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Postprint: Anti-oxidative Stress and Anti-inflammatory Mechanisms of Chitosan and Its Derivatives

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Abstract

Chitosan and its derivatives are products of chitin degradation via enzymatic and acidic hydrolysis processes. Owing to the biocompatibility and non-toxicity of chitosan, they hold potential value for biological applications. This review primarily summarizes the antioxidant and anti-inflammatory effects of chitosan and its derivatives, and elucidates their underlying mechanisms from the perspectives of in vivo immunomodulatory factors, the nuclear factor B (NF- B) signaling pathway, the mitogen-activated protein kinase (MAPK) signaling pathway, and the regulation of lipid metabolism, thereby providing a theoretical foundation for the further development and utilization of chitosan and its derivatives.

Full Text

Anti-Oxidative Stress and Anti-Inflammatory Mechanisms of Chitosan and Its Derivatives

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Abstract

Chitosan and its derivatives are products derived from the enzymatic and acidic hydrolysis of chitin. Due to their biocompatibility and non-toxicity, these compounds possess significant potential for biological applications. This review summarizes the antioxidant and anti-inflammatory effects of chitosan and its derivatives, exploring their underlying mechanisms from the perspectives of immunomodulatory factors, the nuclear factor- B (NF- B) signaling pathway,

the mitogen-activated protein kinase (MAPK) signaling pathway, and lipid metabolism regulation, thereby providing a theoretical foundation for further development and utilization of these biomaterials.

Keywords: chitosan and its derivatives; antioxidant; anti-inflammatory; mechanism

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Chitosan, also known as deacetylated chitin, is obtained from chitin through deacetylation. Chitin, first isolated from mushrooms by French chemist Henri Braconnot in 1811, is the earliest known polysaccharide and represents the second most abundant natural biopolymer worldwide, with marine biological reserves reaching 10 –10 tons [1]. Chitin can be decomposed by strong acids into acetic acid and chitosan, or further processed by non-specific enzymes such as cellulase, lipase, protease, and chitosanase to generate two major derivatives: chitosan and glucosamine [2]. Through acid hydrolysis and enzymatic degradation, chitin and chitosan yield chitin oligosaccharide (NACOS) and chitosan oligosaccharide (COS). Numerous studies have demonstrated that chitosan is a bioactive cationic polysaccharide with antibacterial, antifungal, antidiabetic, anticancer, and cholesterol-lowering properties, alongside notable antioxidant and anti-inflammatory activities, making it significant for developing green feed additives. The derivatives NACOS and COS exhibit enhanced water solubility, low viscosity, and higher dissolution at neutral pH, and show superior antioxidant activity due to weakened hydrogen bonding, broadening their applications in production and research [3-4]. This review examines the mechanisms underlying the antioxidant and anti-inflammatory actions of chitosan and its derivatives to provide theoretical support for their advanced research and development.

1. Antioxidant and Anti-Inflammatory Effects of Chitosan and Its Derivatives

Chitosan and its derivatives exhibit important biological antioxidant activity. In vivo studies demonstrate that chitosan displays direct antioxidant effects by reducing systemic oxidative stress markers. Dietary chitosan supplementation in rats attenuated isoproterenol-induced oxidative stress in myocardial tissue and enhanced glutathione (GSH)-dependent antioxidant systems in both young and aged rats, thereby exerting anti-aging effects [5]. Research on mouse macrophages confirmed that NACOS inhibits myeloperoxidase (MPO) activity in bone marrow cells [6]. NACOS also increases intracellular catalase (CAT) activity and GSH content, indicating its effectiveness as an antioxidant in living cells [7]. Studies show that COS inhibits intracellular free radical production in mouse melanoma cell lines, increases intracellular GSH content, and protects genomic DNA from oxidative damage [8]. COS also protects human umbilical vein endothelial cells (HUVEC) from hydrogen peroxide-induced oxidative injury. Reactive oxygen species (ROS), which oxidize biomolecules such as lipids, proteins, carbohydrates, and DNA, represent a major class of free radicals caus-

ing cellular oxidative stress [9]. Beyond significantly reducing intracellular ROS levels, COS inhibits lipid peroxidation products such as malondialdehyde, restores endogenous antioxidant activities (including superoxide dismutase and glutathione peroxidase), enhances nitric oxide (NO) capacity, and increases inducible nitric oxide synthase (iNOS) activity. These findings indicate that COS effectively protects HUVEC from hydrogen peroxide-induced oxidative stress, suggesting its potential importance in preventing and treating cardiovascular diseases [10]. Additionally, COS protects human embryonic hepatocytes from hydrogen peroxide-induced oxidative stress, demonstrating its potential to mitigate oxidative stress during clinical liver injury [11].

In dairy cows, dietary chitosan supplementation during the dry period significantly increases serum immunoglobulin G (IgG), immunoglobulin M (IgM), and immunoglobulin A (IgA) levels, suggesting that chitosan may serve as an immune enhancer [12]. Other studies found that chitosan improves 4% fat-corrected milk yield in dairy cows, increases blood active T lymphocyte and B lymphocyte counts, and significantly elevates serum IgM and IgG levels [13]. Appropriate dietary chitosan doses also increase milk production, reduce somatic cell counts in milk, and enhance antioxidant capacity, as evidenced by elevated serum superoxide dismutase (SOD) activity and total antioxidant capacity (T-AOC) [14]. Chitosan may alleviate weaning stress and promote immune function in piglets by improving antioxidant capacity [15]. Studies in beef cattle similarly demonstrated that appropriate chitosan doses enhance antioxidant and immune functions [16]. In broiler chickens, chitosan effects on growth and immunity are dose-dependent. A 0.05% dietary chitosan level improves growth performance, while higher levels enhance immune function but reduce growth performance, making 0.05% the optimal supplementation level. Furthermore, appropriate chitosan doses improve intestinal microecology in broilers [17]. Research on laying hens showed that optimal chitosan levels improve egg quality and yolk antioxidant indices, reduce lipase activity and apparent crude fat digestibility, and increase protease activity and apparent digestibility of other nutrients [18]. COS attenuates ocular inflammation in rats with experimental autoimmune uveitis by reducing oxidative stress and inflammatory responses, thereby preventing retinal ischemia and reperfusion injury [19]. Dietary chitosan at appropriate levels also promotes growth, reduces diarrhea, and alleviates weaning stress in piglets [20].

2.1 Anti-Inflammatory Effects Through Modulation of Immunomodulatory Factors

Tumor necrosis factor- (TNF-) is a monokine primarily produced by monocytes and macrophages, which play crucial roles in immune responses by secreting NO and pro-inflammatory cytokines such as TNF- and interleukin-6 (IL-6) [21]. Lipopolysaccharide (LPS)-activated macrophages produce and release large amounts of iNOS, establishing models for various inflammatory diseases including tissue injury and septic shock [22] to investigate the mechanisms of chi-

tosan' s antioxidant and anti-inflammatory actions. Many studies have reported the anti-inflammatory properties of COS, demonstrating that COS treatment of LPS-stimulated mouse mononuclear macrophage RAW 264.7 cells causes dose-dependent reductions in TNF- and IL-6 secretion and their mRNA expression. COS also decreases LPS-induced NO secretion, and supplementation of RAW 264.7 cell cultures with COS reverses TNF- -mediated reductions in IL-6 and NO content, indicating that COS exerts anti-inflammatory effects by modulating TNF- and consequently reducing NO production [23]. Other studies showed that pretreatment with low-molecular-weight sulfated chitosan oligosaccharides inhibits LPS-induced production of inflammatory mediators NO, IL-6, and TNF- in RAW 264.7 cells. Sulfated chitosan oligosaccharides regulate LPS-induced IL-6 and TNF- production in macrophages through the MAPK signaling pathway, which is activated by the NF- B pathway [24]. Evaluating COS effects through clinical scoring and morphology of the iris ciliary body (ICB) revealed that COS treatment significantly reduced ICB clinical scores in a dose-dependent manner and effectively decreased expression of inflammatory mediators including TNF- and iNOS [25]. Chitosan has been shown to partially inhibit IL-8 and TNF- secretion in mast cells, indicating its potential to reduce allergic inflammatory responses. Since mast cell-derived inflammatory factors are involved in many neuroinflammatory diseases, chitosan and its derivatives may help prevent or alleviate some of these complications [26].

Studies have demonstrated that different chitin fragments stimulate Toll-like receptor 2 (TLR2), mannose receptor, and inflammatory cytokine expression, differentially activating the NF- B signaling pathway and spleen tyrosine kinase (Syk). This promotes phagocytosis by polymorphonuclear leukocytes, production of interleukin-1 (IL-1) and platelet-derived growth factor, and IL-8-mediated immune responses through fibroblasts. These findings indicate that chitin possesses immunomodulatory effects, as medium and small chitin fragments stimulate TNF- production in mouse peritoneal macrophages, while large chitin fragments remain inert [27]. Another study reported the effects of chitosan and quaternized chitosan (HTCC) on IL-1 and TNF- production in LPS-stimulated human periodontal ligament cells, finding that chitosan inhibited while HTCC increased IL-1 and TNF- production [28]. Currently, related research reports are scarce and require further investigation.

2.2 Reducing NO Production Through Inhibition of the NF- B Signaling Pathway

Nitric oxide (NO) is a gaseous signaling molecule and reactive nitrogen radical in organisms that mediates numerous biological functions including host defense, neurotransmission, neurotoxicity, and vasodilation [29]. NO is generated during the conversion of L-arginine to L-citrulline through endogenous synthesis by nitric oxide synthase (NOS), which exists as three isoforms: neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS). Macrophage-derived NO plays important roles in physiological, pathological, and inflamma-

tory responses, with the antiproliferative effects of activated macrophages on antigens partially attributed to NO. While macrophages are important for immune responses through secretion of NO and pro-inflammatory cytokines such as TNF- and IL-6, excessive NO production contributes to various diseases including atherosclerosis, malignancies, rheumatoid arthritis, tissue injury, and septic shock [30].

NF- B was originally identified as a nuclear factor binding to the immunoglobulin light chain enhancer element in activated B cells, and proteins with this specific binding activity possess multiple regulatory functions in most cell types [31]. The transcription factor NF- B plays a crucial role in chronic inflammation and regulates gene expression involved in immune responses. Beyond its role in innate immunity, NF- B signaling controls cell proliferation and apoptosis, with NF- B activation typically upregulating anti-apoptotic genes to enhance cell survival during inflammatory responses. NF- B has been shown to induce cytokines regulating immune responses (such as TNF- , IL-1, IL-6, and IL-8) and adhesion molecules that recruit leukocytes to inflammatory sites [32]. In the canonical activation pathway, excitatory signals mediated through Toll-like receptors (TLR), IL-1 receptors, tumor necrosis factor receptors, and antigen receptors lead to activation of the I B-kinase complex, thereby activating NF- B [33].

In mouse pancreatic -cell line MIN6, sulfated chitosan oligosaccharides (COS-S) protected against hydrogen peroxide-induced oxidative damage by significantly inhibiting NO production, iNOS activity and mRNA expression, and NF- B protein p65 levels [34]. These results suggest that COS-S antioxidant capacity may involve blockade of the NF- B signaling pathway. In a mouse RAW 264.7 cell oxidative stress injury model, COS reduced LPS-induced inflammatory responses and decreased LPS-induced glycosylation modification levels of NF- B/p65. This downregulation of NF- B glycosylation modification may reduce NF- B/p65 nuclear translocation and decrease NF- B pathway activation, consequently downregulating pro-inflammatory cytokine gene expression [35]. Low-molecular-weight chitosan oligosaccharides (LM-COS) prepared by enzymatic digestion of high-molecular-weight chitosan showed anti-inflammatory effects against allergic reactions and asthma both in vivo and in vitro. LM-COS protected against ovalbumin (OVA)-induced lung inflammation in asthmatic mouse models, with oral LM-COS administration significantly reducing mRNA and protein levels of IL-4, IL-5, IL-13, and TNF- [36]. These findings indicate that LM-COS alleviates asthma symptoms by mediating inhibition of Th2 cytokine expression during OVA-induced airway inflammation. Since NF- B regulates pro-inflammatory cytokine expression, LM-COS also inhibits NF- B activation in IgE-antigen complex-stimulated RBL-2H3 cells [37].

2.3 Reducing NO Generation Through Inhibition of the MAPK Signaling Pathway

The MAPK pathway represents one of the important intracellular signaling pathways in pro-inflammatory responses, with myeloid differentiation factor 88 (MyD88) mediating MAPK activation. The MAPK family comprises three subfamilies: extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinases (JNK), and p38 mitogen-activated protein kinases (p38) [38]. These kinases activate downstream NF- B by degrading I B- to regulate inflammatory gene expression. Activation of MyD88 and TRIF-dependent signaling pathways in LPS-stimulated macrophages occurs through iNOS expression [39]. Toll-like receptor 4 (TLR4) is an extracellular receptor that recognizes LPS and releases inflammatory mediators through two fundamental pathways: the MyD88 pathway and the TIR domain-containing adaptor-inducing TRIF pathway. Studies have found that COS inhibits LPS-induced iNOS production in RAW 264.7 macrophages through JNK [40].

Research on COS protective effects in LPS-induced piglet sepsis revealed that COS not only alleviates intestinal organ dysfunction but also improves survival rates after LPS injection. Mechanistic studies examining neutrophils in the intestine and pro-inflammatory markers such as serum TNF- and IL-1 showed that COS treatment significantly reduced these cytokine levels. LPS-induced sepsis in piglets caused increased consumption of GSH and CAT and elevated malondialdehyde levels, leading to redox imbalance that COS could reverse [41]. Additionally, LPS-activated signaling pathways such as JNK and p38 were alleviated by COS treatment, demonstrating that COS protects against LPS-induced oxidative stress models through MAPK signaling pathway inhibition [42]. Studies on COS effects in LPS-induced N9 microglial cells showed that COS pretreatment inhibited NO production by suppressing iNOS expression in activated microglia. COS inhibited LPS-induced phosphorylation of p38 MAPK and ERK, and also suppressed activation of NF- B and activator protein-1 [43]. These results further confirm that the antioxidant stress effects of chitosan and its derivatives are achieved by inhibiting MAPK and NF- B signaling pathway activation, leading to downregulated iNOS expression and consequently suppressed NO generation.

2.4 Antioxidant Stress Effects Through Regulation of Lipid Metabolism

Oxidation of low-density lipoprotein (LDL) is associated with coronary atherosclerosis, as high levels of cholesterol oxidation products in oxidized LDL are toxic to endothelial cells [44]. Macrophages protect against inflammatory responses primarily by clearing immune regulatory factors such as TNF- and IL-1, which stimulate LDL binding to endothelial cells and smooth muscle. Antioxidants exert immunological effects by inhibiting upregulation of monocyte adhesion molecules and enhancing LDL antioxidant capacity in

humans. High-density lipoprotein can suppress cytokine-induced expression of endothelial cell adhesion molecules [45]. Numerous reports have documented cholesterol-lowering effects of chitosan, with studies demonstrating significant reductions in serum triglycerides, total cholesterol, and LDL cholesterol levels [46]. One study confirmed that feeding mice chitosan irradiated with -rays for 12 weeks resulted in significantly lower total cholesterol compared to controls [47]. Low-molecular-weight chitosan can inhibit oxidation of serum albumin commonly observed in hemodialysis patients, thereby reducing uremia-associated oxidative stress. Furthermore, carboxylated chitosan oligosaccharides inhibit free radical-mediated oxidation of cell membrane lipids and proteins while reducing lipid hydroperoxide levels and carbonyl carbon content in mouse macrophages, thereby exerting antioxidant effects.

3. Summary

In summary, chitosan and its derivatives primarily exert antioxidant and anti-inflammatory functions by inhibiting NF- B and MAPK signaling pathways to reduce NO generation, modulating immunomodulatory factors, and regulating lipid metabolism to alleviate oxidative stress.

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