Postprint: Research on the Application of Artemisia annua in Animal Production

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Abstract

Artemisia annua is a herbaceous plant extensively applied in traditional Chinese medicine, possessing multiple biological activities including anti-inflammatory, antioxidant, antimalarial, anthelmintic, and immunomodulatory effects. Furthermore, Artemisia annua is non-toxic and harmless, and does not induce drug resistance, conferring exceptionally high utilization value in animal production. This review summarizes the physiological functions of bioactive compounds in Artemisia annua and their specific applications in animal production, providing a reference for further research on Artemisia annua.

Full Text

Study on Application of Artemisia annua L. in Animal Production

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Abstract: Artemisia annua L. is an herbaceous plant that has been widely used in traditional Chinese medicine and exhibits multiple biological activities, including anti-inflammatory, antioxidant, anti-malarial, anthelmintic, and immunomodulatory effects. Additionally, due to its non-toxic, harmless, and non-resistance-inducing properties, it holds extremely high utilization value in animal production. This review summarizes the physiological functions of bioactive substances in Artemisia annua L. and their specific applications in animal production, providing references for further research.

Keywords: Artemisia annua L.; biological activity; animal production; application research

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Artemisia annua L. is an annual herbaceous plant belonging to the Asteraceae family and Artemisia genus, also known as sweet wormwood, fragrant artemisia, or yellow artemisia. It exhibits extremely strong adaptability and is widely distributed across North America, Europe, Africa, and Asia, with 70% of global resources concentrated in China. The aerial parts of Artemisia annua L. have been used medicinally for their cold nature and bitter, pungent taste, possessing heat-clearing, detoxifying, and anti-malarial effects, and serving as a traditional anti-malarial drug in China [**?**]. It is used to treat symptoms such as summer-heat fever, yin-deficiency fever, night fever with morning coolness, bone-steaming consumptive fever, malarial chills and fever, and damp-heat jaundice, and can be applied externally to treat mosquito bites, sores, and burns [**?**]. These therapeutic properties are primarily attributed to its bioactive components, including sesquiterpenoids (artemisinin), flavonoids, polysaccharides, coumarins, volatile oils, and phenolic compounds. These bioactive substances demonstrate anti-malarial [**?**, **?**], anti-cancer [**?**], anti-inflammatory [**?**], antimicrobial [**?**, **?**, **?**], anti-tumor [**?**], and antioxidant [**?**, **?**, **?**, **?**] effects, as well as strong immunological activity [**?**]. Based on these diverse biological functions, numerous studies have investigated the effects of dietary supplementation with Artemisia annua L. and its extracts in animals.

1 Application of Artemisia annua L. in Rodents

Research using rodent models to study Artemisia annua L. has been relatively extensive. Toxicological studies have found that Artemisia annua L. is nontoxic and harmless within certain dosage ranges [**?**]. In toxicology experiments conducted on Kunming mice and Wistar rats, Artemisia annua extract was administered via gavage at doses of 10,100, 8,000, 6,000, 5,000, and 4,120 mg/kg. The results showed that mice exhibited no obvious signs of poisoning and maintained normal vital signs. However, in rats, toxic symptoms gradually intensified with increasing doses, and at 10,100 mg/kg, rats exhibited tremors, tonic-clonic convulsions, opisthotonus, and death. The median lethal dose (LD50) for Wistar rats was 7,360 mg/kg, with a 95% confidence interval of 6,256.38–8,658.82 mg/kg.

In a study where Artemisia annua powder was used to replace part of the conventional grass meal in rabbit diets, the powder improved rabbit growth performance and feed conversion efficiency [**?**]. Artemisia annua extract also promoted growth in young rex rabbits, significantly increasing average daily gain, reducing feed-to-gain ratio, and decreasing spleen index [**?**]. Furthermore, research revealed that Artemisia annua extract could relax mouse tracheal smooth muscle by blocking L-type calcium channel currents and inhibiting extracellular calcium influx and intracellular calcium release induced by high potassium and acetylcholine (ACh). By inhibiting calcium influx through calcium channels

and other ion channels activated by ACh, the extract demonstrated potential therapeutic effects for asthma [**?**].

Artemisia annua polysaccharides exhibit strong anti-inflammatory activity [**?**] and can regulate four cytokines in mouse serum: interleukin-1, interleukin-2, interleukin-6, and interferon [**?**]. Moreover, Artemisia annua polysaccharides can alleviate cyclophosphamide (CTX)-induced immunosuppression [**?**], relieve spleen atrophy and decreased lysozyme levels caused by CTX, enlarge splenic nodules, increase lymphocyte numbers, and enhance lymphocyte populations in the thymus [**?**].

Studies in rats demonstrated that artesunate, a derivative of the active component artemisinin from Artemisia annua, could alleviate early brain injury and improve neurological function in a rat model of subarachnoid hemorrhage by reducing brain edema index and blood-brain barrier permeability, and preventing the downregulation of endothelial tight junction proteins Occludin and ZO-1 [**?**]. Additionally, artesunate was found to alleviate hepatic steatosis in non-alcoholic fatty liver disease (NAFLD) mice by reducing serum triglyceride and total cholesterol levels, alanine aminotransferase activity, and the expression of Toll-like receptor 4 (TLR4), myeloid differentiation factor 88 (MyD88), and phosphatidylinositol-3 kinase in liver tissue [**?**].

Currently, research on the mechanisms of action of Artemisia annua L. and its derivatives in rodents remains in its preliminary stages and requires further investigation. Bai et al. [**?**] found that TLR4 is an important factor in innate immunity, widely distributed in immune and non-immune cells. In NAFLD mouse experiments, TLR4 expression was elevated, and activated TLR4 promoted the release of various inflammatory factors such as tumor necrosis factor- (TNF-) and interleukin-6 by activating and regulating nuclear factor- B (NF- B), triggering strong inflammatory responses. This suggests that the TLR4 inflammatory pathway is involved in NAFLD pathogenesis. Furthermore, in TLR4/MyD88 signaling pathway-mediated macrophage inflammatory responses, the downstream phosphatidylinositol-3 kinase/serine-threonine protein kinase signaling pathway also plays an important role [**?**]. Artesunate, an artemisinin derivative from Artemisia annua, can reduce NF- B and TNF- production, thereby exerting anti-inflammatory effects and alleviating liver tissue damage caused by NAFLD in mice [**?**].

In summary, Artemisia annua L. and its derivatives are non-toxic within certain dosage ranges. Artemisia annua powder can promote rabbit growth, while its extract can relax mouse smooth muscle, showing potential for asthma treatment, promote growth in young rabbits, and reduce spleen index in rex rabbits. Artemisia annua polysaccharides demonstrate strong anti-inflammatory activity in mice and rats, regulate immune function, alleviate hepatic steatosis, reduce blood lipids, and promote neurological function.

2 Application of Artemisia annua L. in Poultry Production

The application of Artemisia annua L. in poultry production has primarily focused on growth performance, serum biochemical indices, liver function, intestinal mucosal morphology, digestive enzyme activity, immunity, antioxidant capacity, anti-coccidial function, and meat quality in broiler chickens. Studies have found that dietary supplementation with enzyme-treated Artemisia annua L. can alleviate growth performance inhibition caused by heat stress in broilers [**?**, **?**] and improve apparent utilization rates of dietary crude fat, crude protein, and organic matter [**?**]. Additionally, enzyme-treated Artemisia annua L. supplementation increased trypsin and amylase activities in jejunal mucosa [**?**] and enhanced maltase, sucrase activities in jejunal and ileal mucosa, as well as lactase activity in ileal mucosa [**?**], thereby mitigating the adverse effects of heat stress on nutrient apparent utilization and disaccharidase activity in intestinal mucosa and improving intestinal mucosal morphology [**?**].

Dietary supplementation with Artemisia annua L. leaf powder and extract significantly improved both cellular and humoral immune function [**?**] and increased thymus and bursa weights in broilers [**?**]. Wan et al. [**?**] found that dietary enzymatically treated Artemisia annua L. improved meat quality, antioxidant activity, and breast muscle energy status in heat-stressed broilers, possibly by altering mRNA expression of related proteins including actin, heat shock protein 70, heat shock protein 90, avian uncoupling protein (avUCP), and sirtuin 1. Furthermore, dietary supplementation with enzymatically treated Artemisia annua L. (0.75–1.25 g/kg) promoted neuroendocrine system, liver function, and antioxidant capacity in heat-stressed broilers [**?**], alleviated liver oxidative damage [**?**], and improved meat quality and oxidative stability of breast and thigh muscles [**?**].

In experiments with yellow-feathered broilers infected with Eimeria tenella, compared with the control group, all Artemisia annua powder groups showed reduced apparent lesions and histopathological changes, with the powder alleviating swelling and hemorrhage in the cecum and improving the mental state of infected chickens. These results indicate that Artemisia annua powder can alleviate cecal pathological symptoms and tissue lesions caused by Eimeria tenella infection, reduce oocyst excretion, and demonstrate good anti-coccidial effects [**?**]. Comprehensive evaluation based on clinical manifestations, fecal oocyst counts, body weight, cecal lesion scores, packed cell volume, and hemoglobin values revealed that Artemisia annua leaf extract treatment was most effective, reducing fecal oocysts by 74.18%. Both Artemisia annua leaf extract and its active component artemisinin significantly reduced cecal lesion scores [**?**]. Additionally, Guo et al. [**?**] evaluated the anti-coccidial effects of artemisinin and Artemisia annua aqueous extract by adding the aqueous extract to drinking water and artemisinin to feed, finding that both reduced serum nitric oxide and nitric oxide synthase levels, indicating significant anti-Eimeria tenella effects [**?**].

Reports on the mechanisms of Artemisia annua L. and its derivatives in broilers are limited, with scholars having conducted only preliminary investigations. Nuclear factor E2-related factor 2 (Nrf2) is a basic leucine zipper transcription factor that protects cells from oxidative stress and improves cellular antioxidant defense systems by mediating Phase II enzymes through antioxidant response elements, including heme oxygenase-1 (HO-1), glutathione peroxidase (GSH-Px), glutamate-cysteine ligase catalytic subunit (-GCLc), glutamate-cysteine ligase modifier subunit (-GCLm), and superoxide dismutase (SOD) [**?**]. Studies have shown that upregulated HO-1 activity can protect cells from oxidative damage [**?**]. Glutamate-cysteine ligase catalyzes the rate-limiting step in glutathione (GSH) biosynthesis and is a heterodimer composed of catalytic subunit -GCLc and modifier subunit -GCLm [**?**]. Artemisia annua extract supplementation increased gene expression of Nrf2, HO-1, GSH-Px, SOD1, -GCLc, and -GCLm in broilers, alleviating oxidative damage by antagonizing mRNA expression of the Nrf2 antioxidant system [**?**].

In summary, Artemisia annua L. and its extracts can improve intestinal mucosal morphology and digestive enzyme activity, thereby increasing apparent metabolic rate and promoting growth in broilers. Additionally, they demonstrate strong promoting effects on immunity, antioxidant capacity, anti-coccidial activity, and meat quality improvement [**?**].

3 Application of Artemisia annua L. in Swine Production

Research on Artemisia annua L. in swine production is relatively limited, primarily focusing on effects on semen volume in breeding boars, growth performance and diarrhea rates in weaned piglets and growing pigs. Dietary supplementation with Artemisia annua powder increased semen volume and sperm viability in breeding boars, with an optimal dosage of 20 g per head per day [**?**]. Additionally, active components of Artemisia annua L. positively affected production and immune performance in weaned piglets and growing pigs. Studies found that dietary Artemisia annua extract supplementation increased average daily gain and average daily feed intake while reducing feed-to-gain ratio and diarrhea rates in weaned piglets. Similar effects were observed when two types of Artemisia annua active extracts were used as feed additives in growing pigs. These findings indicate that Artemisia annua active extracts can promote growth, reduce disease incidence, improve production performance and feed conversion efficiency, and enhance immune function and serum levels of insulin, urea nitrogen, free triiodothyronine, and free thyroxine in weaned piglets [**?**]. Research also demonstrated that Artemisia annua extract has blocking, inhibitory, and direct killing effects against porcine reproductive and respiratory syndrome virus [**?**]. Clinical treatment trials involving oral administration of Artemisia annua extract to Landrace pigs showed that infection rates of Eperythrozoon suis significantly decreased from 81% to 2%, indicating good therapeutic effects against porcine eperythrozoonosis [**?**].

Mechanistic studies on Artemisia annua L. in swine production have shown

that in high-temperature environments, elevated scrotal and testicular tissue temperatures in boars are detrimental to sperm survival, causing testicular dysfunction and affecting the positive feedback regulation of the hypothalamic-pituitary-testicular axis [**?**], thereby impairing spermatogenesis, reducing semen volume, and decreasing semen quality. Artemisia annua L. has heat-clearing and summerheat-relieving effects [**?**], which can alleviate adverse functional responses in boars under high-temperature conditions and improve semen quality [**?**]. The mechanisms by which Artemisia annua extract promotes growth performance in piglets and growing pigs remain unclear, but existing reports suggest that the extract reduces diarrhea and improves intestinal environment, thereby promoting growth [**?**], possibly due to its antibacterial and bacteriostatic effects [**?**, **?**]. Furthermore, this natural plant contains various amino acids, minerals, vitamins, and other unknown growth-promoting factors [**?**] that promote animal growth.

In conclusion, Artemisia annua L. can improve growth performance and feed conversion efficiency in weaned piglets and growing pigs, reduce diarrhea rates, and demonstrate positive effects on disease treatment.

4 Application of Artemisia annua L. in Ruminant Production

Research on Artemisia annua L. in ruminants has primarily focused on rumen fermentation and milk production performance. Studies found that Artemisia annua ethanol extract did not affect dairy cow milk performance [**?**] but increased conjugated linoleic acid (CLA) content in milk fat, thereby optimizing fatty acid composition [**?**]. In dairy goat experiments, Artemisia annua extract increased t11C18:1, CLA, and c9C18:1 contents while decreasing C18:2 content in blood from the external pudendal artery and mammary vein [**?**]. In vitro culture studies investigating the effects of Artemisia annua extract on goat rumen fermentation and methane production revealed that supplementation at 5 g/kg reduced the acetate/propionate ratio and could replace 15 mg/kg monensin to decrease methane production during rumen fermentation [**?**].

Two mechanisms have been proposed to explain how Artemisia annua extract increases CLA content in goat milk fat. The first is the substrate effect: Asteraceae plants contain high levels of linoleic acid, which undergoes biohydrogenation in the rumen to produce CLA and t11C18:1 fatty acids. These fatty acids reach the mammary gland and are further converted to CLA through desaturation, thereby increasing milk CLA content [**?**]. The second is the antimicrobial effect: active components in Asteraceae plants inhibit Group B bacteria in the rumen, which are responsible for converting unsaturated fatty acids to saturated fatty acids. Inhibiting Group B bacteria subsequently prevents the conversion of CLA and fatty acids to stearic acid, thus increasing milk CLA content [**?**].

Overall, Artemisia annua L. shows no significant effects on milk production performance in dairy cows and goats but has positive effects on milk fat composition

and can reduce rumen methane production.

5 Application of Artemisia annua L. in Aquaculture

Research in aquaculture has primarily investigated the effects of Artemisia annua L. and its extracts on fish intestinal digestive enzymes, blood biochemical indices, and ectoparasites. Experiments using Artemisia annua ethanol extract, artemisinin, and artemisinin derivatives to remove one-week-old monogenean parasites (Heterobranchus longifilis) from fish body surfaces and gills demonstrated that these substances could cause parasite detachment and even death, with effects positively correlated with concentration and duration [**?**]. Dietary supplementation with Artemisia annua extract in rice field eels increased intestinal digestive enzyme activity, blood aspartate aminotransferase and alanine aminotransferase activities, and serum total protein content while decreasing blood glucose and triglyceride levels [**?**].

Preliminary mechanistic investigations in aquatic animals have also been conducted. Dietary Artemisia annua extract supplementation reduced serum total cholesterol and triglyceride levels in fish [**?**], possibly due to hepatoprotective and liver function-enhancing effects that accelerate excretion and reduce lipid absorption, or through increased lecithin-cholesterol acyltransferase activity that accelerates cholesterol decomposition and transport. However, the specific mechanisms of Artemisia annua extract in fish production require further in-depth investigation.

In summary, Artemisia annua extract as a feed additive in aquaculture can significantly improve intestinal digestive enzyme activity in rice field eels, regulate blood biochemical indices, and promote digestion, metabolism, and growth [**?**].

6 Conclusion

As a natural plant rich in various bioactive components, Artemisia annua L. is safe and pollution-free, making it a research hotspot in related fields both domestically and internationally. Application studies in rodent models, poultry, swine, ruminants, and aquatic animals have demonstrated that dietary supplementation with appropriate amounts of Artemisia annua extract can promote animal growth, regulate immune function, improve antioxidant capacity, enhance intestinal digestive enzyme activity, and strengthen disease resistance. Simultaneously, it can alleviate liver damage, exert anti-inflammatory effects, and improve animal production performance. However, current research on the mechanisms of Artemisia annua L. in animal production remains in its preliminary stages, with specific pathways yet to be clearly defined and requiring further in-depth investigation. Moreover, based on its unique biologically active substances, Artemisia annua L. has broad application prospects in animal production across multiple research domains.

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