Effects of Codonopsis pilosula Polysaccharide on Growth Performance, Serum Cytokines, and Intestinal Mucosal Secretory Immunoglobulin A Content in Piglets: Postprint

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Abstract

The present study was designed to investigate the effects of Codonopsis pilosula polysaccharide (CPP) on growth performance, serum cytokines, and intestinal mucosal secretory immunoglobulin A (SIgA) content in piglets.

Full Text

Effects of Codonopsis pilosula Polysaccharide on Growth Performance, Serum Cytokines and Intestinal Mucosal Secretory Immunoglobulin A Contents of Piglets

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Abstract

This experiment was conducted to investigate the effects of Codonopsis pilosula polysaccharide (CPP) on growth performance, serum cytokines, and intestinal mucosal secretory immunoglobulin A (SIgA) contents in piglets. Sixty 1-day-old "Duroc × Landrace × Yorkshire" crossbred piglets from six litters were randomly divided into three groups with two replicates per group and ten piglets per replicate (half male and half female). The trial began at 14 days of age, with the three groups receiving either milk replacer (control group), milk replacer + 1% CPP (low-dose group), or milk replacer + 2% CPP (high-dose group). All piglets were weaned at 21 days of age, and the experimental period lasted 14

days. The results showed that, compared with the control group: (1) At 21 days of age, dietary supplementation with 2% CPP extremely significantly increased average body weight ($P < 0.01$); at 28 days of age, dietary supplementation with 1% and 2% CPP significantly increased average body weight ($P < 0.05$). From 22 to 28 days of age, dietary supplementation with 2% CPP significantly increased average daily gain (ADG) and average daily feed intake (ADFI) ($P < 0.05$). (2) At 21 days of age, dietary supplementation with 2% CPP significantly increased serum interferon-γ (IFN-γ), interleukin-2 (IL-2), and interleukin-6 (IL-6) contents ($P < 0.05$); at 28 days of age, dietary supplementation with 1% and 2% CPP significantly increased serum IL-2, interleukin-4 (IL-4), and IL-6 contents ($P < 0.05$). (3) Dietary supplementation with 2% CPP extremely significantly increased duodenal, jejunal, and ileal mucosal SIgA contents ($P < 0.01$). In conclusion, dietary supplementation with 1% and 2% CPP can improve growth performance and increase serum cytokine and intestinal mucosal SIgA contents in piglets, with 2% CPP demonstrating superior effects to 1% CPP.

Keywords: Codonopsis pilosula polysaccharide; piglets; growth performance; cytokine; intestinal mucosa

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Introduction

Codonopsis pilosula is a traditional Chinese medicinal herb commonly used as a substitute for ginseng in treating spleen-lung qi deficiency, internal heat with thirst, shortness of breath with palpitations, and poor appetite with loose stools. Polysaccharides are the active components of Codonopsis pilosula, and modern pharmacological studies have confirmed that Codonopsis pilosula polysaccharides (CPP) possess antitumor, immunity-enhancing, and anti-fatigue activities [1]. Wang et al. [2] found that in a D-galactose-induced aging mouse model, Codonopsis pilosula enhanced immune function and anti-aging capacity by increasing serum interleukin-2 (IL-2) content. Chen et al. [3] investigated the antitumor mechanism of CPP and its effects on peripheral blood cytokines, demonstrating that CPP significantly inhibited tumor growth in tumor-bearing mice and markedly increased serum cytokine levels including IL-2, interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ). Peng et al. [4] administered different doses of CPP to mice and observed significantly improved weight gain rates and feed utilization efficiency. Other studies have also shown that Codonopsis pilosula extract can promote growth performance in piglets [5].

Secretory immunoglobulin A (SIgA) is the primary effector molecule of the intestinal mucosal immune system and the most abundantly secreted immunoglobulin in the body. SIgA can prevent microorganisms and pathogens from adhering to the intestinal tract, activate the complement C3 alternative pathway, dissolve bacteria, and enhance the bactericidal activity of monocytes [6]. However, the effects of CPP on growth performance and immune function in piglets

have not been previously reported. This study investigated the effects of dietary supplementation with different CPP doses on piglet growth performance, serum cytokines, and intestinal mucosal SIgA content to evaluate its efficacy and provide a basis for future application in piglet diets.

Materials and Methods

1.1 Experimental Materials "Duroc × Landrace × Yorkshire" crossbred piglets were provided by Qingyang Wuxing Breeding Farm in Anhui Province. Codonopsis pilosula medicinal material was purchased from Bozhou Jirentang Pharmaceutical Co., Ltd. in Anhui. ELISA kits for porcine IFN-γ, IL-2, IL-4, and IL-6 were purchased from Shanghai Kexing Trading Co., Ltd., and the porcine SIgA ELISA kit was purchased from Nanjing Senbeijia Biological Co., Ltd. Chloroform, water-saturated phenol, isoamyl alcohol, anhydrous ethanol, sodium acetate, and potassium acetate were purchased from Wuxi Zhanwang Chemical Co., Ltd. Centrifuge tubes and pipette tips were purchased from Axygen Biosciences (USA).

Equipment included a BSD-100 electric thermostatic incubator (Shanghai Boxun Medical Equipment Factory), a TD-100 small extraction and concentration unit (Zhejiang Senli Machinery Technology Co., Ltd.), an MK3 microplate reader (Thermo, USA), and a TGL-18R benchtop high-speed centrifuge (Zhuhai Black Horse Medical Instrument Co., Ltd.).

1.2 Preparation of Codonopsis pilosula Polysaccharide Six kilograms of Codonopsis pilosula were weighed, impurities removed, and washed three times. After draining, 60 L of 84% ethanol was added at a solid-liquid ratio of 1:10 (mass/volume) for extraction three times, each lasting 1 hour, to remove lipids. The material was then dried and weighed. Pure water was added at a solid-liquid ratio of 1:20 (mass/volume), followed by ultrasonic oscillation extraction for 40 minutes. The extract was transferred to a concentration tank for concentration, then vacuum freeze-dried to produce powder. After preparation, the phenol-sulfuric acid method determined that 1 g of crude drug contained approximately 0.11 g of CPP powder.

1.3 Experimental Design and Management Sixty healthy 1-day-old "Duroc × Landrace × Yorkshire" crossbred piglets from six litters were randomly divided into three groups with two replicates per group and ten piglets per replicate (half male and half female). All piglets were introduced to milk replacer at 7 days of age (composition and nutrient levels shown in Table 1). The trial began at 14 days of age, with the three groups receiving either milk replacer (control group), milk replacer + 1% CPP (low-dose group), or milk replacer + 2% CPP (high-dose group). Piglets were weaned at 21 days of age, and diets remained unchanged before and after weaning. Piglets had ad libitum

access to water, and disinfection and vaccination procedures strictly followed the farm management protocol. The experimental period lasted 14 days.

Table 1 Composition and nutrient levels of piglet milk replacer (air-dry basis) %

Ingredients	Content	Nutrient levels[2])	Content
Dried whole milk		ME/(MJ/kg)	
Dried skimmed milk		DM	
Dried whey		CP	
NaCl		Lys	
Premix[1])		Ca	
Total			

[1]) Premix provided the following per kg of diet: VA 7,000 IU, VD_3 2,000 IU, VE 10 IU, VK_3 2.2 mg, VB_1 2.375 mg, VB_2 4.8 mg, VB_6 0.15 mg, VB_{12} 0.0175 mg, nicotinic acid 16 mg, calcium pantothenate 5.75 mg, folic acid 0.85 mg, biotin 0.0175 mg, lysine 0.95 mg, antioxidant 0.045 mg, enzyme preparation 1,100 mg, flavor agents 45 mg, sweet agents 45 mg, Mn (as manganese sulfate) 20.18 mg, I (as potassium iodide) 0.4 mg, Se (as sodium selenite) 0.35 mg.

[2]) ME was a calculated value, while the others were measured values.

1.4 Sample Collection **1.4.1 Serum Preparation** At 14, 21, and 28 days of age, 10 piglets were randomly selected from each group for blood collection via anterior vena cava puncture. After standing for 2 hours, serum was separated by centrifugation at 3,000 r/min for 10 minutes and stored at -20 °C.

1.4.2 Intestinal Tissue Collection and Preservation At the end of the trial, six piglets were randomly selected from each group and euthanized. Duodenum, jejunum, and ileum were collected, opened longitudinally, and mucosa was scraped and stored at -20 °C.

1.5 Growth Performance Measurement At 14, 21, and 28 days of age, individual piglets were weighed before morning feeding to record initial body weight (IBW) and final body weight (FBW), from which average daily gain (ADG) was calculated. Feed intake and residual feed were accurately recorded for each replicate to calculate average daily feed intake (ADFI). Feed-to-gain ratio (F/G) was calculated based on ADFI and ADG.

1.6 Determination of Serum Cytokines and Intestinal Mucosal SIgA Serum IFN-γ, IL-2, IL-4, and IL-6 contents and intestinal mucosal SIgA content were determined by ELISA according to kit instructions.

1.7 Statistical Analysis Data were expressed as means ± standard deviation. One-way ANOVA was performed using SPSS 19.0 software, followed by Duncan' s multiple comparison test. Differences were considered significant at $P < 0.05$ and extremely significant at $P < 0.01$.

Results

2.1 Effects of CPP on Piglet Growth Performance As shown in Table 2 , average body weight was similar across groups at 14 days of age with no significant differences ($P > 0.05$). At 21 days of age, the high-dose group showed extremely significantly higher average body weight than the control group ($P < 0.01$) and significantly higher than the low-dose group ($P < 0.05$). At 28 days of age, the high-dose group exhibited extremely significantly higher average body weight than both the low-dose and control groups ($P < 0.01$), while the low-dose group was significantly higher than the control group ($P < 0.05$).

From 14 to 21 days of age, ADG in CPP-supplemented groups was higher than the control group but without significant differences ($P > 0.05$). From 22 to 28 days of age, ADG in the high-dose group was extremely significantly higher than the control group ($P < 0.01$), while the low-dose group was significantly higher ($P < 0.05$). During the same period, ADFI in the high-dose group was significantly higher than the control group ($P < 0.05$). Feed-to-gain ratio was lower in CPP-supplemented groups compared to the control group ($P > 0.05$).

Table 2 Effects of Codonopsis pilosula polysaccharides on growth performance of piglets

Items	Days of age	Control group	Low dosage group	High dosage group
ABW/kg	14	4.30$±0.42	4.35±0.30	4.58±0.28
	21	5.96±0.31*B*	6.21±0.30*ABb*	6.75±0.32*Aa*
	28	7.2		
d)]	14 21	237.71±44.84	266.86±64.67	309.14±67.24
	22 28	179.14±19.45*Bb*	227.43±38	
d)]	22 28	292.00±31.70*b*	345.69±58.78*ab*	359.00±31.13*a*
F/G	22 28	1.63±0.12	1.52±0.	

In the same row, values with the same or no letter superscripts indicate no significant difference ($P > 0.05$), different lowercase letters indicate significant difference ($P < 0.05$), and different uppercase letters indicate extremely significant difference ($P < 0.01$). The same applies below.

2.2 Effects of CPP on Serum Cytokines **2.2.1 Serum IFN-γ Content** As shown in Table 3 , serum IFN-γ content was similar across groups at 14 days of age ($P > 0.05$). At 21 days of age, the high-dose group showed significantly higher serum IFN-γ content than the control group ($P < 0.05$). At 28 days of age, the high-dose group exhibited extremely significantly higher serum IFN-γ

content than the control group (P < 0.01) and significantly higher than the low-dose group (P < 0.05).

Table 3 Effects of Codonopsis pilosula polysaccharides on serum IFN-γ content of piglets (ng/L)

Days of age	Control group	Low dosage group	High dosage group
14	1,931.67$±15.28|1, 911.67±75.71|1, 928.33±11.55||21|1, 875.00±20.00*b*|1, 888.33±15.28*ab*|1, 91		

2.2.2 Serum IL-2 Content As shown in Table 4 , serum IL-2 content was similar across groups at 14 days of age (P > 0.05). At 21 days of age, the high-dose group showed significantly higher serum IL-2 content than the control group (P < 0.05). At 28 days of age, the high-dose group exhibited extremely significantly higher serum IL-2 content than the control group (P < 0.01), while the low-dose group was significantly higher (P < 0.05).

Table 4 Effects of Codonopsis pilosula polysaccharides on serum IL-2 content of piglets (ng/L)

Days of age	Control group	Low dosage group	High dosage group
14	357.35$±10.60|351.47±13.48|345.59±15.56||21|312.25±14.50*b*|325.00±7.78*ab*|339.71±5.88*a*||28		

2.2.3 Serum IL-4 Content As shown in Table 5 , serum IL-4 content was similar across groups at 14 days of age (P > 0.05). At 21 days of age, no significant differences were observed between CPP-supplemented groups and the control group (P > 0.05). At 28 days of age, the high-dose group showed extremely significantly higher serum IL-4 content than the control group (P < 0.01), while the low-dose group was significantly higher (P < 0.05).

Table 5 Effects of Codonopsis pilosula polysaccharides on serum IL-4 content of piglets (ng/L)

Days of age	Control group	Low dosage group	High dosage group
14	51.18$±2.15|48.84±0.85|49.38±2.36||21|49.92±2.09|52.82±4.09|58.19±6.42||28|50.32±3.37*Bb*|		

2.2.4 Serum IL-6 Content As shown in Table 6 , serum IL-6 content was similar across groups at 14 days of age (P > 0.05). At 21 days of age, the high-dose group showed significantly higher serum IL-6 content than the control group (P < 0.05). At 28 days of age, the high-dose group exhibited extremely significantly higher serum IL-6 content than the control group (P < 0.01), the low-dose group was significantly higher than the control group (P < 0.05), and the high-dose group was significantly higher than the low-dose group (P < 0.05).

Table 6 Effects of Codonopsis pilosula polysaccharides on serum IL-6 content of piglets (ng/L)

Days of age	Control group	Low dosage group	High dosage group
14	518.18$\pm$8.37\|518.70$\pm$12.83\|524.26$\pm$13.98\|\|21\|488.22$\pm$24.12b\|513.15$\pm$22.45ab\|544.63$\pm$17.86a||		

2.3 Effects of CPP on Intestinal Mucosal SIgA Content As shown in Table 7 , the high-dose group exhibited extremely significantly higher duodenal mucosal SIgA content than both the low-dose and control groups ($P < 0.01$). Compared with the control group, the high-dose group showed extremely significantly increased jejunal mucosal SIgA content ($P < 0.01$). The high-dose group also demonstrated extremely significantly higher ileal mucosal SIgA content than the control group ($P < 0.01$) and significantly higher than the low-dose group ($P < 0.05$).

Table 7 Effects of Codonopsis pilosula polysaccharides on intestinal mucosal SIgA content of piglets (μg/mL)

Items	Control group	Low dosage group	High dosage group
Duodenum	22.38$\pm$0.36B\|25.46$\pm$2.31B\|33.18$\pm$3.23A\|\|$Jejunum$\|22.40$\pm$1.56Bb\|27.02$\pm$2.20$ABab$\|32.94$\pm$4.41Aa|		

Discussion

Studies have shown that Codonopsis pilosula extract contains multiple components, including sterols, sugars and glycosides, alkaloids and nitrogenous compounds, volatile components, trace elements, and amino acids. Among these, polysaccharide components can improve animal intestinal microbial diversity and enhance production performance [7]. Polysaccharides can also significantly reduce gastric juice and acid secretion and decrease pepsin activity [8]. Previous reports indicate that dietary supplementation with Codonopsis pilosula in piglets can significantly increase daily gain, reduce feed-to-gain ratio, and improve growth performance and immune function [9], though the specific active component responsible remains difficult to identify. To further explore the effects of CPP, this study selected piglets of the same parity and similar body weight for clinical trials. The results demonstrated that dietary supplementation with both 1% and 2% CPP increased ADG and ADFI while reducing F/G, with 2% CPP showing more pronounced effects. Dietary supplementation with 2% CPP significantly increased average body weight at weaning (21 days) and post-weaning (28 days) and significantly improved ADG and ADFI during the first week post-weaning (22–28 days). These findings indicate that appropriate dietary CPP supplementation can improve piglet growth performance and promote growth, consistent with the results of Zeng et al. [5].

Cytokines are small, biologically active multifunctional molecules involved in immune responses. Interleukins (IL) are a class of cytokines produced by various cell types that participate in numerous physiological and pathological processes [10]. Th1 cells secrete cytokines such as IL-2, interferon-α (IFN-α), and tumor necrosis factor-β (TNF-β), which are primary participants in anti-cancer and anti-viral responses, while Th2 cells secrete IL-4, IL-6, and interleukin-10 (IL-10), which can suppress immune responses [11-12]. IL-2 is a pleiotropic cytokine mainly produced by activated T cells that stimulates T cell growth, proliferation, and differentiation [13]; promotes cytotoxic T precursor cell differentiation into cytotoxic T cells; enhances killing activity; and promotes natural killer cell function and interferon release [14]. IL-4 is a multifunctional cytokine primarily secreted by Th2 cells that stimulates B cell proliferation and differentiation for antibody production and promotes B cell synthesis and secretion of immunoglobulins to mediate humoral immunity [15]. IL-6 can be produced by Th2 cells, fibroblasts, and macrophages. Both IL-4 and IL-6 act on B cells, with IL-4 enhancing IgE-induced immune responses and IL-6 directing IgG synthesis and secretion, both participating in antibody-mediated humoral immune responses [16]. As a pro-inflammatory cytokine, IL-6 can be synthesized by various cells including monocytes-macrophages, endothelial cells, lymphocytes, and fibroblasts, promoting acute-phase protein synthesis and antibody production during infection. Additionally, IL-6 promotes IL-2 receptor expression on T lymphocytes, enhances IL-2 effects, and promotes natural killer cell proliferation, differentiation, and activity, thereby improving immune function [17].

Zhang et al. [18] found that CPP promoted cellular immunity in mice. Cao et al. [19] demonstrated that CPP significantly enhanced IL-2 secretion in chickens. Lin et al. [20] used a nitric acid-sodium selenite method to selenize CPP and studied its effects on immune mechanisms, showing that selenized CPP could reverse cyclophosphamide-induced immune organ atrophy in mice and promote cytokine production including IL-2 and IL-6. Han [21] found that CPP could inhibit cancer cachexia by regulating serum cytokines TNF-α and IL-6 and controlling tumor growth. The present results align with these reports, showing that dietary CPP supplementation at different doses increased serum cytokine levels (IFN-γ, IL-2, IL-4, and IL-6) and enhanced immune function in piglets through cellular immunity, with 2% CPP demonstrating particularly significant effects.

SIgA is produced by plasma cells in the lamina propria of respiratory, urinary, and intestinal mucosa. By binding to antigenic microorganisms, SIgA prevents pathogen adhesion and colonization on cell surfaces, forming the first line of defense in mucosal immunity. In intestinal mucosal immunity, humoral immunity dominated by SIgA plays a primary role in preventing pathogen adhesion, neutralizing viruses and toxins, and immune exclusion. Zhao et al. [22] investigated the effects of different concentrations of Isatis root polysaccharide on SIgA cell expression in the duodenum of colostrum-deprived mice, finding that it promoted small intestinal SIgA cell expression in a dose-dependent manner. Wang et al. [23] reported that long-root mushroom polysaccharide could adjust

intestinal flora in dysbiotic mice and increase intestinal mucosal SIgA content. Similarly, this study found that 2% CPP significantly increased duodenal, jejunal, and ileal mucosal SIgA content in piglets through humoral immunity, enhancing intestinal mucosal immunity and improving mucosal barrier function.

In conclusion, dietary supplementation with appropriate levels of CPP can improve piglet growth performance, increase serum cytokine contents to varying degrees, and enhance intestinal mucosal immunity, with 2% CPP demonstrating superior effects to 1% CPP.

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Note: Figure translations are in progress. See original paper for figures.