Immunomodulatory Effects and Mechanisms of Flavonoids: Postprint

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Abstract

Flavonoids are widely distributed in nature and possess multiple biological activities such as anti-inflammatory, antibacterial, antiviral, antitumor, and antioxidant effects. Recent clinical studies and trials have demonstrated that flavonoids also exert important regulatory effects on the immune system of organisms, primarily by influencing immune organs, cellular immunity, humoral immunity, non-specific immunity, and immune-related signaling pathways [the nuclear transcription factor- B (NF- B), Toll-like receptor (TLR), and mitogen-activated protein kinase (MAPK) pathways]. This article reviews relevant research on the immunomodulatory effects of flavonoids on animal organisms and their molecular mechanisms of action by examining national and international literature, aiming to provide research ideas and methods for elucidating the mechanisms of flavonoid immunomodulation and for the research and development of immunomodulatory traditional Chinese medicine in veterinary clinical practice.

Full Text

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Abstract

Flavonoids are widely distributed in nature and possess various biological activities, including anti-inflammatory, antibacterial, antiviral, antitumor, and antioxidant effects. Recent clinical studies and experiments have demonstrated that flavonoids also play an important role in immune regulation, primarily by influencing immune organs, cellular immunity, humoral immunity, nonspecific immunity, and immune-related signaling pathways [nuclear factor-kappa B (NF- B), Toll-like receptor (TLR), and mitogen-activated protein kinase (MAPK) signaling pathways]. This article reviews recent research on the immunomodulatory effects of flavonoids on animal organisms and their molecular mechanisms by examining domestic and foreign literature, aiming to provide research ideas and methods for revealing the mechanisms of flavonoid immunomodulation and for developing traditional Chinese medicines for immunomodulation in veterinary clinical practice.

Keywords: flavonoids; immunomodulation; NF- B; TLR; MAPK

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Flavonoids are widely present in various parts of fruits, vegetables, traditional Chinese medicines, and numerous plants, including roots, leaves, flowers, and seeds. Based on differences in their basic nuclear structure, they can be classified into eight categories: flavonols, flavones, flavanones, flavanols, anthocyanins, isoflavones, dihydroflavonols, and chalcones [1]. Research has revealed that flavonoids play important roles in anti-inflammatory, antibacterial, antiviral, antitumor, and antioxidant activities. In recent years, with deepening research, the immunomodulatory effects of flavonoids have attracted scholars' attention. For example, daidzein, ginkgo flavonoids, sea buckthorn flavonoids, luteolin, quercetin, and genistein exhibit favorable immunomodulatory effects and serve as natural and efficient immunomodulators. These compounds can enhance the cytotoxic activity of natural killer (NK) cells and cytotoxic T cells, promote cytokine release [2], increase antibody titers [3] and immune organ indices, strengthen mucosal immunity [4], and improve the immune system. The regulation of immune cells by flavonoids is closely related to their modulation of cell signaling pathways, primarily by mediating these pathways to regulate the expression of immune-related molecules, genes, and proteins. This review integrates recent research reports on the immunomodulatory effects and mechanisms of flavonoids, aiming to provide research ideas and methods for the development of traditional Chinese medicines for immunomodulation in veterinary clinical practice.

1. Effects of Flavonoids on Immune Organs

The status of immune organs can reflect changes in immune function to a certain extent. In studies of immune function regulation, immune organs such as the spleen, thymus, bone marrow, and bursa of Fabricius are commonly used as research subjects. Currently, the immune organ weighing method is one of the commonly used approaches to study immune organ function. Immune enhancement increases immune organ weight, whereas immune suppression typically causes weight loss [5]. Kamboh et al. [4] demonstrated that dietary supplementation with genistein (5 mg/kg) and hesperidin (20 mg/kg) in lipopolysaccharide (LPS)-induced immunosuppressed broilers significantly increased spleen, thymus, and bursa indices. Additionally, total flavonoids from vine bean pods have been reported to significantly increase thymus and spleen indices in mice, promoting thymus and spleen development [6]. Zhang et al. [7] found that in 8-day-old Arbor Acre (AA) broiler chickens with cyclophosphamide-induced immunosuppression (80 mg/kg), administration of bamboo leaf flavonoids (1.6 g/kg) until 35 days of age resulted in significantly increased thymus index and extremely significantly increased bursa index compared with the immunosuppression model group. Similarly, dietary supplementation with Scutellaria flavonoids in AA broilers increased spleen index in all treatment groups at 21 days of age, with significantly improved bursa index in groups receiving 5 and 10 mg/kg doses; at 49 days of age, the group receiving 10 mg/kg showed significantly increased thymus index. These findings indicate that Scutellaria flavonoids can promote immune organ development and enhance immune function in broiler chickens [8].

2.1.1 Effects of Flavonoids on Antibody Expression Levels

Humoral immunity is primarily mediated by B cells through antibody production to protect the organism. Studies have shown that bamboo leaf flavonoids can extremely significantly increase antibody levels against avian influenza and Newcastle disease in immunosuppressed broilers [7]. Liang et al. [8] found that dietary supplementation with different doses (5, 10, 15, 20 mg/kg) of Scutellaria flavonoids in AA broilers significantly increased immunoglobulin G (IgG) content in all treatment groups at 49 days of age. Other research has demonstrated that long-term dietary supplementation with soy isoflavones in Holstein dairy cows significantly increased surface immunoglobulin A (IgA) content in milk samples and mammary glands, along with significantly elevated IgA mRNA expression in mammary tissue [9], thereby regulating immune function in animals.

2.1.2 Effects of Flavonoids on Antibody Titers

Antibody titer reflects antibody affinity for antigens and immune efficacy. Rasouli et al. [3] demonstrated that genistein significantly increased antibody titers against infectious bronchitis virus in broilers. Additionally, studies have shown that both genistein and hesperidin can improve humoral immunity by increasing antibody titers against Newcastle disease virus (NDV) and avian influenza in broilers [4]. Zhao et al. [10] found that total flavonoids from vine tea increased IgG and immunoglobulin M (IgM) content in piglets, while also increasing complement 3 (C3) and complement 4 (C4) levels to a certain extent, thereby enhancing humoral immune function and reducing diarrhea incidence.

2.1.3 Effects of Flavonoids on Serum Hemolysin

Serum hemolysin content serves as an important indicator of humoral immune function in animals [11]. Liu et al. [12] reported that total flavonoids from Oenanthe javanica increased serum hemolysin content in mice sensitized with chicken red blood cells. Medium and high doses (100, 200 mg/kg) of sea buckthorn flavonoids significantly increased serum hemolysin content in D-galactose-induced aging rats, thereby enhancing humoral immune function [13].

2.2 Cellular Immunity

Cellular immunity is primarily mediated by immune cells such as T cells and NK cells. Zhan et al. [14] found that certain concentrations of alfalfa flavonoids reduced Fas gene expression levels in dairy cow lymphocytes, regulated Fas protein synthesis, and inhibited lymphocyte apoptosis. Furthermore, alfalfa flavonoids regulated immune function by significantly reducing total lymphocyte count and proportion while extremely significantly increasing neutrophil proportion [15]. Total flavonoids from Astragalus and Cinnamon Five-Substance Decoction have been reported to enhance cellular immunity by increasing lymphocyte proliferation activity and CD3+ T cell levels in mice [16]. Genkwanin and naringenin significantly improved T lymphocyte cytotoxic activity and NK cell killing activity [17]. Muqier et al. [18] discovered that Allium mongolicum flavonoids (33 mg/kg) significantly increased the proportion of S-phase cells in peripheral blood lymphocytes of meat sheep while promoting cell cycle transition to G2/M phase and enhancing cell division capacity. These results indicate that Allium mongolicum flavonoids enhance DNA repair function in lymphocytes and strengthen specific immunity in meat sheep. Cao et al. [6] found that total flavonoids from vine bean pods extremely significantly promoted spleen lymphocyte proliferation in mice in a dose-dependent manner, with proliferation effects gradually increasing with dosage. Additional studies have shown that 100 mg/kg of sea buckthorn flavonoids extremely significantly increased the percentage of acid non-specific esterase lymphocytes in peripheral blood and significantly elevated white blood cell counts in D-galactose-induced aging rats [13].

3.1.1 Effects of Flavonoids on Macrophages

Macrophages are important components of the innate immune system and play crucial roles in inflammation, defense, repair, and metabolism. Zhao [19] found that Allium mongolicum flavonoid intake increased nitric oxide (NO) content in mouse blood, thereby activating macrophages to exert nonspecific bactericidal and tumor-inhibiting effects. Gu et al. [20] reported that flavonoid aglycones from Oxytropis falcata significantly enhanced macrophage phagocytosis percentage, carbon clearance index K, and phagocytosis coefficient α values in cyclophosphamide-induced immunosuppressed mice, thereby strengthening macrophage phagocytic function. Studies have shown that total flavonoids from vine bean pods extremely significantly increased macrophage phagocytic activity in a dose-dependent manner, thereby elevating nonspecific immune levels in mice [6]. Additional literature has reported that total flavonoids from Broussonetia papyrifera exhibit similar immunological activity [21].

3.1.2 Effects of Flavonoids on Dendritic Cells (DCs)

DCs are the most potent antigen-presenting cells known in vivo and the only specialized cells capable of activating naive T cells. Williams et al. [22] demonstrated that proanthocyanidins induced anti-inflammatory phenotype differentiation in human DCs and selectively downregulated helper T cell (Th cell) 1 responses in naive T cells, exerting immunomodulatory effects. Quercetin inhibited DC activation by blocking LPS-induced activation of extracellular regulated protein kinase (ERK), c-Jun N-terminal kinase (JNK), protein kinase B (Akt), and nuclear factor-kappa B (NF- B), reducing pro-inflammatory cytokine and chemokine production, and decreasing expression levels of major histocompatibility complex (MHC) class II molecules and costimulatory molecules. This effectively suppressed LPS-induced DC activation and DC-induced antigen-specific T cell activation. Additionally, quercetin specifically blocked DC endocytosis and reduced LPS-induced DC migration [23]. Zhang et al. [24] reported that chrysin inhibited DC function, differentiation, and maturation, ameliorating inflammatory responses in experimental autoimmune encephalomyelitis. Wei et al. [25] found that soy isoflavones inhibited expression of DC maturation markers (CD83, CD80, and CD86) and MHC class I molecules in vivo.

3.1.3 Effects of Flavonoids on NK Cells

NK cells are immune cells closely associated with tumors, viral infections, and immunomodulation. Valentová et al. [26] reported that rutin enhanced NK cell killing activity and promoted T cell proliferation. Maatouk et al. [27] found that heat-treated naringenin enhanced NK cell killing activity in mice while inhibiting T cell cytotoxicity.

3.2 Effects of Flavonoids on Cytokines

Cytokines are small molecular proteins with extensive biological activity synthesized and secreted by immune cells upon stimulation. Morimoto et al. [28] used real-time fluorescence quantitative PCR to detect expression of interleukin-13 (IL-13) and interleukin-13 receptor $ 2(IL − 13R 2)genesinthesmallintestineandlungsofC3H/HeNfemalemiceafter10daysoforalrutinadministration.
inflammatoryimmuneactivitybyregulatingcytokines.Haghmoradetal.[29]reportedthathesperidinincreasedi
10(IL − 10)andtransforminggrowthfactor− $ (TGF-β) production by T cells in multiple sclerosis mice, alleviating central nervous system inflammation. Zhu et al. [9] found that dietary soy isoflavone supplementation regulated mammary immune function in dairy cows by increasing defensive immune factor secretion while downregulating inflammatory factor expression. At a dietary supplementation level of 30 mg/kg, tumor necrosis factor-α (TNF-α) content was significantly reduced in serum, milk samples, and mammary tissue. Cell co-culture experiments demonstrated that soy isoflavones (0.5 mg/mL)

also significantly decreased TNF-α secretion and TNF-α mRNA expression in mammary mast cells. Cao et al. [6] found that total flavonoids from vine bean pods significantly increased interferon-γ (IFN-γ) mRNA expression in mouse serum in a dose-dependent manner, inducing Th1/Th2 balance shift toward Th1 direction, thereby promoting cellular immunity while suppressing humoral immunity.

3.3 Effects of Flavonoids on Immune Barriers

The immune barrier is a physiological and anatomical structure that prevents foreign substances from entering the body or specific body parts, known as the body’ s “first line of defense.” Wei et al. [25] found that dietary isoflavones inhibited mucosal immune responses to intranasal ovalbumin sensitization in mice, while genistein and hesperidin improved mucosal immunity by significantly increasing intestinal intraepithelial lymphocyte numbers [4].

4.1 NF- B Signaling Pathway

NF- B is a key factor regulating cell gene transcription. Under normal conditions, NF- B remains inactive when bound to inhibitor of NF- B (I B). Upon stimulation, the I B kinase (IKK) complex is activated, catalyzing I B phosphorylation and dissociation from NF- B, thereby activating NF- B and enabling its translocation to the nucleus to directly initiate and regulate transcription of immune response-related genes and control cytokine and adhesion molecule expression [30]. Baicalin reduced expression of Toll-like receptor (TLR) 2, TLR4, myeloid differentiation factor (MyD88), phosphorylated NF- B (p-NF- B), and phosphorylated I B (p-I B) proteins in rats with renal ischemia-reperfusion injury, regulating immune-inflammatory responses [31]. Xie [32] found that liquiritigenin significantly reduced inflammatory cytokine secretion and NF- B phosphorylation levels by inhibiting the nuclear factor B inhibitor kinase α (IKK-α)/I B-α signaling pathway in a mouse model of diabetes complicated with myocarditis. Quercetin significantly inhibited concanavalin A (ConA)-induced I B-α degradation and regulated NF- B p65 nuclear translocation in the liver [33]. Icariin attenuated renal injury in an IgA nephropathy rat model by inhibiting NF- B activation and subsequent nucleotide oligomerization domain (Nod)-like receptor protein 3 (NLRP3) inflammasome activation [34], and also downregulated stress-induced corticosterone-enhanced LPS-induced immune-inflammatory responses by inhibiting NF- B p65 protein levels and NLRP3 inflammasome activation [35]. These studies demonstrate that flavonoids exert immunomodulatory effects by inhibiting I B degradation, NF- B activation, and NF- B nuclear translocation.

4.2 TLR Signaling Pathway

TLRs can initiate innate immunity immediately upon pathogen recognition and subsequently trigger acquired immunity through signal transduction, playing important roles in immune defense, with TLR4 being particularly significant in immune responses. Research indicates that TLR4 activates interferon regulatory factor 3 transcription factors and downstream NF- B signaling pathways through MyD88 and TIR domain-containing adaptor inducing interferon-β (TRIF) pathways, thereby promoting cytokine/chemokine and type I interferon production [36]. Wogonin inhibited LPS-induced expression of TLR4, MyD88, and transforming growth factor-activated kinase 1 (TAK1) in Caco-2 cells and the interactions among these molecules, while also blocking NF- B translocation to the nucleus [37]. Baicalin reduced expression of TLR2, TLR4, MyD88, p-NF- B, and p-I B proteins in rats with renal ischemia-reperfusion injury [31]. Quercetin decreased high mobility group box 1 (HMGB1), TLR2, and TLR4 mRNA and protein expression levels in liver tissues of ConA-induced hepatitis mice [33]. In summary, flavonoids can exert immunomodulatory effects by regulating TLR signaling pathways, particularly through modulating TLR2 and TLR4 expression.

4.3 MAPK Signaling Pathway

MAPK is a group of serine-threonine protein kinases activated by different extracellular stimuli (cytokines, neurotransmitters, hormones, cellular stress, and cell adhesion). Mammalian MAPK family members mainly include three types: ERK, JNK, and p38MAPK. The MAPK signal transduction pathway constitutes a three-tiered kinase cascade system. Under normal conditions, MAPK remains inactive; upon external stimulation, MAPK kinase kinase (MAPKKK) is phosphorylated and activated, subsequently activating MAPK kinase (MAPKK), and finally activating MAPK through dual-site phosphorylation, which promotes phosphorylated transcription factor translocation to the nucleus to regulate related gene transcription [38]. Dong et al. [39] reported that hesperidin and kaempferol influenced cellular immune responses by selectively modulating MAPK pathways. Hesperidin upregulated p38MAPK and JNK expression and activation levels, thereby enhancing cell-autonomous immunity, whereas kaempferol significantly downregulated p38MAPK and JNK expression and activation levels, thereby suppressing cell-autonomous immunity. Other studies have found that kaempferol protects against acute lung injury induced by H9N2 swine influenza virus. Both in vivo and in vitro experiments demonstrated that kaempferol significantly inhibited TLR4, MyD88, I B-α, and NF- B p65 phosphorylation while blocking MAPK phosphorylation upregulation, thereby exerting anti-inflammatory immunomodulatory effects [40]. Zhang et al. [41] discovered that p38MAPK, ERK1/2, and JNK expression was elevated in diabetic mice with myocarditis, but liquiritigenin could inhibit the activity of these three enzymes and alleviate immune-inflammatory responses. Additionally, sea buckthorn flavonoids could inhibit p38MAPK phosphorylation and the stress-activated protein kinase/JNK MAPK pathway to reduce immune-inflammatory effects [42].

Conclusion

In recent years, domestic and international researchers have conducted in-depth studies on the immunomodulatory effects and mechanisms of flavonoids at the cellular, genetic, and protein levels, achieving certain research outcomes, particularly in exploring signaling pathways. However, the clinical application of flavonoids as immunomodulatory drugs is limited by several factors: diverse structural types, complex mechanisms of action, widespread distribution of action sites, relatively slow drug effects, and lack of specificity and selectivity for certain diseases. Nevertheless, with continuous development and improvement of scientific technology and research methods, the immunomodulatory effects and mechanisms of flavonoids will gradually be elucidated, promoting the development of flavonoids into immunomodulatory drugs and laying a research foundation for the clinical application of traditional Chinese medicines for immunomodulation.

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