti-inflammatory, immunomodulatory	Broad-spectrum efficacy against bacteria and viruses; enhances host immunity and intestinal health; negligible residue accumulation and no allergic reactions compared to antibiotics; reduces reliance on conventional antibiotics	Dose-dependent cytotoxicity observed at high concentrations (> 250 mg/mL); limited large-scale validation under commercial farming conditions; bioavailability and stability challenges; undesirable taste	Arbab et al. 2022; Kim et al. 2008; Li L et al. 2021; Ren et al. 2011
Conventional Antibiotics	Single-target: Primarily antibacterial	Highly effective against specific bacterial pathogens	Promotes antibiotic resistance development; drug residues in products can disrupt gut flora and cause allergies; public health threat and increasing regulatory restrictions	Li L et al. (Li, et al., 2021)
Probiotics	Modulates gut microbiota, enhances immune function	Improves intestinal health and reduces diarrhea	Efficacy can be strain-specific and variable; may require cold chain for storage, increasing cost; primarily focuses on gut health, less direct antiviral/antibacterial action	Xu et al. 2022a
Organic Acids	Lowers intestinal pH, inhibiting pathogenic bacteria	Low cost and easy to apply	Primarily effective against bacteria, no direct antiviral effect; may negatively affect palatability	Cheng G et al. 2014a; Heo et al. 2013; Seal et al. 2013

extraction methods across studies complicate direct comparisons of efficacy data. Critical limitations persist in translating these findings to commercial production, including the following: 1) most efficacy data derive from rodent models or cell lines (e.g., IPEC-J2, RAW264.7), which may not fully replicate porcine physiological responses under field conditions; 2) current study designs rarely account for large-scale farming variables such as high-density housing and feed variability; and 3) optimal dosing established in controlled trials (e.g., quercetin at 25 mg/kg) may not be economically feasible for commercial herds. Moreover, additional pig models, including different breeds and different growth stages, need to be verified.

To address these gaps, a translational research roadmap from "lab to field" is proposed: (1) Active Compound Identification and Standardization: Purify and quantify key compounds via advanced techniques such as UHPLC-Q/TOF-MS (Yu et al. 2022). (2) Long-term safety and efficacy trials: Large-scale animal studies should be conducted to validate growth performance, immune modulation, and residue kinetics. (3) Formulation innovation: Microencapsulated or sustained-release systems have been developed to increase bioavailability and mask undesirable tastes (Yang et al. 2025). (4) System Biology Integration: Apply multiomics and chemoproteomic approaches (e.g., CETSA, DARTS, ABPP) to uncover host-microbe interactions and metabolic mechanisms (Hu et al. 2024; Kim et al. 2025; Zhang et al. 2025). (5) AI-driven optimization: AI-driven optimization utilizes deep learning models (e.g., transformer-based architectures) for dose-response modeling, target prediction, and synergistic combination screening with probiotics or other botanicals (Yang et al. 2025).

Moreover, *H. cordata* extracts face dual regulatory and commercial challenges. Safety evaluation follows TCM principles requiring efficacy-toxicity balance assessment during prolonged use. Commercialization barriers include developing scalable extraction methods and establishing rigorous safety protocols. Practical limitations involve addressing bioavailability issues through sustained-release formulations and masking bitter taste via microencapsulation. Large-scale trials under commercial farming conditions are needed to confirm the efficacy of these methods. To clarify the competitive advantages of *H. cordata* extract as an antibiotic substitute, a systematic comparison with traditional antibiotics, probiotics, and organic acids (common alternatives in swine husbandry) is provided in Table 2 on the basis of action mechanisms, efficacy, safety, cost, and application scenarios.

Conclusion

Collectively, these findings support *H. cordata* extract as a viable alternative antibiotic with multifaceted benefits. The literature extensively reports the prospective uses of *H. cordata* extract in swine production, including its multifunctional properties, such as antimicrobial, antioxidant, and immunomodulatory activities, while also revealing significant knowledge gaps: tissue-specific effect variations, narrow therapeutic windows, and uncharacterized compound interactions that necessitate caution in application. The present research delineates the chemical components of the extract, the functional pathways affecting pig health, and its production-related advantages. While progress has been made in practical applications, current limitations include insufficient large-scale validation and variable efficacy reporting across studies. Future efforts must prioritize validating long-term safety, optimizing extraction processes, and enhancing bioavailability through advanced delivery systems. Key research gaps include identifying active compounds, evaluating toxicity, and innovating formulations to refine *H. cordata*-based feed additives. As a validated antibiotic alternative, it addresses antimicrobial resistance, oxidative stress, and productivity challenges in pig farming. However, barriers to commercial adoption include the following: 1) limited validation in diverse commercial environments (e.g., varying biosecurity levels, climate stresses); 2) knowledge gaps in residue depletion kinetics during withdrawal periods; and 3) economic constraints in scaling extraction processes. Therefore, commercialization demands scalable extraction methods. Rigorous safety protocols are equally essential. Future work should explore large-scale trials and synergistic probiotic combinations for enhanced efficacy.

Authors' contributions

LLX and LMZ write this manuscript, DHC revised it.

Funding

This study was underpinned by the National Natural Science Foundation of China (No. 32472981, 32172808), the Wuhan University of Bioengineering High-level Talent Research Start-up Fund (2024KQ03), and the open funds of the State Key Laboratory of Agricultural Microbiology (AMLKF202512).

Data availability

As a synthesis of literature, this review article incorporates no novel experimental datasets. All sources referenced are accessible via cited publications.

Declarations

Ethics approval and consent to participate

This manuscript, being a review of prior studies, neither includes nor necessitates original experiments involving humans or animals. Consequently, it does not require ethics approval or participant consent.

Consent for publication

Not applicable.

Competing interests

The authors declare the absence of any monetary or individual associations potentially creating undue bias in this paper.

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Received: 3 April 2025 Accepted: 16 September 2025

Published online: 28 November 2025

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