Effects of Artemisia ordosica on Animal Immune and Antioxidant Functions and Its Mechanisms: Postprint

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Abstract

Artemisia ordosica contains various active constituents, including polysaccharides, organic acids, glycosides, and flavonoids, which exhibit certain effects in immunomodulation, antioxidation, and growth promotion. In recent years, reports on Artemisia ordosica, particularly its extract as a feed additive for promoting animal health and growth, have been increasing. This paper primarily reviews the research progress on the effects of Artemisia ordosica on animal immune and antioxidant functions and their underlying mechanisms, providing a reference for further investigation into the regulatory mechanisms of Artemisia ordosica on animal immune and antioxidant functions.

Full Text

Artemisia ordosica Affect Immune and Antioxidative Function of Animals and Its Mechanism

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Abstract

Artemisia ordosica contains various bioactive components including polysaccharides, organic acids, glycosides, and flavonoids, which play important roles in immune regulation, antioxidation, and growth promotion. In recent years, increasing numbers of reports have described the use of Artemisia ordosica, particularly its extracts as feed additives, to promote animal health and growth performance. This review summarizes research progress on the effects of Artemisia ordosica on animal immune and antioxidative functions and their underlying

mechanisms, providing a reference for further investigation into the regulatory mechanisms of Artemisia ordosica on these functions.

Keywords: immunity; antioxidation; Artemisia ordosica; Artemisia ordosica extract

Artemisia ordosica, also known as oil wormwood, seed wormwood, Ordos wormwood, or "Hala-Shabaga" in Mongolian, is widely distributed in northwestern China, particularly in Inner Mongolia and Shaanxi provinces, with a cultivation area exceeding 370,000 mu [1]. This common Asteraceae species exhibits excellent windbreak and sand-fixation properties. Artemisia ordosica has a long history of medicinal application, demonstrating anti-inflammatory, swelling-reducing, chest-widening, qi-regulating, and hemostatic effects [2], along with insecticidal activity in agriculture [3]. Due to its rich content of crude protein, fat, vitamins, and trace elements, Artemisia ordosica also holds an important position in animal husbandry. Research indicates that its bioactive components primarily include polysaccharides, flavonoids, volatile oils, and triterpenoids [4], which can enhance animal immunity, improve antioxidative function, and thereby promote animal growth [5-9]. This review primarily elaborates on research progress regarding the effects of Artemisia ordosica, especially its extracts, on animal immune and antioxidative functions and the associated mechanisms, providing references for further study of its regulatory mechanisms.

1 Effects of Artemisia ordosica on Animal Immune Function and Its Mechanisms

The bioactive components of Artemisia ordosica mainly include polysaccharides, organic acids, glycosides, and flavonoids. Studies have shown that polysaccharide compounds can effectively regulate immune function, while organic acids and glycosides can enhance the phagocytic activity of macrophages and the reticuloendothelial system [10], and flavonoids can inhibit nitric oxide (NO) production in the body [4]. Initial research by Liu Xiaojing [5] investigated the effects of dietary supplementation with Artemisia sphaerocephala seed powder on broiler immune function, finding that it significantly increased serum levels of soluble CD4 antigen (sCD4) and immunoglobulin G (IgG). Subsequent researchers conducted more intensive studies using aqueous extracts of Artemisia ordosica in both in vivo and in vitro experiments, revealing that appropriate doses added to the diet promoted immune organ development in broiler chickens while significantly increasing serum IgG and immunoglobulin M (IgM) content [6]. The extracts also elevated serum Newcastle disease antibody titers, NO and inducible nitric oxide synthase (iNOS) levels, and iNOS gene expression in tissues, indicating enhanced immune performance in broilers [7]. Additionally, Artemisia ordosica aqueous extract reduced elevations in serum tumor necrosis factor- (TNF-), interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), immunoglobulin A (IgA), IgG, and NO content, as well as iNOS activity induced by bacterial lipopolysaccharide (LPS), thereby exert-

ing anti-inflammatory and immunomodulatory effects [8]. Furthermore, studies using rodent models demonstrated that Artemisia ordosica aqueous extract could also increase serum IgM, IgG, and IL-1 levels in mice [9].

In recent years, Artemisia sphaerocephala polysaccharide has attracted increasing attention due to its promotion of immune cell growth and regulation of immune function. Researchers isolated and purified polysaccharides from Artemisia sphaerocephala seeds and added them to mouse spleen cell cultures under concanavalin A stimulation, finding that appropriate doses promoted spleen cell proliferation [11-12]. Zhang Jing [13] added Artemisia sphaerocephala polysaccharide to natural killer (NK) cells and peripheral blood mononuclear cells (PBMC) in vitro, observing that both PBMC and NK cell proliferation rates initially increased then decreased with increasing polysaccharide dosage. These findings indicate that Artemisia sphaerocephala polysaccharide can regulate immune cells in vitro and enhance their immune capacity. Subsequent studies further investigated its effects on animal immune function in vivo, demonstrating that dietary supplementation promoted immune organ development, enhanced immunity, improved animal growth performance, and facilitated the generation and activation of T and B lymphocytes [14] while increasing serum IgA content [10].

In actual animal production environments, various pathogens (bacteria, viruses, endotoxins) and non-pathogens can disrupt homeostasis. When homeostasis is disturbed, animals often exhibit depression, loss of appetite, fatigue, and retarded or stagnant growth, leading to more severe immune stress [15]. The nuclear transcription factor-kappa B (NF- B) pathway is crucial for immune regulation, serving as an important signaling pathway controlling immune-related gene expression and regulating the production and release of pro-inflammatory factors such as IL-1, IL-6, and TNF- . NF- B can be activated by various cell surface receptors through external signals, with the two most widespread activation pathways being the myeloid differentiation factor 88 (MyD88)-dependent and MyD88-independent pathways. Studies have shown that artemisinin (an extract of Artemisia annua) can effectively prevent the degradation of NF- B inhibitors and NF- B nuclear translocation induced by LPS, IL-1, interferon- (IFN-), and TNF- mixed factors [16-17], thereby inhibiting NF- B activity. These results suggest that the molecular mechanism of anti-inflammatory and immunosuppressive effects of Artemisia plants is closely related to NF- B activity inhibition. Therefore, research on the NF- B signaling pathway mechanism is of important academic value for revealing mechanisms that alleviate animal immune stress mediated by LPS and other factors. Studies have found that continuous intraperitoneal injection of LPS solution in broiler chickens activated the NF- B signaling pathway, causing significant upregulation of downstream inflammation-related genes including IL-1 , IL-6, TNF- , and iNOS mRNA levels, while dietary supplementation with Artemisia ordosica aqueous extract effectively alleviated this LPS-induced upregulation of inflammatory gene expression, suggesting that the NF- B signaling pathway is one of the pathways through which Artemisia ordosica aqueous extract regulates immune response

[8]. Additionally, dietary supplementation increased serum NO and iNOS content and iNOS gene expression in liver and intestine [7], indicating that the extract promotes NO generation by activating iNOS gene expression. As an important signaling molecule, NO plays a vital role in regulating immune function, and the regulatory effects of Artemisia ordosica aqueous extract on broiler cytokines may be achieved through modulation of the NO pathway. Besides NF- B and NO signaling pathways, other immune-related signaling transduction pathways include mitogen-activated protein kinase (MAPK) and Kelch-like ECH-associated protein 1-nuclear factor E2-related factor 2-antioxidant response element (Keap1-Nrf2-ARE) signaling pathways [18], though the specific mechanisms of Artemisia ordosica effects on these pathways require further investigation.

2 Effects of Artemisia ordosica on Animal Antioxidative Function and Its Mechanisms

During normal growth and metabolism, organisms produce reactive oxygen species (ROS) that can damage biological macromolecules, destroy cell structure and function, and impair lipids, proteins, and nucleic acids if not promptly eliminated, leading to metabolic disorders. Liu Xiaojing [5] added appropriate doses of Artemisia sphaerocephala seed powder to broiler diets and collected blood via jugular vein after 21 days of feeding to investigate effects on serum antioxidant enzymes, finding that the powder significantly increased catalase (CAT) activity. Similar findings were observed in rodents, where dietary supplementation with Artemisia ordosica aqueous extract enhanced total superoxide dismutase (T-SOD) and glutathione peroxidase (GSH-Px) activities and total antioxidant capacity (T-AOC) in serum and tissues while reducing malondialdehyde (MDA) content [7]. Under conventional rearing conditions, appropriate dietary supplementation with Artemisia ordosica aqueous extract increased antioxidant enzyme activities in serum and tissues and promoted expression of related antioxidant enzyme genes [5]. Li Kun [8] established an immune stress model in broilers through intraperitoneal LPS injection and found that dietary supplementation with Artemisia ordosica aqueous extract increased serum CAT and GSH-Px activities, decreased serum MDA content, and promoted gene expression of CAT, superoxide dismutase (SOD), and GSH-Px in broiler tissues, indicating that the extract alleviates LPS-induced immune stress by improving antioxidative function. Artemisia ordosica contains various bioactive components with antioxidant functions, such as polysaccharides, flavonoids, organic acids, and vitamin E, which likely form the basis of its antioxidant activity by directly or indirectly scavenging generated free radicals or inhibiting excessive free radical production, ultimately reducing free radical accumulation and promoting antioxidative function. However, current studies have not identified the specific components of Artemisia ordosica aqueous extract, and its exact composition and antioxidant mechanisms require further investigation.

Studies using diabetic rats as models found that oral administration of

Artemisia sphaerocephala polysaccharide significantly increased serum insulin content while decreasing glucagon levels, promoted conversion of glucose to hepatic glycogen, and facilitated repair of damaged pancreatic islet cells [19]. The polysaccharide also increased SOD activity and decreased MDA content in heart, liver, and kidney tissues [20], enhanced SOD activity in serum and liver tissue, and significantly reduced hydroxyl radical (· OH) and MDA content [21]. These findings demonstrate that Artemisia sphaerocephala polysaccharide can enhance animal antioxidant capacity. Li Juan [14] isolated and purified a polysaccharide component ASP- from Artemisia sphaerocephala polysaccharide and investigated its antioxidant capacity, finding that it could scavenge free radicals such as diphenylpicrylhydrazyl (DPPH), · OH, and superoxide anion radicals (O), with scavenging capacity comparable to mannitol. Similar results were reported by Li Shengli [10] in sheep, where dietary supplementation with Artemisia sphaerocephala polysaccharide significantly increased serum SOD and CAT activities while decreasing MDA content and improving T-AOC. These studies indicate that Artemisia ordosica and its main active component polysaccharide possess significant antioxidant effects, reducing ROS production while enhancing activity of major antioxidant enzymes and improving ROS scavenging capacity. Recent research on Artemisia ordosica polysaccharide antioxidant activity has focused primarily on in vitro antioxidant activity and structure-activity relationships, with fewer and inconsistent results from animal experiments, particularly in animal production applications, necessitating more in-depth and extensive research.

The immune and antioxidant systems are closely linked and mutually influential. When immune stress occurs, the antioxidant system becomes imbalanced, leading to oxidative stress, with the NF- B signaling pathway serving as a crucial hub connecting these two systems [22]. LPS can regulate downstream target genes while activating the NF- B pathway, causing massive ROS production and release [23]. Under normal physiological conditions, ROS are products of cellular metabolism, and their levels directly reflect the oxidative status. Excessive ROS can activate the NF- B pathway [24] while also resisting external stimuli through activation of the Keap1-Nrf2-ARE signaling pathway to inhibit or reduce cellular oxidative damage and enhance antioxidant capacity [25-26]. Studies have shown that Artemisia ordosica aqueous extract can enhance antioxidant enzyme activity, effectively scavenge ROS, and inhibit NF- B activation, thereby reducing expression of inflammatory cytokines such as IL-1 , IL-6, and TNF- , which may represent one pathway through which the extract alleviates oxidative damage [8]. The Nrf2-ARE signaling pathway is the primary pathway protecting cells from exogenous stimuli and oxidative damage, regulating antioxidant function by controlling downstream phase II detoxifying enzymes and antioxidant genes including heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO-1), glutamate-cysteine ligase catalytic subunit (GCLC), glutamate-cysteine ligase modifier subunit (GCLM), SOD, CAT, and glutathione S-transferase (GST) [27]. Additionally, the Nrf2-ARE pathway can exert anti-inflammatory effects by recruiting inflammatory cells and regulating

anti-inflammatory gene expression to block inflammatory responses [28]. Li Kun [8] reported that LPS injection significantly decreased gene expression of CAT, SOD, and GSH-Px in broiler tissues, indicating that LPS stimulation inhibited antioxidant enzyme expression and reduced antioxidant capacity, while dietary supplementation with Artemisia ordosica aqueous extract increased gene expression of these enzymes in broiler tissues and antioxidant enzyme activity in serum. However, whether this effect is mediated through regulation of the Nrf2-ARE pathway in vivo requires further verification. As previously mentioned, both NF- B and Nrf2-ARE signaling pathways may participate in regulating oxidative damage by Artemisia ordosica extract and jointly function in redox regulation. Whether the antioxidant regulatory effects of Artemisia ordosica extract are accomplished through these two pathways separately or through some synergistic or antagonistic mechanisms remains unclear, as few studies have addressed this question. Therefore, whether common pathways or intersection points exist in the regulation of immunity and antioxidation by Artemisia ordosica extract represents an important research direction.

3 Summary

In intensive and large-scale livestock production, animals experience various stressors during growth and production that directly or indirectly alter immune status and induce immune stress. Artemisia ordosica contains multiple bioactive substances, among which immune-active compounds are the most important, capable of improving immune function and antioxidant capacity, thereby enhancing disease resistance and stress tolerance and improving animal production performance. Therefore, dietary supplementation with Artemisia ordosica or its extracts to regulate immune stress and antioxidant capacity represents a feasible approach to alleviate negative effects caused by stress. However, to date, the application effects of Artemisia ordosica and its extracts as feed additives in animal production and the specific mechanisms underlying their therapeutic and preventive roles in immune stress-induced damage remain unclear and require further in-depth investigation.

References

[1] Zhao Y. Excellent characteristics and utilization of Artemisia ordosica[J]. China Forestry, 2011(17):45.
[2] Jiangsu New Medical College. Dictionary of Chinese Medicine: Volume 2[M]. Shanghai: Shanghai Scientific and Technical Publishers, 1997:3333.
[3] Liu C R. Biological activity of Artemisia ordosica extract against Mythimna separata and preliminary separation of active components[D]. Master' s thesis. Lanzhou: Gansu Agricultural University, 2007.
[4] Zhong Y, Feng X S, Liu Y R. Chemical constituents and biological activities of Artemisia ordosica[J]. Chemistry and Bioengineering, 2016, 33(3):36-38.
[5] Liu X J. Effects of Artemisia sphaerocephala seed on growth, immunity and intestinal indices in broilers[D]. Master' s thesis. Hohhot: Inner Mongolia

Agricultural University, 2011.
[6] Yue Y X. Effects of Artemisia ordosica aqueous extract on growth performance and immune function in broilers[D]. Master' s thesis. Hohhot: Inner Mongolia Agricultural University, 2016.
[7] Tong M M. Effects of Artemisia ordosica aqueous extract on antioxidant and immune function and related gene expression in broilers[D]. Master' s thesis. Hohhot: Inner Mongolia Agricultural University, 2017.
[8] Li K. Effects of Artemisia ordosica aqueous extract on immune and antioxidant function and its mechanism in LPS-challenged broilers[D]. PhD thesis. Hohhot: Inner Mongolia Agricultural University, 2017.
[9] Qin Z. Effects of Artemisia ordosica aqueous extract on growth performance, immune and antioxidant function and its toxicology in mice[D]. Master' s thesis. Hohhot: Inner Mongolia Agricultural University, 2017.
[10] Li S L. Effects of quorum quenching enzyme and Artemisia sphaerocephala polysaccharide on rumen microecology, nutrient metabolism and immunity in sheep[D]. PhD thesis. Hohhot: Inner Mongolia Agricultural University, 2016.
[11] Sun X. Isolation and purification of water-soluble polysaccharide from Artemisia sphaerocephala seed and study on structure and activity of component ASP-A[D]. Master' s thesis. Xi' an: Northwest University, 2008.
[12] Hao Y Q, Sun X, Huang L J, et al. Isolation, purification and immune activity of two water-soluble gum polysaccharides from Artemisia sphaerocephala seed[J]. Food Science, 2009, 30(7):11–14.
[13] Zhang J. Effects of Artemisia sphaerocephala gum polysaccharide on immune cells and on physiology and intestinal flora of HFA mice[D]. Master' s thesis. Yangling: Northwest A&F University, 2015.
[14] Li J. Study on contents of Artemisia sphaerocephala seed, purification of its polysaccharide and structure and antioxidant activity of ASP-1[D]. Master' s thesis. Beijing: Beijing Forestry University, 2016.
[15] JOHNSON R W. Inhibition of growth by pro-inflammatory cytokines: an integrated view[J]. Journal of Animal Science, 1997, 75(5):1244–1255.
[16] ALDIERI E, ATRAGENE D, BERGANDI L, et al. Artemisinin inhibits inducible nitric oxide synthase and nuclear factor NF- B activation[J]. FEBS Letters, 2003, 552(2/3):141–144.
[17] LI W D, DONG Y J, TU Y Y, et al. Dihydroarteannuin ameliorates lupus symptom of BXSB mice by inhibiting production of TNF-alpha and blocking the signaling pathway NF-kappa B translocation[J]. International Immunopharmacology, 2006, 6(8):1243–1250.
[18] Qi X L. Effects of conjugated linoleic acid on antioxidant function in laying hens[D]. PhD thesis. Beijing: Chinese Academy of Agricultural Sciences, 2013.
[19] Zhang J. Structure and hypoglycemic activity of Artemisia sphaerocephala polysaccharide[D]. PhD thesis. Lanzhou: Northwest Normal University, 2005.
[20] Huang Y L. Hypoglycemic effect of Artemisia sphaerocephala polysaccharide[D]. Master' s thesis. Lanzhou: Northwest Normal University, 2006.
[21] Xing X H. Functional characteristics of Artemisia sphaerocephala gum and its effect on alleviating type II diabetes[D]. Master' s thesis. Yangling: Northwest A&F University, 2008.

[22] Li H Y, Zhong R Z, Fang Y, et al. Research progress on oxidative stress and immunity in animals[J]. Chinese Journal of Animal Nutrition, 2014, 26(11):3217-3221.
[23] OGANDO D G, PAZ D, CELIA M, et al. The fundamental role of increased production of nitric oxide lipopolysaccharide–induced embryonic resorption mice[J]. Reproduction, 2003, 125(1):95-110.
[24] REIMUND J M, HIRTH C, KOEHL C, et al. Antioxidant and immune status in active Crohn' s disease: a possible relationship[J]. Clinical Nutrition, 2000, 19(1):43-48.
[25] KIM K C, KANG K A, RUI Z, et al. Up-regulation of Nrf2-mediated heme oxygenase-1 expression eckol, a phlorotannin compound, through activation of Erk PI3K/Akt[J]. International Journal of Biochemistry & Cell Biology, 2010, 42(2):297-305.
[26] SIES H, BERNDT C, JONES D P. Oxidative stress[J]. Annual Review Biochemistry, 2017, 86(1):715-748.
[27] RAMOUS-GOMEZ M, KWAK M K, DOLAN P M, et al. Sensitivity to carcinogenesis is increased and chemoprotective efficacy of enzyme inducers is lost in Nrf2 transcription factor-deficient mice[J]. Proceedings of the National Academy of Sciences of the United States of America, 2001, 98(6):3410-3415.
[28] AHMED S M U, LUO L, NAMANI A, et al. Nrf2 signaling pathway: pivotal roles in inflammation[J]. Biochimica Biophysica Acta: Molecular Basis Disease, 2017, 1863(2):585-597.

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