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Efficacy of High Specific Volume Polysaccharide – A New Type of Dietary Fiber – On Molecular Mechanism of Intestinal Water Metabolism in Rats With Constipation

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCD 1 **Liang Cong**
EF 1 **Li-Wei Duan**
G 2 **Wei-Ping Su**
AC 3 **Shuhong Hao**
AC 1 **Dong-Fu Li**

1 Digestive System Department, The Second Hospital of Jilin University, Changchun, Jilin, P.R. China
2 Key Laboratory of Polymer Ecomaterials, Chinese Academy of Sciences, Changchun, Jilin, P.R. China
3 Department of Hematology and Oncology, The Second Hospital of Jilin University, Changchun, Jilin, P.R. China

Corresponding Authors: Shuhong Hao, e-mail: 267311158@qq.com, Dong-Fu Li, e-mail: 317659725@qq.com

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Background: The aim of this study was to evaluate the effects of a new type of dietary fiber – high specific volume polysaccharide (HSVP) – on fecal properties, serum vasoactive intestinal peptide (VIP) concentration, intestinal flora count, and expression of the VIP-cAMP-PKA-AQP3 signaling pathway.

Mareria/Methods: Compound diphenoxylate was used in 48 healthy Wistar rats to establish a constipation model. Rats were divided into a normal control group, a constipation model group, an HSVP low-dose group, an HSVP medium-dose group, an HSVP high-dose group, and a fructose control group. We used colony count method, ELISA, WB, and RT-PCR to determine fecal moisture content, fecal hardness, fecal passage time, serum VIP concentration, number of intestinal bacteria, and VIP-cAMP-PKA-AQP3 signal pathway protein expression.

Results: The constipation model was established successfully. HSVP (the medium dose was 10% and the high dose was 15%) improved fecal moisture content, reduced hardness, shortened fecal emptying time, increased intestinal bacteria, reduced serum VIP concentration, downregulated cAMP and PKAm RNA transcription, reduced protein expression, and reduced intestinal AQP3 expression.

Conclusions: HSVP improved constipation, increased the number of intestinal bacteria, and elevated expression of the VIP-cAMP-PKA-AQP3 signaling pathway. The mechanism of HSVP in regulating intestinal water metabolism in constipated rats may occur through the VIP-cAMP-PKA-AQP3 signaling pathway, and be closely related to changes in intestinal bacteria. The important role of the brain-gut-microbiome axis in the pathogenesis of constipation has been confirmed in this study.

MeSH Keywords: **Aquaporin 3 • Constipation • Probiotics • Vasoactive Intestinal Peptide**

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/916526

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Background

Constipation is a common disease worldwide and is believed to be mainly caused by diet, lifestyle, and social psychology [1]. There are 3 pathogenic factors causing constipation: neuropsychological factors, intestinal motility factors, and intestinal bacteria abnormalities [2]. In recent years, the brain-gut-microbiome axis (BGMA) theory [3] has become a hot topic of research in the pathogenesis of constipation. Intestinal bacteria can affect central and peripheral nervous functions through neural signaling pathways [4]. The fermentation products of intestinal bacteria facilitate the synthesis of various neurotransmitters by the host and regulate the secretion of signal molecules [5]. The gastrointestinal tract wall is a rich receiving system from the lumen of various stimulus neural devices [6]. The hypothalamus, through the release of the neurotransmitter stimulation of gastrointestinal tract wall internal primary sensory neurons, adjusts the movement and the secretion of the enteric nervous system, causing abnormalities in intestinal bacteria [7]. *Bifidobacterium*, *Lactobacillus*, and *Escherichia coli* are the 3 main probiotics in the intestinal flora of rats [5]. After integration of the intestinal bacteria gene and host gene, the extrinsic primary sensory neurons stimulated by neurotransmitters release signals again. These signals are uploaded to the central nervous system, and the information is integrated and sent to the target organ, thus completing the BGMA [3,8].

One of the most important signaling pathways is the VIP-cAMP-PKA-AQP3 signaling pathway [9]. AQP is a group of proteins that specifically transport water, and is involved in the secretion, absorption, and balance of water inside and outside the cell. The important role of this membrane-penetrating aquaporin (AQP) is to help water molecules pass through the cell membrane rapidly [10]. It has been proven through experiments [11] that injecting vasoactive intestinal peptide (VIP) into rats with diarrhea increases the VIP expression in serum and intestinal tissues, and the protein expression of AQP is regulated by VIP activity, and the signal pathway of VIP/PKA/AQP in colon epithelial cells is affected, changing the molecular mechanism of intestinal water metabolism and causing the disappearance of diarrheal symptoms [8,12].

The chemical composition of dietary fiber determines its unique physical and chemical properties, which include: high water retention, cation exchange, adsorption, fermentation, solubility, and viscosity [13]. High specific volume polysaccharide (HSVP) [14], a newly discovered type of dietary fiber, is a polymerized polysaccharide extracted from the outer layer of *Artemisia sphaerocephala Krasch* (AsK) seeds by the Key Laboratory of Polymer Ecomaterials, Chinese Academy of Sciences [14]. A proposed partial structure for HSVP is shown in Figure 1: R can be one or several of the following groups: 3-α-Araf_n, T-α-Gal*p*, T-α-Glc*p*, T-Ara*f,* and T-Ara*p*). AsK seeds contain D-glucose, D-galactose, D-mannose, L-arabinose, and DL-xylose, and are a traditional Chinese herb and food additive with reported antidiabetic, detumescent, and antioxidant effects. They are also widely utilized as a thickener, stabilizer, and water-retention and film-forming agent. In a mouse acute oral toxicity test, HSVP demonstrated an LD_{50} >10 g/kg, indicating its low level of toxicity. In China, *Artemisia* polysaccharide was first extracted from AsK seeds in 1985 and showed a molecular weight of ~30 kDa. However, the molecular weight of HSVP is 50.82 kDa, which is much higher than that of other common polysaccharides. This high molecular weight enables HSVP to absorb relatively large amounts of water. In our previous studies [14], HSVP was proven effective in treating functional constipation and irritable bowel syndrome with constipation, without significant adverse effects.

In this study, a rat constipation model was created using compound diphenoxylate, which is composed of diphenoxylate hydrochloride and atropine sulfate. The synergetic effect of diphenoxylate and atropine sulfate weakens gastrointestinal motility and causes constipation by reducing the content of diphenoxylate.

The aim of the present study was to study the effects of HSVP on colonic water metabolism in rats with constipation at a molecular mechanism level. We measured changes in the symptoms of constipation, in the number of intestinal bacteria, in serum VIP, and in the colon VIP-cAMP-PKA-AQP3 signaling pathway. We also sought to confirm the existence of BGMA.

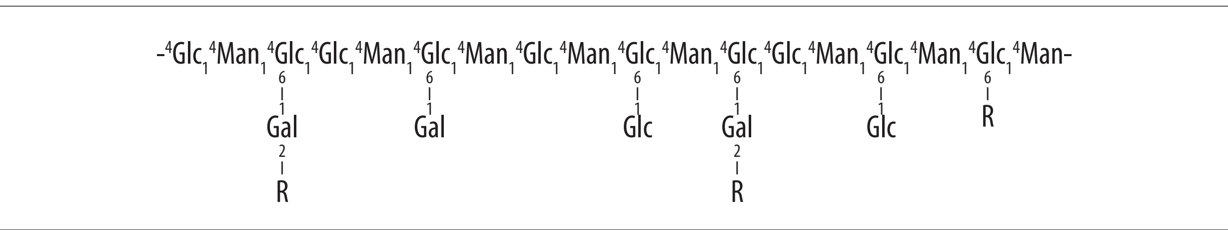

Figure 1. The partial structure of HSVP.

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Table 1. Sex, age, body weight, and food intake of rats in each group.

GROUP	Sex		Week age	Body mass (g)	Food intake (g)
	Male	Female			
Normal control group	4	4	11	201±20	27.50±8.45
Constipation model group	4	4	11	205±20	22.34±6.22
HSVP low-dose group	4	4	11	198±21	23.89±8.12
HSVP medium-dose group	4	4	11	203±22	26.88±5.20
HSVP high-dose group	4	4	11	199±24	24.75±7.42
Fructose control group	4	4	11	200±21	22.19±6.16

Material and Methods

Animal preparation

Forty-eight Wistar mice (200±20 g) were obtained from the Jilin University Laboratory Animal Center, Changchun, China (License No: SCXK JI 2016-0001). Before the experiment, the sex, age, and body mass of the rats were statistically analyzed (Table 1). For 5 days before the experiment, rats were kept in a temperature-controlled environment (22±2°C) of 50±5% relative humidity, with a 12-h light–dark cycle, and fed standard chow with feeding noise <45 db. Throughout the experiment, rats were allowed free access to food and water. At 9: 00 a.m. every day, the food intake of each rat within the previous 24-h period was recorded. The food intake of the rats was analyzed and there were no statistical differences in intake (Table 1).

All of the experimental groups were gavaged with diphenoxylate hydrochloride suspension (3 mg/kg, 1604009, Changzhou Kangpu Pharmaceutical Co.) once a day (at 12: 00 a.m.) from day 1 to day 14 to induce constipation. By day 7, 48 rats were divided into a normal control group, a constipation model group, an HSVP low-dose group, an HSVP medium-dose group, an HSVP high-dose group, and a fructose control group by using a randomized block design. Rats in the HSVP low-dose group, HSVP medium-dose group, and the HSVP high-dose group were given separate feed with 5%, 10%, and 15% HSVP, respectively.

Methods

Determination of moisture content and hardness of rat feces

From day 7 to day 14, the feces of each group were collected and weighed while wet. After drying for 12 h at 60°C constant temperature, the dry feces were weighed. The fecal relative moisture content was calculated (Fecal Wet Weight–Fecal Dry Weight)/Fecal Wet Weight. For 3 consecutive days, from day 12 to day 14, the fresh feces of each group of rats were collected during the daytime, and the fecal hardness was measured with a hardness tester.

Determination of fecal passage time

On day 14, all the rats were gavaged with 1 mL of a medicinal charcoal tablet suspension (10%). After 40 min, the rats were euthanized, and the entire intestine (from the pylorus to the end of the rectum) was removed and placed on a tray. The length of the intestine (from the pylorus to the end of the rectum) was measured. The length from the pylorus to the border of medicinal charcoal tablets was measured as the displacement of the medicinal charcoal tablets. The medicinal charcoal tablets propulsion rate (the fecal passage time) was calculated: Fecal passage time (%)=Movement distance of medicinal charcoal tablets/Whole length of intestine ×100.

Blood and colon collection

After the rats were euthanized, blood was collected by removing the eyeballs. The rat blood flowing from the orbit into the Eppendorf tube was centrifuged, and the serum was collected. The contents of the large intestine were extruded and stored in sterilized Eppendorf tubes for determination of intestinal flora. To segment the colon, it was washed with physiological saline, scraped for colonic mucosa, and quickly placed in liquid nitrogen.

Assays of intestinal bacteria

In an aseptic operating room, 0.1-g samples of intestinal contents were weighed with an analytical scale and placed in sterilized test tubes containing 9.9 ml normal saline, and then homogenized with an oscillator. Then, l ml was added into sterilization tubes containing 9 ml normal saline. At this time, the concentration gradient was 10^{-3} and the procedure was repeated until a dilution of 10^{-7} was obtained. Three suitable diluents were selected and inoculated on selective medium of *Bifidobacterium*, *Lactobacillus*, and *Escherichia coli*, and incubated at 37°C for 48 h.

The colony counting methods consisted of assessing colony-forming units (CFU) by microscopic forming, size, color, and

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Table 2. AQP3, cAMP, PKA, and VIP primer nucleic acid sequence.

Gene	Forward primer	Reverse primer	Product length
AQP3	GCCATTGTTGACCCTTATAACAAC	AGTGAAAAGGCGAGGTCCAA	150 bp
cAMP	GGGTTTAGGCGCCACATAGGCGCT	GCAGGTGAGGGCCGTTCTAGG	127 bp
PKA	GTTCCTGGGTTCCTTCTTAGC	CCTGTCCTCCTTCTTGTGGT	146 bp
VIP	TGCCTTAGCGGAGAATGACA	CCTCACTGCTCCTCTTCCC	210 bp
β-tubulin	TGGATTCCTGTGTCATCCATGAAAC	TAAAACGCAGCTCAGTAACAGTG	110 bp

gram staining. According to the count and dilution of the viable bacterial colonies on the culture medium, the viable bacterial count formula was used to count, and the result was expressed as the logarithm of the CFU in each gram of fresh feces. LgCFU/g=l g (number of colonies×dilution times×number of ml of each dilution sample)/(number of ml of inoculation sample×number of grams of sample).

Elisa

We used an ELISA kit (GN-R31190, Shanghai Gaining Biological Co., China) to detect the VIP concentration in serum. The ELISA results revealed that the absorbance of each hole should be determined within 15 min after the end of the reaction. The determination wavelength was set at 450 nm, and the absorbance was set as the OD value. The concentration and OD value of the standards were used as the ordinate and the abscissa, respectively. The standard curve was constructed, and the linear regression equation was calculated accordingly. The following formula was used for this calculation: The actual concentration of the final sample=the concentration of the required sample×the dilution factor.

Western blot analysis

The expression levels of AQP3, cAMP, PKA, and VIP in colon tissues were detected with Western blotting. Tissue samples were obtained from rats from each group and total protein was isolated using the Illustra triplePrep kit (Bio-Rad, Hercules, CA, USA). After extraction, we followed the instructions provided in the kit.

Quantitative real-time PCR

We searched the NCBI GenBank database and used β-tubulin as an internal reference gene for designing the primers using Primer 5.0 software (Table 2). NCBI BLAST verified the specificity of these primers, which were then synthesized by Shanghai Bioengineering Technology Services. Water was treated using DEPC. Total RNA concentration and $OD_{260/280}$ values were determined (1.8–2.0 was qualified). We performed real-time fluorescent quantitative PCR using the detection kits as per the manufacturer's instructions: the total volume of the system was 20 μL (SYBR mix, sample cDNA, water, upstream, and downstream primers volumes were 10.0, 2.0, 6.8, 0.4, and 0.4 μL, respectively); the reaction conditions were set as 95°C premodified for 30 s, 60°C for 5 s, and 95°C for 30 s, all for 40 cycles; finally, the dissolution curve was added (60°C for 1 min, 95°C for 15 s, and 95°C for 15 s). Reaction was performed on a PCR instrument. Each sample was subjected to assays with a set negative control. We obtained a sample by comparing the software threshold cycle number (threshold cycle, Ct) and a copy of the relative quantitative, then comparing these between the samples again. The 2–ΔΔCt method was used for data analysis, the normal control group value was set to 1.

Statistical analysis

We used SPSS for Windows, Version 15.0. (Chicago, IL, USA) for analysis of data. The paired *t* test and non-parametric test were used for determining the statistical significance of differences. A P value <0.05 was regarded as statistically significant. The results are expressed as mean ±SD.

Results

Moisture content, hardness, and intestinal transit time of rat feces

As shown in Figures 2–4, compared to that of the normal control group, fecal hardness was higher, moisture content was lower, and the fecal passage time was decreased in the constipation model group. HSVP effectively reduced fecal hardness, increased moisture content, and increased the carbon propulsion rate in the HSVP low-dose group, the fructose control group, and the constipation model group. In rats feed 10% and 15% HSVP in the basal feed, fecal hardness was higher, moisture content was lower, and the fecal passage time was decreased. In rats feed with 5% HSVP in the basal feed, the fecal hardness, moisture content, and the fecal passage time did not improve, and there was no improvement in the fructose control group.

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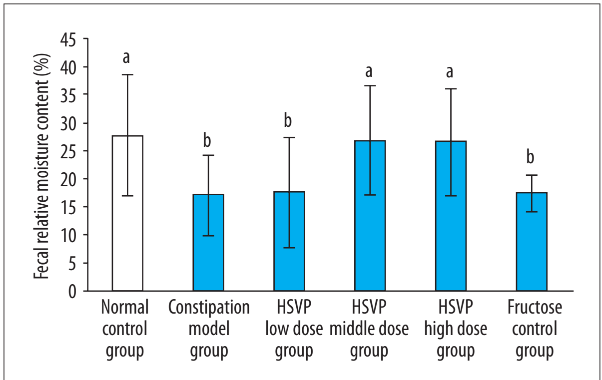


Figure 2. Fecal relative moisture content. The same letter (a, b) means no significant difference (P>0.05). Different letters (a, b) indicate a significant difference (P<0.05).

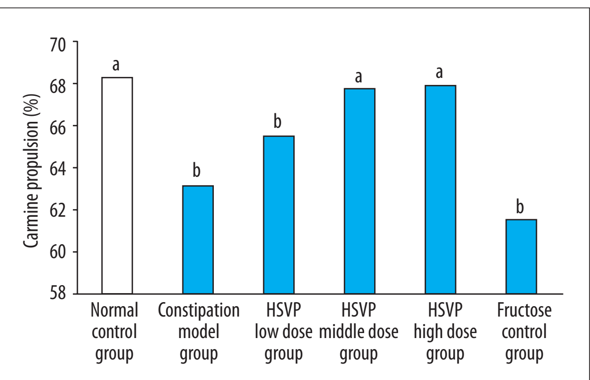


Figure 4. Fecal passage time. The same letter (a, b) indicates no significant difference (P>0.05). Different letters (a, b) indicate a significant difference (P<0.05).

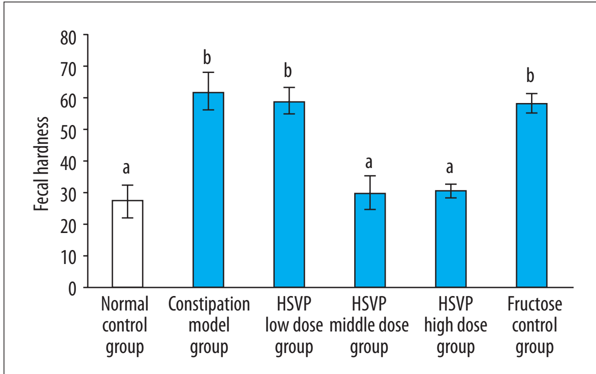


Figure 3. Fecal hardness. The same letter (a, b) indicates no significant difference (P>0.05). The different letters (a, b) indicate a significant difference (P<0.05).

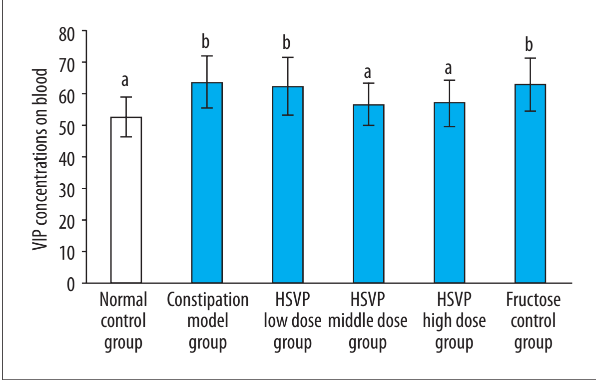
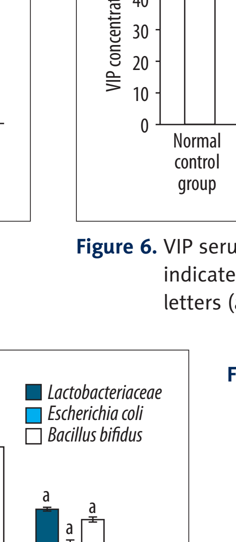


Figure 6. VIP serum concentrations. The same letter (a, b) indicates no significant difference (P>0.05). Different letters (a, b) indicate a significant difference (P<0.05).



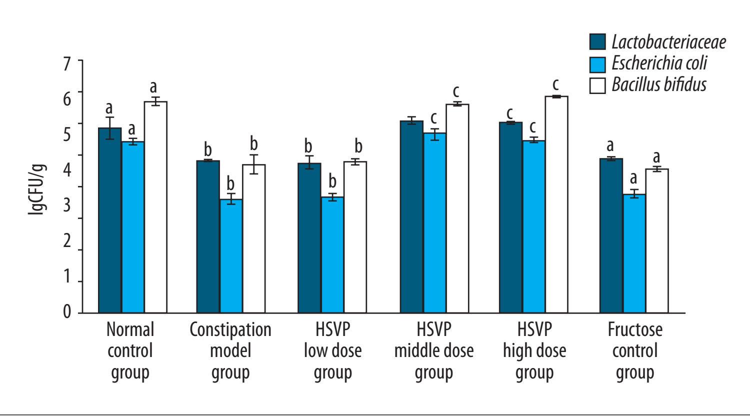


Figure 5. lgCFU/g of *Bifidobacterium*, *Lactobacillus* and *Escherichia coli*. The same letter (a, b, c) indicates no significant difference (P>0.05). Different letters (a, b, c) indicate a significant difference (P<0.05).

Results of intestinal bacteria

As shown in Figure 5, the lgCFU/g of *Bifidobacterium*, *Lactobacillus*, and *Escherichia coli* of the constipation model group were higher than those of the normal control group. In the colons of rats fed 10% and 15% HSVP in the basal feed, the lgCFU/g of the *Bifidobacterium*, *Lactobacillus*, and *Escherichia coli* was elevated. There was no improvement in the 5% HSVP group of the fructose control group.

VIP concentrations in blood

As shown in Figure 6, the concentration of VIP in the serum of the constipation model group was higher than that of the

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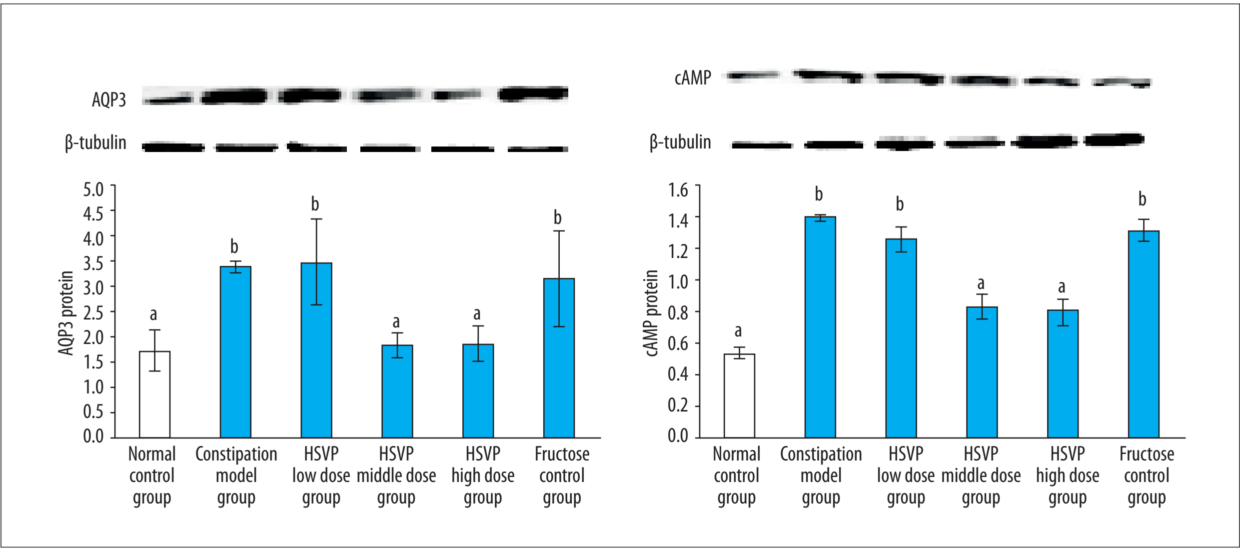

Figure 7. AQP3 and cAMP protein expression. The same letter (a, b) indicates no significant difference (P>0.05). Different letters (a, b) indicate a significant difference (P<0.05).

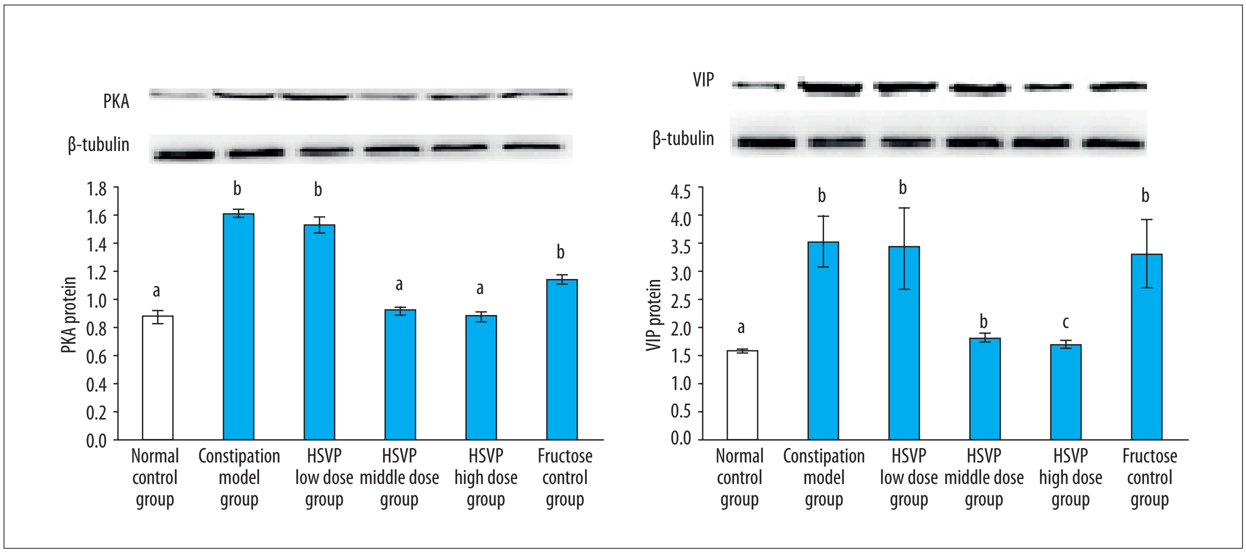

Figure 8. PKA and VIP protein expression. The same letter (a, b) indicates no significant difference (P>0.05). Different letters (a, b) indicate a significant difference (P<0.05).

normal control group. In the colons of rats fed 10% and 15% HSVP in the basal feed, the VIP concentration was increased. There was no improvement in the 5% HSVP group or the fructose-added group.

AQP3, cAMP, PKA, and VIP protein expression

As shown in Figures 7 and 8, the concentrations of AQP3, cAMP, PKA, and VIP protein expression of the constipation model group was higher than that of the normal control group. In the colons of rats fed 10% and 15% HSVP in the basal feed, the protein expression was increased. There was no improvement in the 5% HSVP group or the fructose-added group.

AQP3, cAMP, PKA, and VIP mRNA transcription

As shown in Figures 9, and 10 the concentrations of AQP3, cAMP, PKA, and VIP mRNA transcription of the constipation model group was higher than that of the normal control group. In the colons of rats fed 10% and 15% HSVP in the basal feed, the mRNA transcription was increased. There was no improvement in the 5% HSVP group or the fructose-added group.

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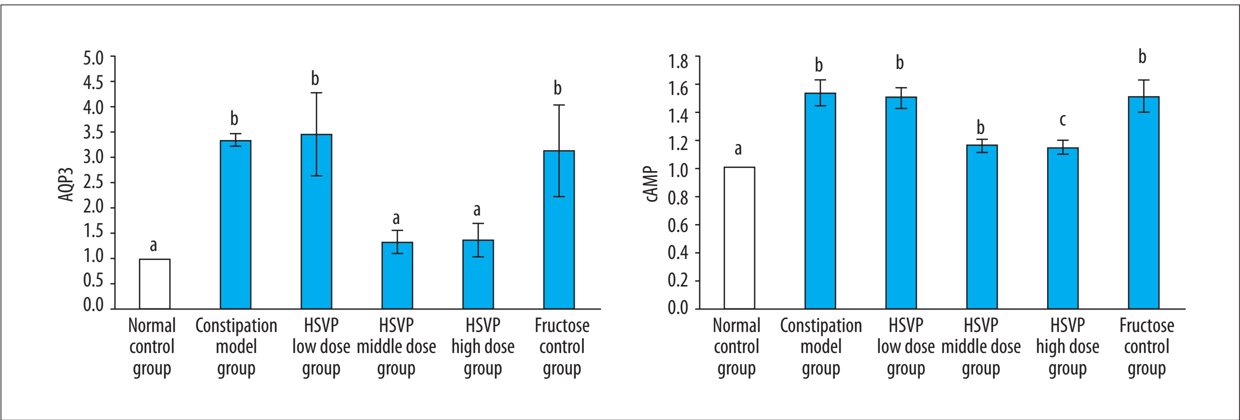

Figure 9. AQP3 and cAMP mRNA transcription. The same letter (a, b) indicates no significant difference (P>0.05). Different letters (a, b) indicate a significant difference (P<0.05).

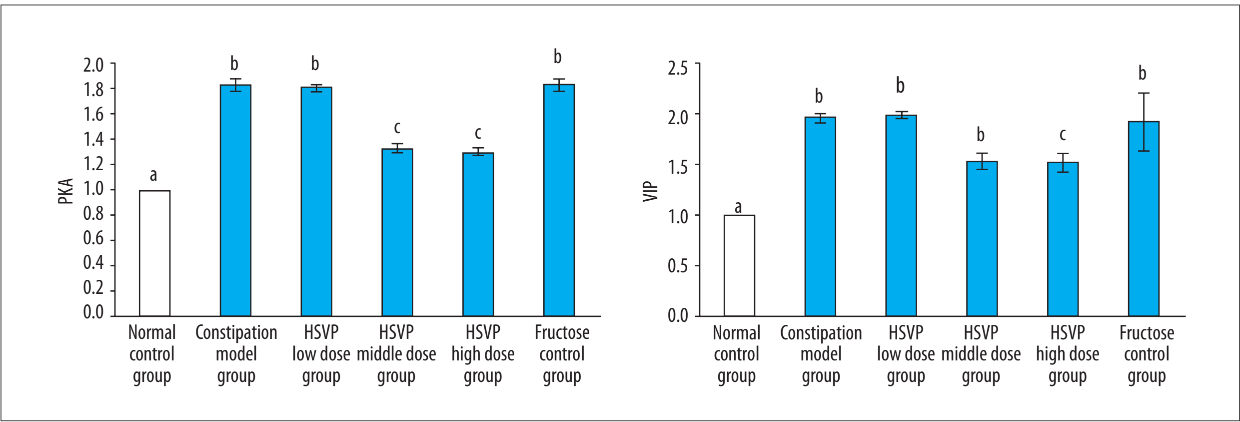

Figure 10. PKA and VIP mRNA transcription. The same letter (a, b) indicates no significant difference (P>0.05). Different letters (a, b) indicate a significant difference (P<0.05).

Discussion

In this study, a rat constipation model was successfully established by using compound diphenoxylate. Utilizing this model, we observed that different concentrations of HSVP promoted intestinal water metabolism, reduced fecal hardness, reduced fecal passage time, and increased intestinal beneficial. The addition of 10% and 15% (medium and high dose, respectively) of HSVP to the basic feed was found to be the best ratio to improve water content, hardness, and fecal emptying time. Compared with the constipation model group, the water content, hardness, and fecal passage time of rats in the fructose group did not change, indicating that fructose, as a monosaccharide, did not improve constipation. The serum VIP concentrations and intestinal AQP3, cAMP, PKA, and VIP mRNA transcription and protein expressions in the constipation model group were higher than those in the normal control group. After model establishment, the BGMA is activated. The expression of VIP released from the hypothalamus to serum was upregulated, the level of serum VIP was elevated, intestinal VIP was increased, and VIP was combined with the corresponding receptors. ATP is converted into cAMP, and then cAMP-dependent PKA is activated. PKA phosphorylates intracellular AQP3. The increased expression of AQP3 increases the metabolism of intestinal water, thereby alleviating constipation. From the above, we believe that the decreased colonic motor function in constipation is related to abnormality of the VIP-cAMP-PKA-AQP3 pathway. The results of this experiment showed that there was no statistically significant difference between the HSVP medium-dose group and the HSVP high-dose group, indicating that the addition of an appropriate proportion (10–15%) of HSVP can inhibit the high expression of VIP-cAMP-PKA-AQP3. It also indirectly indicates that AQP3 plays an important role in intestinal water absorption.

The results of this study also show that, in constipated rats, fecal moisture content decreased, hardness increased, serum VIP reactivity increased, intestinal VIP-cAMP-PKA-AQP3 pathway was activated, intestinal AQP3 expression increased, and intestinal beneficial bacteria abundance was decreased. After applying the appropriate doses of HSVP, fecal moisture content and hardness of rats increased, the serum VIP reactivity

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decreased, intestinal VIP-cAMP-PKA-AQP3 pathway activity decreased, intestinal AQP3 expression decreased, and intestinal beneficial bacteria abundance increased. The trends of fecal hardness, fecal moisture content, intestinal bacteria numbers, serum VIP concentration, and the expression of intestinal VIP-cAMP-PKA-AQP3 pathway were consistent. Our study supports the suggestion by other researchers that the mechanism of HSVP in regulating intestinal water metabolism in constipated rats occurs through the VIP-cAMP-PKA-AQP3 signaling pathway, and it is closely related to changes in intestinal bacteria.

Conclusions

The important role of BGMA in the pathogenesis of constipation was confirmed in this study. Our research has created a theoretical foundation for developing a new preparation of cellulose to improve constipation, and has shown the potential of HSVP as a new preparation of cellulose to improve constipation.

Conflicts of interest

None.

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