

Study on the Mechanism of *Acanthopanax Senticosus* Polysaccharides Alleviating Anxiety- and Depression-like Behaviors in DSS-induced Colitis Mice

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Abstract: The purpose of this study is to investigate the alleviating effect and mechanism of *Acanthopanax senticosus* polysaccharides (ASP) on anxiety- and depression-like behaviors in mice with DSS-induced colitis. Mice were divided into the Control group, DSS group, ASP-L group, ASP-H group and mesalazine group. The effects were evaluated by observing general conditions, conducting behavioral tests and performing RT-qPCR detection. The results showed that mice in the DSS group exhibited colitis symptoms such as weight loss, diarrhea and hematochezia, accompanied by obvious anxiety- and depression-like behaviors. Meanwhile, the expressions of IL-6, IL-1 β and TNF- α in colon tissues were increased, and the expression of BDNF in cerebral cortex was decreased. ASP could improve the above symptoms in a dose-dependent manner, reduce the levels of inflammatory factors and up-regulate the expression of BDNF, with the effect of high-dose ASP being similar to that of mesalazine. These findings indicate that ASP may alleviate colitis and its accompanying mental and behavioral abnormalities by inhibiting intestinal inflammation and regulating central nervous factors, providing experimental basis for the treatment of related diseases.

Keywords: *Acanthopanax Senticosus* Polysaccharides, DSS, Colitis, Anxiety, Depression, Inflammatory Factors, BDNF

1. Introduction

Inflammatory bowel disease (IBD) is a group of diseases characterized by chronic intestinal inflammation. Its harms are not limited to local intestinal mucosal damage, recurrent diarrhea, and hematochezia. More importantly, approximately 40%-60% of patients suffer from concurrent mental and behavioral abnormalities such as anxiety and depression, which exacerbate the complexity of the condition. This "gut-mental" comorbid state can intensify intestinal inflammation through stress responses, forming a vicious cycle and severely reducing patients' quality of life ^[1]. Recent studies have confirmed that gut-brain axis dysfunction is the key mechanism underlying this phenomenon: the intestine and the central nervous system achieve bidirectional regulation through neural, immune, endocrine, and other pathways. However, the excessive presence of inflammatory factors, damage to the intestinal barrier, and imbalance of neurotransmitters can all disrupt this balance and induce mental symptoms ^[1]. The dextran sulfate sodium (DSS)-induced colitis model is widely used because it can accurately replicate the pathological characteristics of human ulcerative colitis. By damaging the intestinal epithelial barrier, this model activates immune cells such as macrophages to release a large number of inflammatory factors, triggering intestinal mucosal congestion and ulcers. At the same time, it affects the central nervous system through the blood circulation, causing mice to exhibit behaviors similar to human anxiety and depression, such as reduced exploratory behavior and anhedonia, thus providing an ideal tool for studying gut-brain axis interactions ^[2].

Acanthopanax senticosus, as a traditional Chinese medicine for reinforcing vital energy, has its polysaccharide component (ASP) with fully confirmed pharmacological activities. Modern research has shown that ASP can alleviate local inflammation by inhibiting inflammatory signaling pathways such as NF- κ B, regulate the activity of immune cells, and promote the repair of nerve cells, demonstrating the potential for "intestinal-central" dual regulation ^[3]. However, there is still no systematic conclusion on whether ASP can improve emotional abnormalities associated with IBD and whether it exerts its effects by regulating intestinal inflammatory factors and brain neurotrophic factors. In this study, by establishing a DSS-induced colitis model and combining behavioral evaluation with molecular biological detection,

we explored the alleviating effect of *Acanthopanax senticosus* polysaccharides on emotional abnormalities in colitis mice and its association with intestinal inflammatory factors and brain-derived neurotrophic factor (BDNF), aiming to provide experimental basis for elucidating its mechanism of action and clinical application.

2. Materials and Instruments

2.1 Experimental Animals

Fifty SPF-grade male ICR mice, 6-8 weeks old and weighing 20-22 g, were provided by the Experimental Animal Center of Heilongjiang University of Chinese Medicine., with the license number: SYXK (Hei) 2021-010. The mice were housed in an environment with a constant temperature ($22\pm1^{\circ}\text{C}$) and constant humidity ($55\pm5\%$), under a 12-hour light-dark cycle, with free access to food and water. After 1 week of adaptive feeding, the experiment was conducted.

2.2 Test Drugs

The Chinese herbal decoction pieces of *Acanthopanax senticosus* were produced by Heilongjiang Lin's Shengtai Pharmaceutical Co., Ltd., with the batch number 1808001. The *Acanthopanax senticosus* polysaccharides used in this experiment were crude polysaccharides obtained by extracting, purifying and deproteinizing *Acanthopanax senticosus* in the early stage of the laboratory. After optimizing the extraction process, deep eutectic solvent was used to extract the polysaccharides, which were then precipitated with 80% (v/v) ethanol. After centrifugation at 8000 rpm for 10 minutes to remove the supernatant, the remaining substance was freeze-dried under vacuum for 72 hours. The precipitate, from which proteins were removed by the elution procedure after being re-collected five times via centrifugation (10000 rpm, 10 minutes), was used.

2.3 Experimental Reagents and Instruments

Dextran sulfate sodium (DSS, purity $\geq 98\%$) was purchased from Beijing Bo'ao Tuoda Technology Co., Ltd., with the batch number: D6320D; Mesalazine enteric-coated tablets, 0.25 g per tablet, were purchased from Heilongjiang Tianhong Pharmaceutical Co., Ltd., with the batch number: 20240408; Primers for IL-6, IL-1 β , TNF- α , BDNF, and internal reference β -actin were synthesized by Shanghai Sangon Biotech Co., Ltd. The primer sequences are shown in Table 1; Elevated plus maze device was purchased from Shanghai Xinruan Information Technology Co., Ltd.; Real-time fluorescent quantitative PCR instrument (CFX96) was purchased from Bio-Rad (USA); High-speed refrigerated centrifuge (Centrifuge 5417R) was purchased from Eppendorf (Germany); Ultra-clean workbench (SW-CJ-2FD) was purchased from Suzhou Purification Equipment Co., Ltd.

Table 1: Primer Sequences.

Gene	Forward Primer (5'-3')
IL-6	CTGCAAGAGACTTCCATCCAG
IL-1 β	GAAATGCCACCTTTTGACAGTG
TNF- α	GGTGCCTATGTCTCAGCCTCTT
BDNF	ATGGATGCTGGGGATGTCGT
β -actin	TGGAATCCTGTGGCATCCATGAAAC

3. Methods

3.1 Experimental Grouping and Model Establishment

Fifty SPF-grade male ICR mice were randomly divided into 5 groups by body weight, with 10 mice in each group. The specific grouping and treatments are as follows:

The normal control group (Control group) continuously drank sterile water and was given intragastric administration of 0.9% normal saline daily, with an experimental period of 21 days. The DSS model group (DSS group) was given intragastric administration of 0.9% normal saline from day 1 to 7; from day 8 to 21, they drank 3% (mass fraction) DSS solution for modeling, and were simultaneously given intragastric administration of 0.9% normal saline. The low-dose *Acanthopanax senticosus*

polysaccharide group (ASP-L group) was given intragastric administration of 50 mg/kg *Acanthopanax senticosus* polysaccharide solution from day 1 to 7; from day 8 to 21, they drank 3% DSS solution for modeling, and were simultaneously given intragastric administration of 50 mg/kg *Acanthopanax senticosus* polysaccharide solution. The high-dose *Acanthopanax senticosus* polysaccharide group (ASP-H group) was given intragastric administration of 200 mg/kg *Acanthopanax senticosus* polysaccharide solution from day 1 to 7; from day 8 to 21, they drank 3% DSS solution for modeling, and were simultaneously given intragastric administration of 200 mg/kg *Acanthopanax senticosus* polysaccharide solution. The positive drug group (mesalazine group) was given intragastric administration of 200 mg/kg mesalazine suspension from day 1 to 7; from day 8 to 21, they drank 3% DSS solution for modeling, and were simultaneously given intragastric administration of 200 mg/kg mesalazine suspension.

On the 14th day after modeling, the body weight and disease activity index (DAI) of the mice were monitored; subsequently, anxiety- and depression-like behavioral tests such as the elevated plus maze test and sucrose preference test were performed; on the 15th day, the mice were dissected to detect fecal water content and measure colon length.

3.2 Behavioral Tests

3.2.1 Elevated Plus Maze Test

The test was conducted on day 1 after modeling. The device consisted of 2 open arms (30 cm×5 cm), 2 closed arms (30 cm×5 cm×15 cm), and a central area (5 cm×5 cm), with a height of 50 cm from the ground. Mice were placed in the central area, facing the open arm, and the number of entries into open and closed arms and the residence time in each arm within 5 min were recorded. The percentage of open arm entries (number of open arm entries / total entries × 100%) and the percentage of open arm residence time (open arm residence time / total residence time × 100%) were calculated. A higher percentage indicated a lower level of anxiety.

3.2.2 Sucrose Preference Test

The test was conducted on day 1 after the elevated plus maze test. Mice were adapted to sucrose water 24 h before the test: each cage was provided with two identical water bottles containing 1% sucrose solution and distilled water, respectively, for 24 h. After adaptation, water was deprived for 24 h, then 1% sucrose solution and distilled water were provided in separate bottles, and the consumption of both liquids within 1 h was recorded. Sucrose preference rate = (sucrose solution consumption / total liquid consumption) × 100%. A higher preference rate indicated a lower level of depression.

3.3 RT-qPCR Detection for Inflammatory Genes in Mouse Colon Tissues (*IL-6*, *IL-1β*, *TNF-α*) and *BDNF* Expression in Mouse Cerebral Cortex

After the behavioral tests, the mice were sacrificed. The colon tissues and cerebral cortex were quickly isolated, snap-frozen in liquid nitrogen, and stored at -80°C for later use.

RNA extraction: Total RNA was extracted from the tissues according to the kit instructions. The concentration and purity of RNA were determined using an ultraviolet spectrophotometer (OD260/OD280 ratio ranged from 1.8 to 2.0).

Reverse transcription: 1 μg of total RNA was taken to synthesize cDNA following the instructions of the reverse transcription kit.

qPCR reaction: The reaction system was 20 μL, consisting of 10 μL SYBR Green Mix, 0.5 μL of each forward and reverse primer, 2 μL cDNA template, and 7 μL ddH₂O. The reaction conditions were as follows: pre-denaturation at 95°C for 30 s; followed by 40 cycles of denaturation at 95°C for 5 s and annealing at 60°C for 30 s. With β-actin as the internal reference, the relative expression level of the target gene was calculated using the $2^{-\Delta\Delta C_t}$ method.

3.4 Statistical Analysis

SPSS 26.0 software was used for statistical analysis. Measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$). One-way analysis of variance (ANOVA) was used for comparison among multiple groups, and LSD-t test was used for pairwise comparison between groups. A *P*-value <0.05 was considered statistically significant.

4. Results

4.1 Effect of *Acanthopanax senticosus* Polysaccharides on General Conditions of DSS-induced Colitis Mice

Mice in the Control group showed good mental state, active activity, steady weight gain during the experiment, smooth and shiny fur, normal granular feces, and no diarrhea or hematochezia. Mice in the DSS group exhibited obvious listlessness, significantly reduced activity, decreased appetite, and continuous weight loss 3-5 days after DSS administration. Their fur became rough and dull, and diarrhea (loose feces) and hematochezia appeared successively from day 7, worsening over time. Mice in the ASP-L group had milder symptoms than the DSS group, with smaller weight loss, delayed onset, and milder diarrhea and hematochezia. The ASP-H group showed more significant improvement, with near-normal mental state, significantly alleviated weight loss, and only a few mice with mild diarrhea. The mesalazine group had similar effects to the ASP-H group, with stable weight, basically normal fecal traits, and no obvious hematochezia. The weight changes of each group are shown in Table 2.

Table 2: Comparison of Body Weight Changes in Each Group ($\bar{X} \pm s$, $n=10$, g).

Group	Initial Weight	Weight on Day 14	Weight Change Rate (%)
Control group	20.5 $\pm$ 1.2	26.3 $\pm$ 1.5	28.3 $\pm$ 2.1
DSS group	20.3 $\pm$ 1.1	15.8 $\pm$ 1.3	-22.2 $\pm$ 3.2**
ASP-L group	20.4 $\pm$ 1.0	18.6 $\pm$ 1.2	-8.8 $\pm$ 2.5##
ASP-H group	20.6 $\pm$ 1.1	21.5 $\pm$ 1.4	4.3 $\pm$ 2.0## Δ
Mesalazine group	20.5 $\pm$ 1.0	21.2 $\pm$ 1.3	3.4 $\pm$ 1.8##

Note: Compared with Control group, ** $P<0.01$; Compared with DSS group, ## $P<0.01$; Compared with ASP-L group, $\Delta P<0.05$.

4.2 Results of Behavioral Tests

Mice in the Control group had significantly higher percentages of open arm entries (36.5 $\pm$ 4.2%) and residence time (34.2 $\pm$ 3.8%) than other groups. The DSS group had the lowest values in both indices (14.2 $\pm$ 3.1%, 12.8 $\pm$ 2.9%), indicating obvious anxiety-like behavior. The ASP-L group (23.6 $\pm$ 3.5%, 21.5 $\pm$ 3.2%) showed significantly higher values than the DSS group, and the ASP-H group (32.1 $\pm$ 3.7%, 29.8 $\pm$ 3.5%) showed more significant improvement, approaching normal levels. The mesalazine group (30.5 $\pm$ 3.6%, 28.2 $\pm$ 3.3%) had no statistical difference from the ASP-H group (Table 3, Figure 1).

Table 3: Comparison of Behavioral Indicators in Each Group ($\bar{X} \pm s$, $n=10$).

Group	Open Arm Entry Rate (%)	Open Arm Residence Time (%)	Sucrose Preference Rate (%)
Control group	36.5 $\pm$ 4.2	34.2 $\pm$ 3.8	79.2 $\pm$ 5.1
DSS group	14.2 $\pm$ 3.1**	12.8 $\pm$ 2.9**	41.8 $\pm$ 4.7**
ASP-L group	23.6 $\pm$ 3.5##	21.5 $\pm$ 3.2##	57.5 $\pm$ 4.9##
ASP-H group	32.1 $\pm$ 3.7## Δ	29.8 $\pm$ 3.5## Δ	69.8 $\pm$ 4.6## Δ
Mesalazine group	30.5 $\pm$ 3.6##	28.2 $\pm$ 3.3##	68.3 $\pm$ 4.5##

Note: Compared with Control group, ** $P<0.01$; Compared with DSS group, ## $P<0.01$; Compared with ASP-L group, $\Delta P<0.05$.

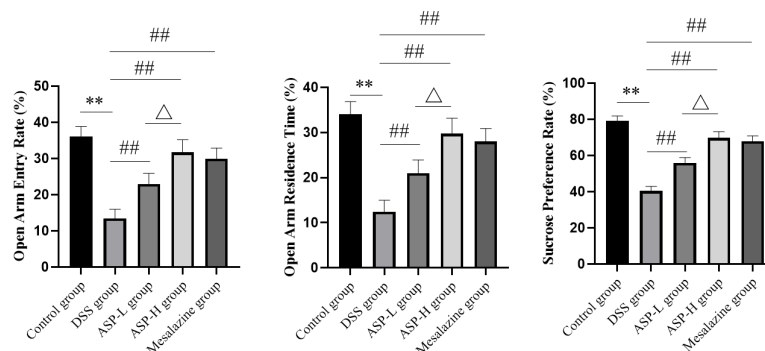


Figure 1: Comparison of Behavioral Indicators in Each Group ($\bar{X} \pm s$, $n=10$)

4.3 Results of RT-qPCR Detection

Regarding colonic inflammatory factors, the mRNA expression levels of IL-6, IL-1 β , and TNF- α in the DSS group were significantly higher than those in the Control group ($P<0.01$); the expression of these factors in the ASP-L group was lower than that in the DSS group ($P<0.05$), and the reduction was more significant in the ASP-H group ($P<0.01$), which was close to the level of the mesalazine group (Table 4). For BDNF mRNA expression in the cerebral cortex, the DSS group was significantly lower than the Control group ($P<0.01$); BDNF expression in the ASP-L group rebounded ($P<0.05$), with a more obvious rebound in the ASP-H group ($P<0.01$), and there was no statistical difference between the mesalazine group and the ASP-H group (Table 5).

Table 4: Comparison of Relative mRNA Expression of Colonic Inflammatory Factors in Each Group ($\bar{X} \pm s$, $n=10$).

Group	IL-6	IL-1 β	TNF- α
Control group	1.02 $\pm$ 0.11	1.03 $\pm$ 0.10	1.01 $\pm$ 0.12
DSS group	3.56 $\pm$ 0.32**	3.85 $\pm$ 0.32**	4.02 $\pm$ 0.38**
ASP-L group	2.25 $\pm$ 0.23#	2.85 $\pm$ 0.26#	2.72 $\pm$ 0.25#
ASP-H group	1.56 $\pm$ 0.15##	1.68 $\pm$ 0.15##	1.52 $\pm$ 0.16##
Mesalazine group	1.48 $\pm$ 0.14##	1.55 $\pm$ 0.14##	1.51 $\pm$ 0.15##

Note: Compared with Control group, ** $P<0.01$; Compared with DSS group, # $P<0.05$, ## $P<0.01$.

Table 5: Comparison of Relative mRNA Expression of BDNF in Cerebral Cortex of Each Group ($\bar{X} \pm s$, $n=10$).

Group	BDNF
Control group	1.03 $\pm$ 0.10
DSS group	0.42 $\pm$ 0.08**
ASP-L group	0.68 $\pm$ 0.09#
ASP-H group	0.92 $\pm$ 0.11##
Mesalazine group	0.90 $\pm$ 0.10##

Note: Compared with Control group, ** $P<0.01$; Compared with DSS group, # $P<0.05$, ## $P<0.01$.

5. Conclusions

Inflammatory bowel disease (IBD), a group of disorders characterized by chronic non-specific intestinal inflammation, presents diverse clinical phenotypes. It not only manifests as local symptoms such as persistent intestinal mucosal damage, recurrent diarrhea, and mucopurulent bloody stools but also frequently accompanies mental and behavioral abnormalities like anxiety, depression, and sleep disorders. This "gut-mental" comorbid state significantly impairs patients' quality of life and increases treatment challenges [4,5]. In recent years, with the in-depth research on the gut-brain axis theory, the academic community has gradually recognized the existence of a complex bidirectional regulatory network between the gut and the central nervous system, involving multiple dimensions such as neural conduction, immune activation, endocrine regulation, and metabolite exchange. Dysfunction of the gut-brain axis is considered the core mechanism underlying IBD-associated mental disorders [5].

This study employed a dextran sulfate sodium (DSS)-induced colitis mouse model. By disrupting the intestinal mucosal barrier and activating innate immune responses, this model can accurately simulate the intestinal pathological features of human ulcerative colitis, including mucosal hyperemia and edema, ulcer formation, and inflammatory cell infiltration. Experimental results showed that mice in the DSS group exhibited significant weight loss (with a weight change rate of -22.2%) 3-5 days after modeling, accompanied by typical colitis symptoms such as loose stools and hematochezia. The colon length was shortened by approximately 27% compared with the normal control group, and the disease activity index (DAI) increased significantly, confirming the successful establishment of the intestinal inflammation model. Meanwhile, behavioral assessments further revealed that in the elevated plus maze test, the percentage of entries into and time spent in the open arms of mice in the DSS group were only 39% and 37% of those in the normal control group, respectively, and the sucrose preference rate dropped to 41.8%. These findings indicate significant anxiety- and depression-like behaviors, which are highly consistent with the high incidence of mental symptoms in IBD patients observed clinically and align with previous reports on the association between "intestinal inflammation and emotional abnormalities". This demonstrates that the model can be effectively used for research on gut-brain axis-related mechanisms

[2].

Acanthopanax senticosus, a traditional tonic Chinese herb, has a medicinal history dating back to “Shennong’s Classic of Materia Medica”. Modern pharmacological studies have confirmed that *Acanthopanax senticosus* polysaccharides (ASP) are the core active components responsible for its pharmacological effects, exhibiting extensive anti-inflammatory, immunomodulatory, and neuroprotective activities [6,7]. In this study, two dose groups (low: 50 mg/kg; high: 200 mg/kg) were set to systematically evaluate the intervention effect of ASP on DSS-induced colitis in mice. Results showed that the weight loss rate of mice in the ASP-L group was 60.4% lower than that in the DSS group, the onset of diarrhea and hematochezia was delayed by 2-3 days, and the DAI score decreased by 34.9%. The ASP-H group showed more significant improvements, with even positive weight gain (a change rate of 4.3%), basically normalized stool characteristics, and a 30.6% longer colon length compared with the DSS group. Moreover, the above improvement effects exhibited a clear dose dependence. Notably, various indicators of the positive drug mesalazine group (200 mg/kg) showed no statistical difference from those of the ASP-H group, which not only verified the reliability of the experimental system but also suggested that the efficacy of ASP in improving intestinal inflammation is comparable to that of first-line clinical drugs, providing important evidence for its potential as a therapeutic agent.

In-depth exploration of its mechanism revealed that the association between local intestinal inflammation and central emotional abnormalities may be achieved through the “cross-border transmission” of pro-inflammatory factors. Pro-inflammatory factors such as IL-6, IL-1 β , and TNF- α play key roles in the pathogenesis of IBD. They can not only directly damage the intestinal mucosal barrier but also cross the blood-brain barrier through the bloodstream, activate central microglia, trigger neuroinflammation, and thereby affect the functions of emotional regulation centers such as the hippocampus and prefrontal cortex [8,9]. RT-qPCR results in this study showed that the mRNA expression levels of IL-6, IL-1 β , and TNF- α in the colon tissues of mice in the DSS group were 3.5, 3.5, and 3.6 times those in the normal control group, respectively. In contrast, the ASP-H group reduced the expressions of these three factors respectively, and the effect was comparable to that of the mesalazine group. These results suggest that ASP may alleviate anxiety- and depression-like behaviors by inhibiting intestinal inflammatory responses, reducing the excessive release of pro-inflammatory factors, and blocking the “intestinal inflammation-central damage” signaling pathway.

On the other hand, the regulation of central neurotrophic factors may be another important pathway through which ASP improves emotional abnormalities. Brain-derived neurotrophic factor (BDNF), a key regulator of neural plasticity, plays a central role in neuronal survival, synapse formation, and neurotransmitter balance. Reduced expression of BDNF is considered an important molecular marker of mental illnesses such as depression and anxiety [10,11]. This study found that the mRNA expression level of BDNF in the cerebral cortex of mice in the DSS group was only 40.8% of that in the normal control group, while the ASP-H group restored BDNF expression to 89.3% of the normal level. This effect may be related to ASP reducing pro-inflammatory factor-induced damage to nerve cells and promoting neurotrophic signal transmission. Meanwhile, the BDNF expression level in the mesalazine group was close to that in the ASP-H group, suggesting that the improvement of central neurotrophic status by anti-inflammatory drugs may be a common mechanism for their “simultaneous treatment of gut and brain” effects.

In summary, this study confirms that *Acanthopanax senticosus* polysaccharides can alleviate anxiety- and depression-like behaviors in DSS-induced colitis mice through dual pathways: on one hand, inhibiting the expression of pro-inflammatory factors such as IL-6, IL-1 β , and TNF- α in colon tissues to reduce intestinal inflammation and systemic inflammatory load; on the other hand, upregulating the expression of BDNF in the cerebral cortex to improve central neural plasticity and emotional regulation functions. This finding provides experimental support for explaining the advantages of natural medicines in “multi-target and holistic regulation” and opens up a new perspective for the treatment of IBD-associated mental and behavioral abnormalities. However, this study has limitations. For example, it did not deeply explore the impact of ASP on the structure of the intestinal flora. As an important intermediate link in the gut-brain axis, intestinal flora and their metabolites (such as short-chain fatty acids and tryptophan metabolites) may be involved in the mechanism of ASP [9]. In addition, the direct regulatory effect of ASP on central neuroinflammation needs further verification. Future studies can combine metagenomic sequencing, metabolomics, and cell co-culture techniques to more comprehensively reveal the molecular network through which ASP exerts its effects, providing a more solid theoretical basis for its clinical transformation.

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