

Advances in immunomodulatory effects and mechanisms of *Dendrobium officinale* polysaccharides

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Abstract

Dendrobium officinale polysaccharide (DOP), a significant active ingredient extracted from the traditional Chinese medicine *Dendrobium officinale*, has been demonstrated to possess considerable potential in regulating the immune function of the body. The present study systematically investigates the structure–activity relationship of DOP and its underlying multilevel immunoregulatory mechanisms. It has been found that DOP not only promotes the function of immune organs such as bone marrow, thymus, and spleen but also enhances both the phagocytic activity of macrophages and cytokine secretion. Concurrently, DOP has been demonstrated to stimulate the proliferation and differentiation of T/B lymphocytes and antibody production, enhance natural killer (NK) cell activity, and promote the maturation and antigen presentation of dendritic cells (DCs). In addition, DOP has demonstrated regulatory potential in immune-related disease models, such as diabetes, intestinal inflammation, Sjögren's syndrome, neuroinflammation, and epilepsy. The goal of this study is to provide a comprehensive summary of the research progress on the immunomodulatory effects and mechanisms of DOP, thereby offering a valuable theoretical foundation for related fields.

KEYWORDS

Dendrobium officinale polysaccharide, immunomodulation, mechanism, structure–activity relationship

1 | INTRODUCTION

Immunity, as the organism's core defense mechanism, helps maintain health by eliminating pathogens. Therefore, normal immune regulation is crucial for the health of the organism. However, factors such as environmental stressors, poor lifestyle choices, and diseases can compromise immune function. This dysregulation may lead to various disorders, including autoimmune diseases, chronic

inflammation, increased infection susceptibility, and even tumors. According to the differences in pathogenic mechanisms, immune-related diseases are mainly categorized into immunodeficiency diseases, autoimmune diseases, allergic diseases, and transplantation rejection reactions.¹ Immunodeficiency diseases comprise two distinct categories. Primary immunodeficiencies encompass a heterogeneous group of disorders characterized by dysfunctional innate immunity.² Secondary immunodeficiencies arise from acquired

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conditions, with human immunodeficiency virus (HIV) infection serving as a cardinal paradigm wherein the virus selectively depletes CD4⁺ T lymphocytes, thereby driving progressive immune collapse.³ In contrast, autoimmune diseases emerge from an imbalance in the body's immune tolerance, resulting in the production of antibodies that attack normal tissues. The fundamental pathological feature is an imbalance in the ratio of the Th17 helper T cell subset to regulatory T cells (Treg).⁴ IgE-mediated type I hypersensitivity reactions, which involve mast cell degranulation and the cascading release of inflammatory factors, are the primary cause of allergic disorders.⁵ The incidence of immune-related adverse events (irAEs) still surpasses 50% despite the extensive use of innovative immunotherapies, making the discovery of safe and efficient immunomodulators for synergistic interventions especially critical.⁶

With the increasing research on medicinal plant resources in the field of immunomodulation, plant extracts have shown significant research value and potential because of their remarkable immunomodulatory activities. Existing evidence has confirmed that plant extracts, especially plant polysaccharides, have clear immunomodulatory effects, such as *Astragalus membranaceus* polysaccharides, *Atractylodes macrocephala* polysaccharides, *Panax ginseng* polysaccharides, and *Medicago sativa* polysaccharides.^{7,8} In contemporary pharmacology and functional food development, the immunomodulatory effects of polysaccharides manifest as multi-level, multi-target actions: it can activate core immune cells such as macrophages, dendritic cells, natural killer cells, and T/B lymphocytes; regulate secretion of key cytokines including interleukins, interferons, and TNF- α ; enhance functions of immune organs (such as the thymus and spleen); and modulate systemic immune homeostasis via indirect regulation of gut microbiota.^{9,10} This complex immunomodulatory activity is highly dependent on the structural characteristics of polysaccharides, including molecular weight, monosaccharide composition, glycosidic bond type, degree of branching, and higher-order conformation. These structural features collectively determine the recognition and binding ability of polysaccharides to receptors on the surface of immune cells, forming a complex structure–activity relationship.^{11,12} Therefore, these natural compounds continue to motivate researchers to identify new immunotherapeutic possibilities from plant-derived substances due to their multi-channel, multi-target, and multi-level action characteristics.¹³ Plant active ingredients possess complex and diverse structures along with rich biological activities. They exhibit milder and broader-spectrum effects compared to chemically synthesized drugs and biologics. This characteristic allows them to address clinical challenges such as high costs, serious adverse effects, and multidrug resistance commonly associated with chemotherapy, thereby significantly enhancing therapeutic safety.¹⁴ *Dendrobium officinale*, a traditional medicinal herb, possesses active components characterized by distinct chemical structures and biological functions. *Dendrobium officinale* contains a variety of active substances, including polysaccharides, alkaloids, flavonoids, phenolics, and amino acids. Among these, polysaccharides are the most abundant and are recognized as the key bioactive components of the plant.¹⁵ Studies indicate that *Dendrobium officinale* polysaccharides (DOP) exhibit various physiological effects,

including antioxidant, antitumor, antimetabolic disease properties, and the regulation of intestinal microecology.^{16–19} The physiological functions are intricately linked to immune regulation, underscoring their significant potential in immune intervention.

However, although a large number of studies have revealed a variety of biological activities of DOP, there is still a lack of systematic summary of the structure–activity relationship between its structural characteristics and immunomodulatory functions. In addition, the multi-level regulation mechanism of DOP in different immune cells, organs, and disease models has not been integrated. In order to address these gaps in the literature, this review aims not only to systematically analyze the structure–activity relationship between the structural characteristics of DOP and its immune activity, but also to comprehensively explain its multi-level mechanisms spanning immune cells, factors, organs, and diseases. Through the systematic induction and comparison of the existing evidence, this paper aims to provide a solid theoretical basis for the in-depth analysis of the immunomodulatory effects of DOP, and provide a clear research and development idea for the development of new immunotherapy adjuvant drugs and functional foods based on DOP characteristics.

2 | STRUCTURE–ACTIVITY RELATIONSHIP BETWEEN STRUCTURAL CHARACTERISTICS AND IMMUNOLOGICAL ACTIVITIES OF *DENDROBIUM OFFICINALE* POLYSACCHARIDES

2.1 | Structural characteristics of *Dendrobium officinale* polysaccharides

Currently, the structural characterization of *Dendrobium officinale* polysaccharides relies on an integrated approach involving multiple analytical techniques. Monosaccharide composition (the types and quantities of simple sugars present) is typically determined using high-performance liquid chromatography (HPLC), whereas molecular weight (Mw, a measure of the size of the polysaccharide molecules) is commonly assessed by high-performance gel permeation chromatography coupled with refractive index detection (HPGPC–RID). For more detailed structural features—such as glycosidic linkage patterns (how the sugar units are connected)—analyses often combine Fourier-transform infrared spectroscopy (FT–IR, which identifies molecular bonds), gas chromatography–mass spectrometry (GC–MS, which separates and detects chemical components), and nuclear magnetic resonance (NMR, which provides detailed molecular structure information).^{20–22} Building upon these analytical approaches, recent research has shown that the molecular weight of *Dendrobium officinale* polysaccharides ranges from several to several thousand kDa. Their monosaccharide composition is dominated by mannose (Man) and glucose (Glc). Structural studies indicate that the backbone is primarily composed of 1,4- β -D-mannopyranose (1,4- β -D-Manp) and 1,4- β -D-glucopyranose (1,4- β -D-Glcp) residues. Furthermore, these polysaccharides have been identified as O-acetylated glucomannans,

with acetylation occurring predominantly at the O-2 or O-3 positions of mannose residues, and displaying variability in both substitution degree and pattern.^{23,24} Key structural aspects are illustrated in Figure 1.

2.2 | The relationship between *Dendrobium officinale* polysaccharide structure and immunomodulatory action

The immunological activity of polysaccharides is governed by key structural features, including monosaccharide composition, molecular weight, glycosidic linkages, and conformation. As a structurally complex and functionally diverse bioactive compound, the immunomodulatory effects of DOP are intrinsically determined by these same characteristics. Consequently, elucidating the influence of specific structural attributes of DOP, particularly its monosaccharide profile, molecular weight, and glycosidic bond types, on immune responses is critical. These structure–activity relationships form the focus of the subsequent discussion. As illustrated in Figure 2, key structures and immunological activity aspects are demonstrated.

2.2.1 | Monosaccharide composition

The composition of monosaccharides is a primary research focus in examining the structural properties, physicochemical characteristics, and conformational relationships of plant polysaccharides,²⁵ with biological activity increases with the complexity of the monosaccharide composition.²⁶ The analysis of monosaccharide composition typically employs colorimetric methods alongside various chromatographic techniques combined with hydrolysis, such as thin-layer chromatography (TLC), high-performance liquid chromatography (HPLC), gas chromatography (GC), and gas chromatography–mass spectrometry (GC–MS).²⁷ *Dendrobium officinale* polysaccharides predominantly consist of glucose, mannose, and galactose.^{28,29} Variations in the species, sources, and extraction techniques of *Dendrobium officinale* substantially influence the monosaccharide composition and lead to discrepancies in the immunoreactivity of the extracted polysaccharides.³⁰ The molar ratio of mannose, glucose, galactose, and arabinose in DOP extracted via ultrasound-assisted enzymatic method was approximately 74.17:47.80:9.03:1. The immunoreactivity was markedly superior to that obtained through the conventional hot water extraction–ethanol precipitation method, primarily attributable to the elevated proportion of mannose and the disruption of the plant cell wall, which may lead to variations in the composition and chemical structure of the monosaccharides. In a mouse model of immunosuppression caused by cyclophosphamide, DOP reduced damage to the thymus and spleen, raised leukocyte counts, controlled the percentage of T lymphocytes and associated factors, improved macrophage phagocytosis, and raised immunoglobulins IgA and IgG to amplify the effects of particular immune functions.³¹

In the S180 tumor-bearing mouse model induced by cyclophosphamide (CTX), the isolated and purified DOP exhibited significant immunological activity. It has been hypothesized that the proliferation of splenocytes could be significantly promoted, with concomitant enhancement of the activities of natural killer (NK) cells and cytotoxic T lymphocytes (CTL). Furthermore, a balance of the Th1/Th2 immune response could be achieved, and levels of both non-specific and tumor antigen-specific antibodies could be increased. In comparison with the model group, the inhibition rate of DOP on S180 tumors was as high as 67%. The polysaccharide predominantly consists of D-mannose, D-glucose, and D-galactose, with a molar ratio of roughly 3:2:1, with a significant proportion of mannose.¹⁶ Furthermore, three polysaccharides were isolated from *Dendrobium officinale* polysaccharides through the incorporation of a novel lactic acid probiotic (DU-106) into *Dendrobium officinale* stems, specifically unfermented *D. officinale* stems (UDP-1), fermented *D. officinale* stems (FDP-1), and polysaccharides from the fermentation broth (FLP-1). Prior to fermentation, glucose constituted the predominant monosaccharide in UDP-1 and FLP-1, whereas the proportion of mannose escalated from 35.65% to 53.97% (w/w) after fermentation, peaking in FDP-1. Cell proliferation assessed via MTT assay revealed that UDP-1, FDP-1, and FLP-1 at concentrations ranging from 12.5 to 200 µg/mL stimulated the proliferation of RAW264.7 macrophage cells and enhanced the secretion of NO and IL-1β, thereby significantly augmenting the immunomodulatory activity of these polysaccharides.³² Thus, the content and specific ratios of monosaccharides significantly influence the regulation of immunoreactivity, with a high proportion of mannose being crucial for its expression.

2.2.2 | Influence of molecular weight

The relative molecular mass significantly influences the activity of DOP, and its size is closely associated with biological activity. The primary techniques for determining the molecular weight of polysaccharides include high performance gel permeation chromatography with refractive index detection (HPGPC-RID) and size exclusion chromatography coupled with multi-angle laser scattering (SEC-MALLS).³³ Research indicates that polysaccharides possess a diverse range of molecular weights, with those exceeding 100 kDa generally demonstrating more pronounced immunomodulatory effects.³⁴ This may be due to the fact that higher molecular weights bind more effectively to immune cells or receptors, thereby activating pertinent signaling pathways. Nevertheless, molecular weights that are excessively high may exhibit a relatively low solubility and increased steric hindrance, which can impede their ability to bind effectively to immune cells or receptors and impact their bioavailability. In the ICR female mouse tumor model utilizing S180 cells, both low molecular weight products, dextranase-hydrolyzed DOP (GDOP) and mannanase-hydrolyzed DOP (MDOP), significantly increased the mRNA expression levels of the chemokines CCL3, CCL4, CCL5, CCL10, CCL22, CXCR2, and CXCL10 in tumor tissues, with MDOP showing a

of sugar residues.³⁸ The polysaccharide DOPS-1 extracted from *Dendrobium* stems primarily consists of (1 → 4)-β-D-Glcp, (1 → 4)-β-D-Manp, and 2-O-Acetyl-(1 → 4)-β-D-Manp residues, with glycopyranosidic bonds that exhibit both α and β conformations, with a predominance of the α-mannopyranosidic bond. The DPPH radical scavenging capability of DOPS-1 shows a positive correlation with concentration, signifying its concentration-dependent antioxidant activity. DOPS-1 demonstrated substantial cytotoxicity against three human cancer cell lines: MDA-MB-231, A549, and HepG2. The anticancer activity indicates that DOPS-1 may possess significant immunomodulatory capabilities.³⁹ In vitro experiments, DG2, a novel *Dendrobium officinale* polysaccharide composed of (1 → 3)-β-D-Glc, (1 → 4)-β-D-Glc, (1 → 3,6)-β-D-Gal, and (1 → 6)-β-D-Gal, up-regulated the mRNA expression of TNF-α, IL-6, and iNOS in RAW 264.7 macrophage cells. It subsequently activating these cells and enhancing the production of TNF-α, IL-6, and NO. DG2 significantly stimulated RAW 264.7 cells to produce higher levels of IL-6 and NO compared to *Dendrobium*-origin polysaccharides, indicating that DG2 exhibits stronger immunostimulatory activity.⁴⁰ The neutral polysaccharide DTPS-N, which was obtained from the hybrid of two medicinal *Dendrobium* species, was identified as a mixed-linkage (1 → 3, 1 → 4)-β-D-mannan. The polysaccharide demonstrated significant immunomodulatory effects, notably enhancing the phagocytic activity of macrophages and increasing the cytotoxicity of NK cells. DTPS functions as a significant innate immunomodulator.⁴¹ Two products are derived from the hydrolysis of DOP: a glucanase hydrolysis product (GDOP) and a mannanase hydrolysis product (MDOP). MDOP primarily comprises →6)-α-d-Glcp-(1→ and →4)-β-d-Manp-(1→ residues, demonstrating significant antitumor activity. It is proposed that the structural units →6)-α-d-Glcp-(1→ and →4)-β-d-Manp-(1→ may serve as the structural foundation of *Dendrobium officinale* polysaccharides for the reconstruction of the tumor immune microenvironment.³⁵ In addition, in an immunosuppressive animal model, the administration of *Dendrobium officinale* and its two polysaccharide fractions (crude and purified polysaccharides) significantly enhances spleen/thymus indices, stimulated lymphocyte proliferation, and mitigated cyclophosphamide-induced apoptosis in male BALB/c mice, thereby experimentally confirming that the structure comprising (1 → 4)-β-D-Manp and O-acetyl is responsible for the immunoreactivity of the polysaccharide.⁴² In summary, polysaccharides with various structures possess numerous mechanisms for immune activation.

2.2.4 | Effect of acetyl groups

The structure of DOP primarily consists of varying ratios of D-mannose and D-glucose, interconnected by β-1,4-glycosidic linkages. Acetyl groups in DOP are predominantly monosubstituted at the O-2 or O-3 positions, whereas a small quantity of disubstituted forms (connected to both O-2 and O-3 of a mannose ring) has also been identified.⁴³ Acetyl groups are reported to be crucial for the immunomodulatory activity of polysaccharides, and their removal or

addition impacts immune function.^{44–46} It has been shown that *Dendrobium officinale* polysaccharides are effective in attenuating cyclophosphamide-induced immunosuppression in vivo and can enhance the production of sIgA, a key effector of intestinal mucosal immunity, through multiple pathways, as shown in Figure 3. Acetylation-modified polysaccharides (Ds-DOPs) promoted sIgA secretion more effectively than unmodified DOPs, and this promotion showed a dose-dependent effect. However, the immunomodulatory activity did not increase infinitely with the degree of acetylation. Moderate substitution (DS 0.29–0.89) correlated positively with activity, whereas excessive acetylation (DS 0.89–1.33) decreased activity, suggesting the existence of an optimal modification degree.⁴⁷ The relationship between acetylation and activity was further demonstrated in the investigation of alkali-treated polysaccharide subfractions. The acetylation levels of the three fractions were ranked as follows: DOP (8.87%) > DADOP-1 (3.77%) > DADOP-2 (1.18%). Correspondingly, the magnitude of their immunomodulatory effects on immunosuppressed mice was ordered as DADOP-1 > DOP > DADOP-2. The acetylation degrees of the ultrasound-treated polysaccharide UDOP-2 and the alkali-treated DADOP-1 were comparable, at 3.68% and 3.77%, respectively; however, UDOP-2, possessing a lower molecular weight, exhibited superior immunomodulatory activity, likely attributable to its enhanced solubility and compact coiled conformation.⁴⁸ In vitro experiments demonstrated that DOP-1-1, an acetylated glucomannan derived from *Dendrobium officinale*, enhances the secretion of cytokines IL-1β and TNF-α by macrophages. Different concentrations of DOP-1-1 activated the NF-κB signaling pathway. Its effect on Erk1/2 signaling was concentration-dependent; specifically, it up-regulated Erk1/2 phosphorylation at 25 μg/mL while inhibiting phosphorylation at higher concentrations. This indicates that DOP-1-1 may enhance immune activity via alternative or complex signaling networks, with the Erk1/2 pathway exhibiting heightened sensitivity to its concentration variations. The bidirectional regulatory effects on the immune system collectively mediate the overall immune-enhancing activity of DOP-1-1.⁴⁹ Furthermore, the primary structure of the purified polysaccharide has been identified as O-acetylglucomannan, and a higher purity of *Dendrobium officinale* polysaccharide correlates with better immunomodulatory activity. This further confirms that the presence of acetyl groups is a key structure for the immunomodulatory function of *Dendrobium officinale* polysaccharides.⁵⁰ In conclusion, the immunoregulatory activity of DOP is significantly enhanced by acetylation modification. However, the degree of acetylation and the activity are not linearly related, and an optimal range exists. The precise boundaries of this range require further exploration.

2.2.5 | Others

The physicochemical characteristics and biological functions of polysaccharides are intricately influenced by their extraction techniques. Research indicates that among the polysaccharides recovered from *Dendrobium officinale* leaves (DLP), both hot water extraction and

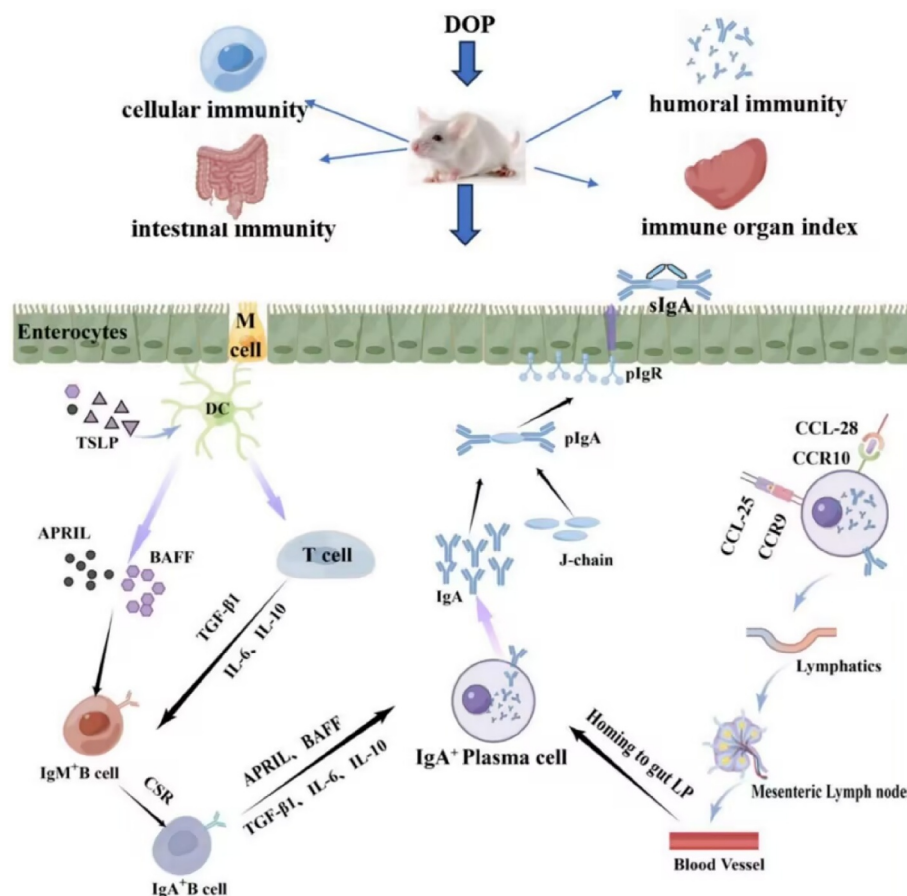


FIGURE 3 The immunoregulatory function of DOP and the mechanism of promoting sIgA production.⁴⁷

ultrasonic-assisted extraction procedures effectively preserve the triple-helical conformation of the polysaccharides.⁵¹ This structure enabled the isolated DLP to markedly enhance the release of nitric oxide (NO) and the secretion of TNF- α , IL-6, and IL-1 β from RAW 264.7 macrophages, thereby demonstrating exceptional biological activity. This finding aligns with the established view that polysaccharides with a triple-helical conformation typically possess enhanced biological activity.^{15,51} In addition, plasma treatment markedly enhanced the physicochemical properties of DOPs, resulting in increased solubility, decreased viscosity, reduced particle size, and improved thermal stability. In vitro cellular experiments demonstrated that plasma-treated DOPs significantly enhanced nitric oxide (NO) release from RAW 264.7 macrophages compared to untreated DOPs, indicating notable immunostimulatory activity. The capacity to induce NO production increased significantly with extended plasma treatment duration. Plasma treatment also markedly improved the capacity of DOPs to stimulate the secretion of essential cytokines by macrophages. At a concentration of 800 $\mu\text{g/mL}$, plasma treatment resulted in significant increases in the release of TNF- α , IL-1 β , IL-6, and IL-10 by 20.70%, 26.94%, 25.32%, and 13.03%, respectively. These data indicate that plasma treatment effectively enhances the expression of inflammatory factors induced by DOPs and augments their immunostimulatory activities.⁵¹ This study also summarizes the fundamental structural information of immunologically active DOPs, as

outlined in Table 1. In conclusion, the distinct structural characteristics of *Dendrobium officinale* polysaccharides serve as a crucial foundation for modulating their immunoreactivity. These findings establish a vital foundation for a comprehensive understanding the immunoregulatory mechanisms of *Dendrobium officinale* polysaccharides, as well as their applicability in functional food and pharmaceutical development. Current structural investigation of *Dendrobium officinale* polysaccharides primarily emphasizes monosaccharide composition, molecular weight, and glycosidic linkages, necessitating further examination of their advanced structures. Moreover, most studies regarding the structure-activity relationships of *Dendrobium officinale* polysaccharides are singular in focus, highlighting the need for a more comprehensive analysis of the conformational impacts associated with the structural characteristics.

3 | IMMUNOMODULATORY EFFECTS OF *DENDROBIUM OFFICINALE* POLYSACCHARIDES

3.1 | Regulatory effect of *Dendrobium officinale* polysaccharide on immune organs

Immune organs, as the foundation of the immune system, can be categorized into central and peripheral immune organs based on

TABLE 1 Core structural information and immunological mechanisms of DOPs.

Name	Molecular weight (kDa)	Monosaccharide component	Main structure	Biological activities	References
DOP	189	Man:Glc:Gal = 3:2:1	β -D-Glcp, α -D-Galp; acetyl group	Splenocyte proliferation and antibodies $\uparrow$; NK/CTL cytotoxicity $\uparrow$	16
DOW-5B	39.4	GlcA:Glc = 1.2:19.4	Glc-GlcA heteropolysaccharide	Microbiota diversity $\uparrow$; butyrate $\uparrow$	18
DOP	2200	Man:Glc:Gal: Ara = 74.17:47.80:9.03:1	N/A	Enhances innate and adaptive immunity; macrophage phagocytosis, IgA/IgG $\uparrow$; modulates CD4 ⁺ /CD8 ⁺ ratio	31
DOP	8.5	Man:Glc:Ara: GalA = 6.2:2.3:2.1:0.1	2-O-acetylglucomannan; $\rightarrow$ 4)- β -D-Manp-(1 $\rightarrow$ and $\rightarrow$ 4)- β -D-Glcp-(1 $\rightarrow$	Scavenging hydroxyl radical; chelating metal ions; DPPH radical scavenging	28
UDP-1	492	Rib; Rha; Ara; Xyl; Man;	$\rightarrow$ 4)- β -D-Manp-(1 $\rightarrow$ and $\rightarrow$ 4)- β -D-Glcp-	Promotes proliferation, phagocytosis, NO	32
FDP-1	521	Glc; Gal	(1 $\rightarrow$; Slight triple helix; O-acetyl groups	and IL-1 β	
FLP-1	415				
MDOP	3.489	Glc:Man = 2.14:1	$\rightarrow$ 6)- α -D-Glcp-(1 $\rightarrow$ 6)- α -D-Glcp-(1 $\rightarrow$ 4)- β -D-Manp (1 $\rightarrow$; O-acetyl groups	Anti-tumor, immunomodulatory, reconstruct TME	35
DOPs	4.56	Glc:Man = 1.00:5.78	α -(1,3)-Glc; α -(1,4)-Glc and β -(1,4)-Manp	Macrophage activation (NO/TNF- α) $\uparrow$; T/B-cell proliferation; SOD/CAT and ROS $\uparrow$	36
DOP	264	Man:Glc = 4.56:1; Man: Glc = 5.30:1; Man: Glc = 4.79:1	$\rightarrow$ 4)- β -D-Manp-(1 $\rightarrow$, $\rightarrow$ 4)- β -D-Glcp-(1 $\rightarrow$, 2-O- acetyl $\rightarrow$ 4)- β -D-Manp-(1 $\rightarrow$, 3-O- acetyl $\rightarrow$ 4)- β -D-Manp-(1 $\rightarrow$	Macrophage activation and TLR4 $\uparrow$; phagocytosis and cytokines $\uparrow$; macrophages and TLR4/MyD88 $\uparrow$	37
DOP-30	51				
DOP-60	28				
DG2	152.8	Galp:Manp:Glc: Araf = 4.3:1.9:2.8:1.0	1 $\rightarrow$)- β -D-Glc, (1 $\rightarrow$ 4)- β -D-Glc, (1 $\rightarrow$ 3,6)- β -D-Gal, (1 $\rightarrow$ 6)- β -D-Gal	Enhances macrophage phagocytosis; TNF- α , IL-6, NO $\uparrow$	40
DOPS-1	1530	Man: Glc: GalA = 3.2: 1.3: 1	(1 $\rightarrow$ 4)- β -D-Glcp-(1 $\rightarrow$ 4)- β -D-Manp; 2-O-acetyl-(1 $\rightarrow$ 4)- β -D-Manp	Scavenging ($\bullet$ OH, DPPH, O ₂ ⁻ radicals) $\uparrow$; cytotoxic to MDA-MB-231, A549, HepG2 cells	39
c-DOP	N/A	N/A	(1 $\rightarrow$ 4)- β -D-Manp	SOD, CAT, GSH-Px $\uparrow$; MDA $\downarrow$	42
p-DOP					
DOP	649	Man; Glc	β -1,4-Glucomannan; O-acetyl groups	Significantly restores immune organ indices; enhances cellular and humoral immunity; boosts cytokines and IgM $\uparrow$; modulates gut microbiota	48
UDOP-1	134				
UDOP-2	279				
DADOP-1	536				
DADOP-2	616				
DOP-1-1	179	Man:Glc = 5.9:1	An O-acetylated glucomannan with β -d configuration in pyranose sugar forms	TNF- α and IL-1 β secretion $\uparrow$; activates NF- κ B and ERK1/2 pathways	49
HDLP	1800	Man:Glc:GalA = 83.7: 1.3: 9.8	$\rightarrow$ 4)- α -D-Man-(1 $\rightarrow$ 4)- α -D-Glc-(1 $\rightarrow$; contains triple-helix conformation	NO, TNF- α , IL-6, IL-1 β $\uparrow$; macrophage phagocytosis $\uparrow$; potent antioxidant	51
UDLP	656	Man:Glc:GalA = 83.3: 1.3: 10.1			

Abbreviations: Ara, Arabinose; Araf, Arabinofuranose. Gal, Galactose; Galp, Galactopyranose; Glc, Glucose; GlcA, Glucuronic acid; Glcp, Glucopyranose; Man, Mannose; Manp, Mannopyranose; N/A, Not applicable; Rha, Rhamnose; Rib, Ribose; Xyl, Xylose.

their roles, which primarily encompass bone marrow, thymus, spleen, lymph nodes, and mucosal-associated lymphoid tissue.⁵² The immune capacity of the body is contingent upon the development and functionality of both central and peripheral immune organs.⁵³

3.1.1 | Modulation of bone marrow immune function

Bone marrow serves as a source of pluripotent hematopoietic stem cells, functioning as the origin of diverse blood and immune cells.

Current research indicates that DOP exerts inductive effects on bone marrow stem cells, facilitating the differentiation of stem cells into neuron-like cells via the Wnt signaling pathway. Specifically, DOP (25 µg/mL) enhanced the neuronal differentiation of bone marrow mesenchymal stem cells (BMSCs) by up-regulating the expression levels of neuronal markers. This differentiation was associated with the activation of the Wnt signaling pathway, and the inhibition of this pathway resulted in decreased neuronal gene expression. Furthermore, the transplantation of DOP-induced neuron-like cells significantly enhanced neuronal function recovery in vivo, as evidenced by a marked reduction in cerebral infarction volume, neurological severity scores, and inflammatory factor levels.⁵⁴ Subsequent research has indicated that an immunomodulatory activity assay, utilizing Peyer patch-mediated bone marrow cell proliferation in the small intestine, has demonstrated that mice receiving oral treatment with a novel immunomodulatory polysaccharide (DCP-W4) derived from *Dendrobium officinale* have significantly influenced those of immune activity. This was evidenced by changes in immune organ indices, including the spleen and thymus, and the enhancement of Peyer's patch cell supernatant-mediated bone marrow cell proliferation.⁵⁵ The investigation of DOP interactions with the immune microenvironment is essential for understanding and advancing novel and effective immunotherapies. BMSCs serve as critical regulators of immune function due to their capacity for tissue repair and immune system modulation.⁵⁶ An examination of DOP's effect on adipogenic differentiation in rat bone marrow MSCs revealed that DOP concentrations ranging from 0 to 800 µg/mL exhibited no significant toxicity to BMSCs. However, concentrations between 200 and 800 µg/mL significantly inhibited adipogenic differentiation, potentially due to the down-regulation of PPARG, LPL, and FABP4 gene expression in BMSCs.⁵⁷ DOP has been shown to regulate both osteogenic and adipogenic differentiation in bone marrow mesenchymal stem cells and in aged mice. In an in vitro assay, DOP mitigated H₂O₂-induced differentiation fate switching of BMSCs. In aged mice, DOP reduced bone loss and bone marrow adipose tissue (MAT) accumulation by activating the NRF2 antioxidant signaling pathway. Consequently, administration of DOP to aged mice resulted in a significant increase in bone mass, a reduction in MAT, and a decrease in oxidative stress in BMSCs.⁵⁸ Glucocorticoid-induced osteoporosis (GIOP) is a prevalent adverse effect because of their anti-inflammatory and immunomodulatory properties. However, DOP can promote osteogenesis by inhibiting Nrf2 ubiquitylation, which increases nuclear Nrf2 levels during dexamethasone (DEX) treatment. This mechanism disrupts Nrf2/Keap1 interactions, thereby preventing osteoporosis in the context of DEX administration.⁵⁹

3.1.2 | Immunomodulation of the spleen and thymus

The thymus serves as a central immune organ, facilitating lymphocyte proliferation and differentiation, thereby playing a vital role in cellular immunity.⁶⁰ The spleen, another significant immune organ, is enriched with a large number of T-cells, B-cells, and macrophages

and participates in various immune responses within the organism.⁶¹

Both organs are essential for the investigation of immunomodulatory therapies due to their central roles in the immune system. Research has demonstrated that DOP exerts protective effects on these critical immune organs. In a nude mouse transplantation tumor model using human gastric cancer cells, the spleen and thymus indices of the *Dendrobium officinale* polysaccharide (DOPA) group were not significantly different from those of the negative control group (saline group). However, these indices were significantly higher than those of the positive control group (5-FU chemotherapy group).⁶² The results of the study demonstrated that DOPA was found to be safer, protecting the spleen from immune injury and not exacerbating thymic atrophy in nude mice. Further research demonstrated that *Dendrobium officinale* polysaccharides also possess the capacity to repair immune organs. *Dendrobium officinale* leaf polysaccharide (DOLP) effectively improved the thymic and splenic indices in male mice with cyclophosphamide-induced immunodeficiency. The splenic indices of the low-dose group (50 mg/kg/d) and the high-dose group (200 mg/kg/d) increased significantly by 25.24% and 42.55%, respectively, compared with the control group. The thymic indices increased from 0.36 to 1.07 and 1.31, respectively. These findings suggest that DOLP may have the capacity to reverse the atrophy of immune organs caused by drugs or diseases.⁶³ Intervention with varying doses of *Dendrobium officinale* polysaccharides elevated serum immunoglobulin (IgM and IgG) levels and hemolysis values in cyclophosphamide-induced immunodeficient mice. Correspondingly, the immunodeficient mice exhibited significantly higher spleen and thymus indices following polysaccharide intervention, typically in a dose-dependent manner.⁶⁴ In a spleen-deficient constipation model, the spleen and thymus indices of mice were significantly diminished ($p < 0.01$), indicating severe impairment of immune function. Following high-dose DOP intervention, both indices rebounded to levels comparable to the normal group ($p < 0.01$). Lymphocytes in the spleen exhibited tight alignment and the thymus cortex becoming thickened. This suggests that DOP effectively rehabilitated the immune organs by fortifying the spleen, replenishing qi, and regulating intestinal flora function.⁶⁵ In a cyclophosphamide-induced immunocompromised mouse model, the spleen index and thymus index were measured at 2.24 and 0.92 mg/g, respectively, in the normal DOP group. In contrast, in the selenium-modified *Dendrobium officinale* polysaccharide (SeDOP) group, the spleen index ranged from 2.26 to 2.97 mg/g, whereas the thymus index varied from 0.87 to 1.31 mg/g. These findings indicate that all polysaccharide interventions enhanced the immune organ index, with SeDOP demonstrating a statistically significant improvement over normal DOP ($p < 0.01$). Furthermore, the spleen microsomes in the SeDOP group exhibited structural integrity, and the thymic cortex was thickened, resembling that of the normal group. This suggests that selenium modification enhances the immune repair effects of DOP.⁶⁶ In summary, DOP substantially increases spleen and thymus indices by counteracting the atrophy of immune organs, promoting lymphocyte proliferation, and repairing tissue structure. Its immunomodulatory activity is further enhanced by selenium modification (Se-DOP).

3.2 | Regulation of immune cells by *Dendrobium officinale* polysaccharides

3.2.1 | Immunomodulation of macrophages

Macrophages are widely recognized as fundamental immune cells dispersed across various tissues in the body. Plant polysaccharides have been demonstrated to stimulate macrophages by identifying and attaching to specific receptors on their surface, thereby activating immunological responses and exhibiting immunomodulatory effects.⁶⁷ In addition, polysaccharides can stimulate the secretion of bioactive substances and the release of NO in macrophages. These substances, which primarily include interleukins (IL-1, IL-1 α , IL-1 β , IL-6, IL-8, and IL-12), bone morphogenetic protein 2 (BMP-2), IL-1Ra, IL-10, and transforming growth factor- β (TGF- β), can either promote or inhibit inflammation through their involvement in body immunomodulation.^{68,69} DOP has been reported to exert immunomodulatory effects on macrophages (RAW264.7). For instance, DOP demonstrated a protective effect on lipopolysaccharide (LPS)-induced RAW264.7 cells at concentrations ranging from 1 to 20 mg/mL segmented alcohol precipitation. When DOP at a concentration of 1 mg/mL, the optimal concentration for immunomodulation in this context, it significantly promoted the proliferation of RAW264.7 cells, enhanced macrophage phagocytic activity, reduced the release levels of TNF- α , IL-6, and NO from macrophages, and promoted the secretion of TGF- β 1 and polarization to the M2 type.⁷⁰ Investigation of DOP's impact on the RAW264.7 mouse macrophage cell line revealed that *Dendrobium officinale* polysaccharides, at concentrations between 20 and 160 mg/mL, significantly enhanced cell proliferation. The underlying mechanism may involve the reduction of intracytoplasmic I-KB protein levels, activation of the nuclear transcription factor NF-KB, and induction of TNF- α mRNA expression.⁷¹ Furthermore, the immunomodulatory effects of DOP on RAW264.7 macrophages were investigated. It was established that purified DOP demonstrated no evidence of cellular toxicity towards RAW264.7 cells within a concentration range of 3.125–4001.1 g/mL. The results of the study demonstrated a substantial enhancement in the expression of mRNA for IL-1 β , IL-10, IL-12 p40, and IL-6. Furthermore, the secretion of IL-10, IL-12 p40, and IL-6 was promoted, and a significant increase in the expression of p-JNK, p-ERK, and p-P65 proteins was observed. The sustained immunomodulatory effects were noted to persist for up to 120 min.⁷² Polysaccharides may function by either adhering to the surface of RAW264.7 cells or by penetrating the cell interior. Research indicates that crude polysaccharide (DOPW) and purified polysaccharides (DOPW-1 and DOPW-2) enhance the proliferation of macrophages and lymphocytes, as well as macrophage phagocytic activity. This effect is particularly pronounced at elevated polysaccharide concentrations, suggesting that the immunological efficacy of purified polysaccharides surpasses that of crude polysaccharides. The underlying mechanism may involve the high mannose content in purified polysaccharides, which appears to facilitate immunomodulatory functions, including endocytosis, in DOPW-1 and DOPW-2-mediated

cellular activation.⁷³ In conclusion, DOP can exert immunomodulatory roles not only by promoting inflammatory gene expression, stimulating cytokine secretion, and triggering NF-kB and MAPK pathways to activate RAW264.7 cells but also by adhering to the cell surface or entering the cell interior.

3.2.2 | Immunomodulation of T and B lymphocytes

T and B lymphocytes, as crucial component of immune cells, play significant roles in the immunoregulatory processes.⁷⁴ T lymphocytes (T cells) are lymphoid stem cells originating from the bone marrow, which produce cytokines to mediate inflammation and regulate other immune cell types during immune responses.⁷⁵ B lymphocytes (B cells) are effector cells responsible for mediating antibody response. They recognize external antigens via B cell receptors (BCRs) located on their surface, a crucial step in the production of protective antibodies and the establishment of immune memory.⁷⁶ Oral administration of DOP (0.5 mg) significantly increased the count of peripheral leukocytes and enhanced the leukocyte migration inhibitory index in mice. This indicates that *Dendrobium officinale* polysaccharides exert a bidirectional immunomodulatory effect, particularly on non-specific immunity (leukocyte elevation) and cellular immunity.⁷⁷ DOP significantly enhanced the proliferation of splenic lymphocytes in vitro in a cyclophosphamide-induced immunosuppression mouse model, partially reversing the immunosuppressive state induced by cyclophosphamide. The optimal proliferation of mouse T lymphocytes occurred at a DOP concentration of 20 μ g/mL, which significantly enhanced the division and proliferation of spleen T lymphocytes in normal mice. Additionally, the most effective concentration for spleen lymphocytes was 40 μ g/mL.⁷⁸ In addition, treatment with *Dendrobium officinale* polysaccharides at a concentration of 1 μ g/mL in a desiccation syndrome model resulted in decreased abnormal lymphocyte infiltration and apoptosis, while promoting the influx of extracellular calcium ions via M3 muscarinic receptor activation, indicating its potential to enhance immune function.⁷⁹ DOP was shown to enhance the proliferation of splenic T and B cells in vivo in cyclophosphamide-induced immunosuppressed mice, contributing to the normalization of T lymphocyte subpopulations and achieving a near-normal CD4⁺/CD8⁺ ratio in the spleens of these mice.⁴² CD8⁺ T cells are essential in activating host immune responses mediated by DOP.⁸⁰ In summary, DOP enhances immunosuppression resistance and tumor immunity by promoting T and B lymphocyte proliferation, increasing relevant cytokine secretion, and balancing T cell subsets.

3.2.3 | Immunomodulation of natural killer cells

Natural killer cells (NK cells) are essential components of the innate immune system and serve as a critical link between innate and adaptive immune responses.⁸¹ NK cells exert significant immunomodulatory effects on other immune cells, including T cells, B cells,

and dendritic cells, through the secretion of soluble factors and/or direct cell-to-cell contact.⁸² Their regulatory capacity stems from the diverse activating and inhibitory receptors present on the cell surface, with the activation state being precisely regulated by the balance of signals from these receptors. Studies have demonstrated that oral administration of varying doses of *Dendrobium officinale* and its polysaccharides to healthy BALB/c mice significantly enhances NK cell activity and substantially increases interferon-gamma (IFN- γ) production by splenocytes.⁸³ IFN- γ , produced by activated T cells, NK cells, and B cells, can induce an antiviral state and plays important roles in immunomodulation and cytotoxic responses.⁸⁴ In S180 tumor-bearing mouse models, DOP exhibits notable antitumor efficacy, primarily attributable to its immunomodulatory properties. DOP effectively induces a specific humoral immune response without compromising the overall immunity of tumor-bearing mice. Treatment with DOP significantly enhances NK cell cytotoxicity and splenocyte activity in S180-bearing mice, regulates T-cell subpopulation balance, and increases the secretion of Th1-type cytokines such as IL-2 and IFN- γ .¹⁶ These enhancements contribute to a more robust cellular immune response against tumors while maintaining an improved safety profile. As a natural polysaccharide, DOP has shown potential as a carrier to enhance chemotherapeutic efficacy across various tumor types by promoting NK cell proliferation. For example, DOP functions as a drug delivery carrier to enhance anti-tumor effects. When combined with chemotherapeutic agents, DOP markedly improves chemotherapy-induced immunogenic cell death (ICD). This dual functionality enhances tumor targeting of chemotherapeutic agents while minimizing systemic toxicity, typically through nanoparticle formulations. Additionally, DOP promotes immunogenic cell death, stimulates NK cell proliferation, facilitates dendritic cell maturation, and synergistically modulates various immune cells to elicit anti-tumor responses.⁸⁵ Further investigation using cyclophosphamide-induced immunosuppressed mouse models revealed that *Dendrobium officinale* leaf polysaccharides enhance NK cell antigen recognition capacity by upregulating MHC-I molecule expression, specifically Gm11127, H2-K1, H2-Q10, H2-Q6, and H2-Q7, thereby strengthening innate immune responses. This upregulation improves antigen presentation and immune factor secretion by T cells, resulting in synergistic enhancement of adaptive immune function.⁸⁶ In summary, DOP enhances natural killer cell activity and increases expression of immune factors including IFN- γ and IL-2.

3.2.4 | Immunomodulation of dendritic cells

Dendritic cells (DCs) represent the most potent antigen-presenting cells, capable of capturing and presenting antigens to initiate T cell-mediated immune responses. Simultaneously, DCs maintain immune tolerance functions and participate in establishing both central and peripheral tolerance, as well as resolving prolonged immune responses.⁸⁷ Studies demonstrate that natural polysaccharides can enhance fundamental dendritic cell functions during immune response modulation. These polysaccharides activate signaling

pathways through interactions with pattern recognition receptors (PRRs) on DC surfaces, promoting DC maturation, enhancing metabolic activity, improving antigen presentation, and facilitating T-cell activation for effective immune regulation.⁸⁸ Research shows that DOP exhibits therapeutic effects against colon cancer through photodynamic therapy (PDT) and dual immune mechanisms. Specifically, DOP directly activates DCs while stimulating immunogenic cells to enhance DC maturation via antigens captured by photosensitizers during PDT.¹² In addition, in BALB/c mice inoculated with 4T1 tumors, DOP significantly enhances the maturation rate of dendritic cells, synergizes with chemotherapeutic agents, remodels the immunosuppressive microenvironment, and markedly prolongs survival.⁸⁵ Moreover, various *Dendrobium officinale* polysaccharides can enhance dendritic cell maturation. In a Lewis lung cancer hormonal mouse model, *Dendrobium huoshanense* polysaccharides (DHP) increased the quantity of dendritic cells and promoted the proliferation of splenic lymphocytes, leading to an anti-tumor immune response.⁸⁹ In vivo studies indicate that in an immunosuppressed BALB/c mouse models, *Dendrobium officinale* polysaccharide (cDFP-W1) administered at 200 mg/kg significantly enhanced the proportion of CD4⁺ T-cell subpopulations, B-cells, natural killer cells, and dendritic cells while reducing the proportion of CD8⁺ T-cell subpopulations and increasing the percentage of activated macrophages in the spleens of the mice.⁹⁰ In conclusion, although extant studies have confirmed that *Dendrobium officinale* polysaccharides promote dendritic cell maturation, systematic verification of their direct stimulation of dendritic cell activity regarding antigen uptake, migration, and T cell activation remains lacking.

3.3 | Regulatory effects of *Dendrobium officinale* polysaccharides on immune diseases

3.3.1 | Immunomodulation of diabetes mellitus by *Dendrobium officinale* polysaccharides

The pathogenesis of diabetes mellitus involves immune-mediated attack and destruction of pancreatic β -cells, leading to impaired insulin synthesis and secretion, and subsequently disrupting glucose metabolism. It is therefore vital to preserve normal β -cell function in order to prevent and manage diabetes. The immune system is integral to the disease process while natural polysaccharides safeguard β -cell function by modulating immune signaling pathways, thereby producing an anti-diabetic effect.⁹¹ The secretion function of pancreatic β -cells is imperative for metabolic homeostasis. Type I diabetes (T1D) is characterized by the immune system-mediated destruction of β -cells, which involves both β -cell dysfunction and abnormal immune system activation.⁹² In contrast, type II diabetes (T2D) progression primarily involves metabolic regulation dysfunction in β -cells, as demonstrated by inadequate responses to insulin resistance and failure to maintain glucose homeostasis.⁹³ Studies demonstrate that DOP (400 mg/kg) alleviates diabetes by restoring intestinal flora balance and repairing intestinal barrier function in

high-fat diet and streptozotocin-induced type II diabetic rats. In a diabetic rat model, DOP decreased fasting blood glucose, insulin resistance index, and lipid levels while also lowering serum TNF- α , IL-6, and IL-1 β , resulting in a reduction of systemic inflammation.⁹⁴ In a pre-diabetic mouse model, DOP (200 mg/kg) decreases the relative risk of developing type II diabetes by 63.7%. DOP significantly improves fasting blood glucose levels and insulin sensitivity, increases the abundance of short-chain fatty acid (SCFA)-producing bacteria in the intestinal tract, a promotion in the expression of short-chain fatty acid receptors FFAR2 and FFAR3, and an elevation in the secretion of intestinal hormones GLP-1 and PYY. These effects contributed to the repair of islet damage and the improvement of insulin resistance.⁹⁵ In a type 2 diabetes model using male mice on a high-fat diet, administration of varying doses of *Dendrobium officinale* polysaccharides resulted in a significant reduction in fasting blood glucose levels and a decrease in the insulin resistance index. The present findings suggest that *Dendrobium officinale* polysaccharides may effectively regulate blood glucose levels improve insulin sensitivity, potentially exerting a hypoglycemic effect through the protection of β -cell function.⁹⁶ Type II diabetes has been linked to metabolic abnormalities, including insulin resistance and mild inflammation. It has been demonstrated that DOP treatment has the capacity to reduce fasting glucose, insulin, glycosylated serum protein, and lipid levels (TC, TG, LDL-c, and NEFA) while increasing high-density lipoprotein cholesterol concentrations in a rat model of type II diabetes. The DOP treatment resulted in a reduction in oxidative stress damage, as evidenced by enhanced superoxide dismutase activity and total antioxidant capacity, alongside a decrease in malondialdehyde levels.⁹⁷ In addition, *Dendrobium officinale* stem polysaccharide (DOP, 800 mg/kg, optimal) has been shown to mitigate hepatic injury in type II diabetic rats by improving disturbances in hepatic glucose–lipid metabolism. In a type II diabetic rat model, DOP administration enhanced hepatic metabolic disorders, safeguarded the liver against oxidative stress and inflammatory damage, and regulated ceramide and bile acid metabolism.⁹⁸ In summary, DOP has been demonstrated to enhance the management of diabetes-related immunometabolic disorders through the regulation of intestinal microbiota and barrier integrity, suppression of pro-inflammatory cytokines (such as TNF- α , IL-6, and IL-1 β), improvement of antioxidant mechanisms, and reduction of systemic inflammatory responses.

3.3.2 | Immunomodulation of intestinal diseases

The gut maintains intricate connections with the microbiota, where alterations in flora composition and metabolites influence immune system regulation, significantly impacting the onset and progression of intestinal diseases.⁹⁹ Research demonstrates that DOP exerts a significant influence on the host environment and immune metabolic system through the intestinal microbiota. The real-time tracking of DOP's in vivo trajectory in sham-sterile mice through fluorescent labeling indicated that DOP migrates with intestinal contents towards the distal segment of the intestinal tract, where it participates in

metabolic activities. This process likely involves intestinal flora, particularly the keystone species *Bacteroides thetaiotaomicron*, recognizing and metabolizing DOP into oligosaccharide products.¹⁰⁰ These findings indicate that DOP directly interacts with intestinal flora, subsequently influencing intestinal immune function. Animal studies demonstrated that the polysaccharide (DOW-5B) extracted from *Dendrobium ironum* enhanced the diversity of intestinal microbiota in C57BL/6 female mice, particularly increasing the prevalence of butyrate-producing rumenococci, *Fusobacterium*, *Clostridium*, *Parabacterium*, and anti-inflammatory *Acromycobacteria*. Both colon health and immune response in mice were enhanced through a significant increase in butyrate.¹⁸ In vitro colonic simulated fermentation demonstrated that DOP increases beneficial microorganisms, decreases pathogenic bacteria, and significantly enhances butyrate production. In SPF-grade male ICR mice, DOP indirectly influenced the immune system through microbiota modulation, significantly reducing pro-inflammatory factors including CRP, CD3+, CD4+, and TNF- α while increasing CD4+ levels, thereby promoting intestinal health.¹⁰¹

The primary target of DOP, which directly regulates intestinal immune function, is TLR4. In murine models of immunosuppression induced by cyclophosphamide, DOP demonstrated a significant reduction in the expression of TLR4, TNF- α , and NF- κ B proteins, accompanied by a substantial alleviation of inflammation and tissue damage. These results further substantiate that DOP's intestinal immunomodulatory effects involve the TLR pathway.¹⁰² In a DSS-induced mouse model of colitis, DOP was shown to mitigate inflammation by facilitating the release of miR-433-3p-rich small extracellular vesicles (DIE) from intestinal epithelium. These vesicles have been shown to deliver miR-433-3p to macrophages, thereby targeting and inhibiting the MAPK8 gene and consequently obstructing the MAPK signaling pathway and decreasing the production of inflammatory factors.¹⁰³ Furthermore, as illustrated in Figure 4, DOP treatment significantly mitigated chronic colitis and suppressed the development and progression of colitis-associated colon cancer in an AOM/DSS-induced colon cancer mouse models. The underlying mechanisms may involve the inhibition of inflammation, the preservation of epithelial barrier function, and the enhancement of the anti-tumor immune response mediated by tumor-infiltrating cytotoxic T lymphocytes (CTLs).¹⁰⁴ In summary, *Dendrobium officinale* polysaccharides demonstrate significant immunomodulatory effects that promote intestinal health through microbiota regulation and direct interaction with immune targets. These findings suggest their potential role as protective agents against colitis-associated colon cancer.

3.3.3 | Others

Sjögren's syndrome represents a prevalent chronic autoimmune disorder. In vitro experiments using the TNF- α -induced human salivary gland cell line A-253 demonstrated that DOP pretreatment significantly inhibits TNF- α -induced apoptotic factors and stabilizes mitochondrial function. These findings support the hypothesis that DOP modulates immune responses in experimental models of

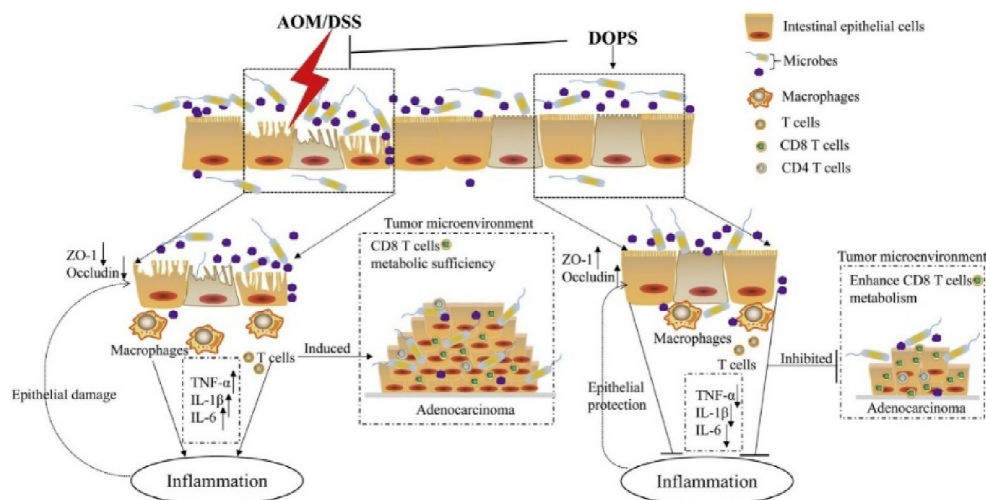


FIGURE 4 The protective mechanism of DOPS in AOS/DSS-induced colitis and colon cancer.¹⁰⁴

Sjögren's syndrome, thereby mitigating chronic autoimmune disease effects associated with salivary glands.¹⁰⁵ In addition, studies using mouse models of Sjögren's syndrome revealed that *Dendrobium officinale* polysaccharide (20 mg/mL) reduces expression of pro-inflammatory cytokines including TNF- α , IL-1 β , and IL-6, thus attenuating immune-mediated inflammation and maintaining inflammatory cytokine homeostasis.¹⁰⁶ Research demonstrates that DOP ameliorates neuroinflammation through immune function modulation via intestinal microbiota. Studies show that DOP exerts protective effects against intestinal barrier disruption and excessive inflammatory responses through the modulation of intestinal bacterial homeostasis and short-chain fatty acid levels. DOP inhibits over-activation of immune and immune-related cells in the central nervous system (CNS) through systemic immune status regulation, consequently protecting neurons and alleviating neurological diseases.¹⁰⁷ In a perimenopausal female mouse model of depression, DOP significantly enhanced the inhibition of pro-inflammatory factor release and microglia activation, regulates intestinal microbiota, and restores hypothalamic-pituitary-adrenal axis function, ultimately improving depression-like behaviors.¹⁰⁸ These findings further support the concept that DOP alleviates neuroinflammation through immunological mechanisms involving intestinal microbiota modulation. Substantial evidence indicates that CNS injury activates both innate and adaptive immunity, which can subsequently trigger seizure activity.¹⁰⁹ In a rat model of pentylenetetrazol (PTZ)-induced epilepsy, DOP (1.5 g/kg) has been shown to reduce brain inflammation and seizure frequency by inhibiting the expression of IL-1 β and TNF- α , along with the MAPK signaling pathway.¹¹⁰

4 | SUMMARY AND PROSPECTS

Dendrobium officinale polysaccharides have attracted considerable attention in the fields of medicine and food science because of their high safety profile, low toxicity, excellent bioavailability, and

structural stability. The advancement of research into immunomodulatory mechanisms has resulted in a growing clarity regarding the structure-activity relationship between its key structural features and immune activity. It is evident that a high mannose content (>50%) significantly enhances recognition by macrophage surface receptors. Furthermore, the molecular weight range (10–1000 kDa) has been demonstrated to optimize tissue penetration capacity, thereby effectively activating immune cells. The synergistic interaction between the main chain $\rightarrow 4$ - β -Manp-(1 $\rightarrow$ and the side chain $\rightarrow 6$ - α -Glc-(1 $\rightarrow$ has been shown to significantly enhance Toll-like receptor binding capacity. Finally, acetyl modifications have been demonstrated to influence complement activation efficacy by regulating spatial conformation. Collectively, these structural parameters underpin DOP's core immunomodulatory activity. Building upon this, DOP exhibits multi-target immune modulation: it not only promotes the development and function of immune organs such as bone marrow, thymus, and spleen, thereby enhancing baseline immunity but also directly activates macrophage phagocytosis and secretion functions, stimulates T/B lymphocyte proliferation, differentiation, and antibody production, elevates natural killer cell activity, and optimizes dendritic cell maturation and antigen presentation capabilities (as illustrated in Figure 5). It is important to note that DOP has been demonstrated to have positive intervention effects across a range of immune-related disease models. These include antitumor activity, improvement of type 2 diabetes, alleviation of intestinal inflammation, mitigation of Sjögren's syndrome symptoms, regulation of neuroinflammation, and potential antiepileptic effects. This finding emphasizes the extensive potential for the regulation of immune homeostasis at various levels.

Despite significant advances in DOP structure-activity relationship studies, future work must focus on the following key directions to overcome translational bottlenecks: A comprehensive investigation into the structure-activity relationships governing how structural features, such as glycan branching and modifying groups, drive specific immune responses is required. In addition, it is

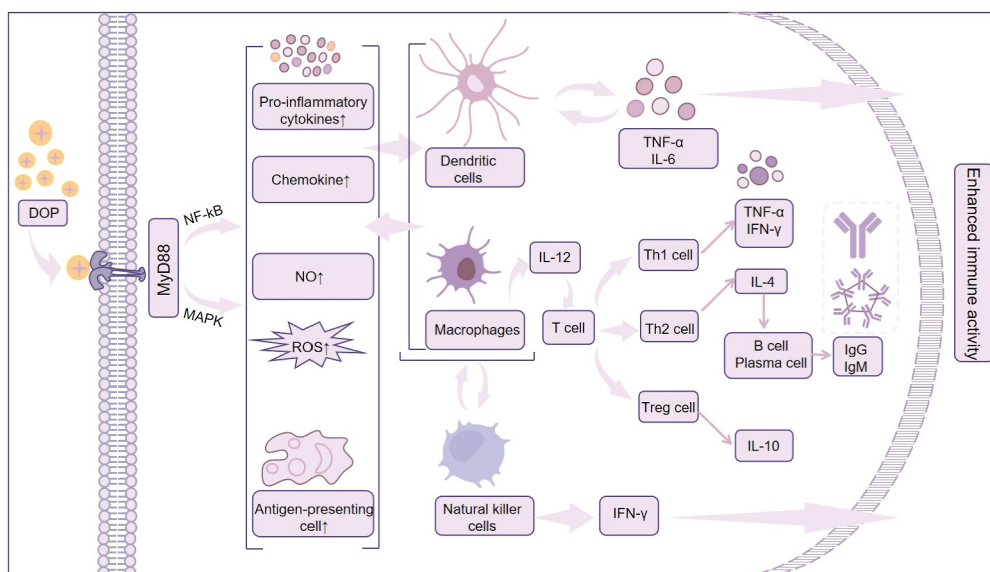


FIGURE 5 Immunomodulatory mechanism of *Dendrobium officinale* polysaccharides.

imperative to elucidate the dynamic regulatory networks of downstream signaling pathways following receptor recognition in order to comprehensively map the action network. Concurrently, future research should transcend single-pathway perspectives by integrating metabolomics, epigenetic regulation, and intercellular communication studies to systematically elucidate the bidirectional regulatory principles by which DOP restores immune balance under pathological conditions. Furthermore, given that extant evidence is predominantly derived from in vitro experiments and animal models, there is an urgent requirement for clinical trials in humans in order to provide evidence-based support for efficacy and safety, thereby accelerating clinical translation. Advancing these research directions will resolve core bottlenecks in DOP transformation and application while providing scientific support for developing innovative Traditional Chinese Medicine (TCM) drugs with well-defined immunomodulatory effects, thereby accelerating TCM modernization.

AUTHOR CONTRIBUTIONS

Hongyue Zhou: Investigation; writing—original draft; writing—review and editing. **Yinshu Li:** Writing—original draft; writing—review and editing. **Zhanhong Huang:** visualization. **Qiankun Liu:** Project administration; resources; software. **Naixia Gong:** Writing—review and editing. **Xu Lu:** Formal analysis; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable—no new data generated, or the article describes entirely theoretical research.

ETHICS STATEMENT

None declared.

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