Echinacea and Its Extracts Modulate Animal Immune Function and Their Mechanism of Action: Postprint

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Abstract

In recent years, numerous in vivo and in vitro studies have demonstrated that Echinacea and its extracts can enhance immune function, thereby exerting anti-inflammatory, antibacterial, and antiviral effects. The immunomodulatory mechanisms of Echinacea and its extracts may involve binding to cell surface receptors, activation of related signaling pathways, and expression of immune-related factors. This article provides a concise overview of recent in vivo and in vitro research on the immunomodulatory effects of Echinacea and its extracts, along with their potential mechanisms of action.

Full Text

Echinacea and Its Extracts: Modulation of Animal Immune Function and Mechanisms of Action

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Abstract: In recent years, numerous in vivo and in vitro studies have demonstrated that Echinacea and its extracts can enhance immune function in animals, thereby exerting anti-inflammatory, antibacterial, and antiviral effects. The immunomodulatory mechanisms may involve binding to cell surface receptors, activation of related signaling pathways, and expression of immune-related factors. This article provides a brief overview of recent research on the immunomodulatory effects of Echinacea and its extracts and their possible mechanisms of action.

Keywords: Echinacea and its extracts; animal immune function; mechanisms
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Echinacea, also known as "purple coneflower," belongs to the Asteraceae family and is a perennial plant native to eastern North America. It has been used medicinally for hundreds of years, initially for treating colds and upper respiratory tract infections [1-2]. Among nine Echinacea species, three are widely used in medicine: *Echinacea purpurea*, *Echinacea angustifolia*, and *Echinacea pallida* [3]. According to statistics, Echinacea ranks as the best-selling herbal product in American and European markets, comprising 10% of total herbal medicine sales [1,4]. In recent years, applications have expanded from clinical use to animal production, with studies showing that Echinacea primarily exerts anti-inflammatory, antibacterial, and antiviral effects by enhancing immunity.

As a feed additive in livestock and poultry production, Echinacea and its extracts improve feed intake and weight gain, enhance newborn survival rates while reducing deformities, strengthen disease resistance, provide antibacterial and antiparasitic protection, and improve product quality [5-6]. These benefits all reflect, to varying degrees, the role of Echinacea in immunomodulation. This review summarizes recent research on the immunomodulatory effects of Echinacea and its extracts, offering references for studying the mechanisms underlying their functions and providing a scientific basis for their promotion and application in animal production.

1.1 In Vivo Studies

Under normal feeding conditions, dietary supplementation with Echinacea or its extracts can modulate immune function in animals. Aly et al. [7] reported that adding 0.25 mg/kg Echinacea extract to tilapia feed significantly increased daily weight gain and blood lysozyme activity. Oskoii et al. [8] found that dietary supplementation with 0.25% or 0.50% Echinacea elevated white blood cell and lymphocyte counts in rainbow trout. Arafa et al. [9] demonstrated reduced mortality in weaned rabbits fed Echinacea-supplemented diets, an effect attributed to enhanced immune function and antioxidant defense systems. Ebrahimi et al. [10] observed increased relative weights of spleen and bursa of Fabricius in broiler chickens fed Echinacea extract, with superior effects compared to organic acid or probiotic supplementation. Hao et al. [11] reported that Echinacea extract improved growth performance and immune organ indices in broiler chickens. Niu et al. [12] showed that Echinacea extract significantly increased infectious bursal disease virus antibody titers and cytokine levels [including interleukin-2 (IL-2) and tumor necrosis factor-α (TNF-α)] in chicken peripheral blood while improving production performance. Ni et al. [13] found that Echinacea enhanced nonspecific T cell activity, CD4+ T lymphocyte content, and the CD4+/CD8+ T lymphocyte subset ratio in chicks, demonstrating significant immunomodulatory effects. Song et al. [14] also showed that Echi-

nacea extract is an effective immune enhancer that promotes immune organ development in broiler chicks and increases Newcastle disease antibody production in peripheral blood. Kim et al. [15] found that dietary Echinacea enhanced antigen-presenting cell function in BALB/c mice by reducing the number and function of regulatory T cells in the spleen. Wu et al. [16] conducted carbon clearance tests in Kunming mice, demonstrating that 0.025 g/g chloroform extract of Echinacea alleviated hydrocortisone-induced suppression of mononuclear phagocyte system function. Li et al. [17] reported significantly increased spleen indices in immunosuppressed mice treated with Echinacea.

Furthermore, dietary Echinacea or its extracts can improve immune function in diseased or challenged animals. Pourgholam et al. [18] demonstrated enhanced immune function in Streptococcus-infected rainbow trout fed Echinacea extract. El-Asely et al. [19] found that Echinacea extract effectively enhanced immune function in Nile tilapia reared in water containing *Aeromonas hydrophila*. Qin et al. [20] showed that Echinacea extract reduced mortality in turbot challenged with *Edwardsiella tarda* by significantly enhancing nonspecific immune function. Ren [21] demonstrated that Echinacea extract effectively enhanced carp immune function and generated strong resistance against *Aeromonas hydrophila*. Xiao et al. [22] reported that Echinacea significantly enhanced immune function and improved resistance to *E. coli* infection in mice challenged by intraperitoneal injection of *E. coli*.

1.2 In Vitro Studies

The immunomodulatory effects of Echinacea and its extracts have been confirmed in vitro. Sasagawa et al. [23] found that Echinacea extract inhibited IL-2 production in T cells from leukemia patients in a dose-dependent manner. Zhai et al. [24] and Sullivan et al. [25] demonstrated that Echinacea extract activated innate immune responses and regulated production of interleukin-6 (IL-6), TNF-α, interleukin-12 (IL-12), and nitric oxide (NO) in mouse peritoneal macrophages, with similar results reported by Yu et al. [26] in chicken peripheral blood mononuclear cells and the mouse macrophage cell line RAW264.7. Classen et al. [27] showed dose-dependent effects of Echinacea extract on IgM production in mouse lymphocytes and NO and IL-6 production in mouse alveolar macrophages. Groom et al. [28] found that Echinacea extract enhanced macrophage phagocytosis and increased interferon-γ synthesis. Fast et al. [29] demonstrated that Echinacea extract inhibited Pam3csk4-induced TNF-α secretion in the human leukemia cell line THP-1. Sharma et al. [30-31] showed in vitro challenges with *Propionibacterium acnes* and rhinovirus that Echinacea extract alleviated inflammatory cytokine production in human bronchial epithelial cells and skin fibroblasts while inhibiting pathogen proliferation.

Collectively, these in vivo and in vitro studies demonstrate that Echinacea and its extracts modulate inflammatory cytokines and lymphokines, enhance antibody production, improve animal immune function, increase survival rates, reduce mortality, and promote weight gain. Moreover, they provide immune

protection in challenged and immunosuppressed animals, exhibiting pathogen resistance and immune-enhancing effects.

Analysis of recent research results suggests that Echinacea and its extracts may modulate immune function through three primary pathways: 1) Upregulating macrophage function through Toll-like receptor 4 (TLR4)-dependent signaling cascades. Sullivan et al. [25] demonstrated that Echinacea polysaccharides activate macrophage effector functions by binding as ligands to TLR4, activating mitogen-activated protein kinase (MAPK) pathway proteins [including extracellular regulated protein kinase (ERK), p38, and c-Jun N-terminal kinase (JNK)], and ultimately activating nuclear factor- B (NF- B), with TLR4-independent mechanisms also identified. Xu [32] confirmed these findings and further discovered involvement of the TLR adaptor molecules myeloid differentiation factor 88 (MyD88) and Toll/interleukin-1 receptor domain-containing adaptor inducing interferon-β (TRIF). 2) Acting as ligands to bind cannabinoid receptor-2 (CB2), activating related signaling pathways to exert immunomodulatory effects. Gertsch et al. [33] showed that Echinacea extract modulates immune function by binding CB2, activating cyclic adenosine monophosphate (cAMP), p38MAPK, and JNK pathways, and increasing activating transcription factor/cAMP-response element binding protein (ATF-2/CREB-1) activity in peripheral blood mononuclear cells, with similar results reported by Chicca et al. [34] in human embryonic kidney HEK cells. 3) Modulating expression of immune-related genes to influence immune function. Wang et al. [35] used targeted functional DNA microarrays to demonstrate that Echinacea extracts from different plant parts affect expression of CD83, CD34, and chemokines (CCL2, CCL3, CCL8, CDIA, CCR1, CCR9, etc.) in dendritic cells. Brush et al. [36] also showed that Echinacea extract increased CD69 expression on T cells.

Innate immunity constitutes the first line of defense against pathogens, with TLRs being critical for immunomodulation. TLR4 is a key member of the TLR family that recognizes pathogen molecules, particularly from Gram-negative bacteria, and plays a vital role in natural immunity [37]. CB2 is primarily distributed in immune tissues and cells with minimal central nervous system expression, participating mainly in immunomodulation and neurodegenerative processes [38]. Echinacea and its extracts can bind as ligands to these receptors (TLR4, CB2), activating downstream pathways to induce immune responses. Additionally, they can enhance defense functions by modulating immune-related genes, thereby rapidly preventing invasion by harmful pathogens.

In summary, Echinacea and its extracts modulate immune function both in vivo and in vitro, and their use as feed additives enhances animal immune function, improves stress resistance, and promotes growth. The mechanisms involve receptor binding (TLR4 and CB2), signaling pathway activation, and immune-related gene expression. However, current research has several limitations: limited application studies in livestock, mechanistic investigations restricted to in vitro cell experiments without animal validation, and scarce safety data for feed additive use. Future research should address these gaps to provide theoretical basis

for safe and efficient application.

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