

Exploring the mechanism of action and efficacy of Shi-Pi-San in the treatment of ascites in cirrhosis based on intestinal microbiota

Meng-Yu Dou¹, Zi-Han Wang^{1*}, Shi-Hao Wang¹, Meng Dong¹, Fei Wang¹, Yu-Xiao Gou¹, Sheng-Jun Sun¹, Yong-Qi Kang¹

¹College of traditional Chinese medicine, Shandong University of Traditional Chinese Medicine, Jinan 250355, China.

*Corresponding to: Zi-Han Wang, College of traditional Chinese medicine, Shandong University of Traditional Chinese Medicine, No. 4655, Guyunhu Street, Changqing District, Jinan 250355 China. E-mail: wang1805222108@163.com.

Author contributions

Dou MY, Wang SH and Dong M conceived the idea; Wang ZH conducted the analyses, review and modify; Wang F, Gou YX, Sun SJ, and Kang YQ provided the data; all authors contributed to the writing and revisions.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

SPS, Shi-Pi-San.

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Abstract

Objective: To investigate the mechanism of action and efficacy of Shi-Pi-San (SPS) in the treatment of cirrhotic ascites based on intestinal flora and to provide new ideas for clinical research. **Methods:** We searched PubMed, CNKI, Wanfang and Wipu Chinese journal databases to collect randomized controlled trials of SPS in the treatment of cirrhotic ascites, extracted relevant data, and summarized them to analyze the relationship between intestinal flora and cirrhotic ascites. **Results:** The disorder of intestinal flora can lead to cirrhotic ascites, and the treatment of cirrhotic ascites with SPS has good efficacy, and SPS has positive effects in improving the status of intestinal flora, increasing the abundance of flora and inhibiting the growth of pathogenic bacteria. **Conclusion:** SPS has good long-term efficacy in the treatment of cirrhotic ascites, but the side effects and dosage criteria have not been extensively studied in clinical practice.

Keywords: Shi-Pi-San; intestinal flora; cirrhotic ascites

Introduction

The development and progression of cirrhosis can lead to changes in the intestinal microecology, and the disruption of the flora can lead to complications such as ascites and bacterial peritonitis, so regulating the intestinal flora is particularly important in preventing the progression of cirrhotic ascites. At present, diuretics are mainly used to treat cirrhotic ascites, but because of their poor target specificity, they act on a variety of receptors throughout the body, are prone to recurrence and cannot be effectively cured after discontinuation, and have many adverse effects and toxic side effects [1]. There are many adverse effects and toxic side effects. Chinese medicine has been found to be effective in improving intestinal flora and treating cirrhotic ascites. The classical formula SPS (Shi-Pi-San) is particularly effective in the treatment of cirrhotic ascites. In this article, we briefly review the research progress of SPS in the treatment of cirrhotic ascites with a view to providing a basis for clinical treatment.

Mechanism of ascites

Western medical mechanisms

Disturbed intestinal flora. Ascites are one of the major complications of cirrhosis, and 20%–75% of cirrhotic patients develop intestinal flora disorders [2]. Kakiyama G [3] et al. found that the relative abundance of *Lachnospiraceae*, *Ruminococcaceae* and *Blautia* in the intestinal flora of patients with cirrhosis was reduced, suggesting that the overgrowth of small intestinal bacteria plays an important role in the progression of disease in patients with chronic liver disease, and the study found a close association between the development of ascites in cirrhosis and dysbiosis of the intestinal flora. Through observation and treatment of 48 inpatients with cirrhosis, Feng Jian-Hua

found that 75% of the ascites were caused by cirrhosis. The mechanism of ascites occurrence in cirrhosis is complex, with portal hypertension and hepatic insufficiency being the most fundamental factors.

Liver dysfunction. Hepatic dysfunction, reduced secretion of plasma proteins, the gradual decrease in plasma colloid osmotic pressure and accelerated formation of ascites. Li Cai-Xia [5] et al. suggest that intestinal flora disorders and cirrhosis are mutually causal, leading to the continued progression of cirrhosis. The mechanism by which ascites is triggered by the liver has not been fully elucidated, but it is now clinically believed that ascites in cirrhosis is mostly associated with increased portal blood pressure, decreased plasma colloid osmotic pressure and increased hepatic lymphatic fluid formation [6, 7]. Increased pressure in the hepatic sinusoidal space due to hepatic venous outflow tract obstruction is the initiating factor for ascites

formation [8]. This is the initiating factor for ascites formation. Increased hydrostatic pressure in the capillaries of the portal vein leads to a disruption of the Starling equilibrium in the capillary bed and the leakage of intravascular fluid into the peritoneal cavity, resulting in a loss of intravascular fluid and a reduction in effective circulating blood volume, which is sensed by cardiopulmonary and arterial receptors and results in sodium retention. One-third to one-half of human lymphatic fluid comes from the liver, and impaired hepatic lymphatic circulation is closely related to the production of ascites; on the one hand, due to mechanical blockage or compression of the lymphatic vessels, resulting in obstruction of lymphatic return, and on the other hand due to excessive lymphatic fluid production and relative narrowing of the lymphatic fluid transport system, resulting in stagnation of lymphatic fluid and alteration of colloid osmotic pressure causing ascites oozing. In summary, ascites is one of the most common conditions in clinical practice, and the pathological mechanisms of its formation are very complex. The causes include systemic factors such as dysbiosis, reduced plasma colloid osmotic pressure, water and sodium retention, or liver cirrhosis due to dysbiosis, which in turn leads to ascites.

Mechanisms in Chinese medicine

The mechanism of ascites formation is considered in Chinese medicine to be the weakening of Qi (This extremely subtle substance, which is very energetic and constantly running in the human body, is considered by Chinese medicine to be one of the basic substances that constitute the human body and maintain human life activities) due to stasis and blood stasis, it is written, Qi Bo said: "The abdomen is bulging, the whole body is swollen, the same as the skin swelling, the skin is bluish yellow, and the abdominal tendons are bursting" [9]. This is the symptom. Patients with ascites have a long duration of illness and a weak constitution and are suffering from Yang deficiency (Decreased or debilitated function, decreased metabolic activity, low body reactivity). It is particularly good at treating Yang deficiency oedema (A chronic edema due to weakened spleen and kidney function). Clinical research has also found that the dried ginger in the formula of SPS has anti-inflammatory and anti-bacterial effects, protects the mucous membrane of the gastrointestinal tract and regulates the micro-ecology of the intestinal tract. In clinical practice, it is often used to treat and reduce ascites [10]. The formula has been used clinically to treat and reduce ascites. The formulas of the six books of medical strategy are Baizhu (*Actractylodis Macrocephalae Rhizoma*), Fuzi (*Radix Aconiti Lateralis Preparata*), Ganjiang (*Zingiberis Rhizoma*), Houpo (*Magnoliae Officinalis Cortex*), Caoguo (*Tsaoko Fructus*), Muxiang (*Aucklandiae Radix*), Fuling (*Poria*), Zexie (*Alismatis Rhizoma*), Zhuling (*Polyporus*), Zhigancao (*Glycyrrhizae Radix et Rhizoma Praeparata cum Melle*), Jiangpi (*gho*) Table 1.

Table1 Progress of Chinese and Western medicine research on the mechanism of ascites in liver cirrhosis

Classification	Mechanism of occurrence	Occurrence conditions	Treatment measures	References
Chinese medicine	Dropsy, Qi stagnation and blood stasis	The dried ginger in the formula has anti-inflammatory and antibacterial effects, protects the gastrointestinal mucosa and regulates the intestinal microecology	Warming Yang, strengthening the spleen, promoting circulation of Qi and promoting water retention, treating Yang deficiency and edema.	[9–10]
Western medicine	Disorders of intestinal flora	Decreased relative abundance of <i>Lachnospiraceae</i> , <i>Ruminococcaceae</i> and <i>Blautia</i> in the intestinal flora: the most primitive factors were portal hypertension and hepatic insufficiency	Increase intestinal flora richness and regulate intestinal flora disorders	[3–4]
	Liver dysfunction	Increased portal blood pressure, decreased plasma colloid pressure and increased hepatic lymphatic fluid formation are associated	Balance plasma colloid osmotic pressure	[5–8]

As the "first medicine for spleen Qi and spleen", its products and concocted products are widely used in the treatment of spleen deficiency and diarrhea, Qi deficiency and self-sweating, spleen deficiency, fetal restlessness and other diseases. He Han et al [11]. Found that Baizhu (*Atractylodis Macrocephalae Rhizoma*) can increase the abundance of Prevotellaceae_UCG-003, of which Prevotellaceae_UCG-003 belongs to the Prevocella, which is a polymorphic bacillus with functions such as maintaining normal intestinal physiology, and this genus may have certain protein activity [12]. The adverse reactions of Baizhu (*Atractylodis Macrocephalae Rhizoma*) are mainly manifested in misuse, Baizhu (*Atractylodis Macrocephalae Rhizoma*) is bitter and dry, and patients on fire are not suitable for a long-term application; Baizhu (*Atractylodis Macrocephalae Rhizoma*) can remove dampness, belongs to dry drugs, dry can hurt Yin (All phenomena that manifest as cold, or that can cause people to feel cold) and blood, yin deficiency, blood deficiency patients are not applicable; Whitening has a laxative effect, and patients with poor spleen and stomach or severe spleen deficiency are recommended to use whitening.

Fuzi (*Radix Aconiti Lateralis Preparata*), spicy, sweet, sexual heat, returning to the heart, kidney, and spleen meridian, has the effect of rejuvenating the Yang (All phenomena that manifest as warmth, or that trigger people's feelings of warmth), replenishing the fire and helping the yang, dissipating cold and relieving pain, is known as the first medicine to rejuvenate the yang, but also the representative importance of the virulence duality, the main pharmacological component is *Aconitum* Biobased, *Aconitum alkaloids* are both bioactive compounds and toxic ingredients in *Aconitum* plants. They produce a wide range of pharmacological activities, including protecting the cardiovascular system, nervous system, and immune system and anti-cancer effects. Notably, *Aconitum alkaloids* also exert strong cardiac toxicity, neurotoxicity and liver toxicity [13].

Tsaoko Fructus [14–16], spicy, warm, spleen, stomach meridian, has the effect of drying and strengthening the spleen, expectorant and malaria. The main treatment of phlegm drinking is chest fullness, abdominal pain, spleen deficiency diarrhea, malaria and other evidence, with antioxidant, anti-inflammatory, antibacterial, anti-proliferation and other pharmacological effects, has the effect of "SPS, Tsaoko Amomum Fruit Drink", has a certain inhibitory effect on the reproduction of bacteria, clinically containing herbs and fruits of the formula: solid spleen, grass fruit drink, grass fruit soup, etc., some scholars have found that taking too much grass fruit will cause damage to irrelevant organs.

Zingiberis Rhizoma, with its spicy taste and sexual heat, belongs to the spleen, stomach, heart, and lung meridians, and is good at warming and Yang, and has the effects of dispersing cold in warmth, rejuvenating the Yang and channeling the veins, and warming the lungs and drinking, and plays the role of publicizing and promoting the upper coke and the warm transportation in the real spleen dispersion [17]. When used in large doses of *Zingiberis Rhizoma*, it will cause patients to get hot, mainly manifested as dry throat and mouth, mouth ulcers, constipation, short urine, etc. [18].

Magnoliae Officinalis Cortex, a bitter taste, warm stomach, lungs, spleen, and large intestine meridian, and has the effect of dryness, Qi, accumulation, and asthma. Its active ingredients are honokiol, alkaloid magnolia dart and volatile oils, etc., small doses of excitatory effect on the intestine, a large doses of intestinal inhibition, but it also has the function of calming the central nervous system, muscle relaxation, antibacterial and so on [19]. *Magnoliae Officinalis Cortex* is a commonly used Chinese medicinal material for drying and dampness to eliminate phlegm and remove full Qi, mainly treating wet stagnant injuries, stagnation of diarrhea, stagnation of appetite, bloating, constipation, phlegm and cough [20]. Zhuang Xuemei [19] et al. found that honokiol, magnolia dart and β -cineole in *Magnoliae Officinalis Cortex* may cause gastrointestinal adverse reactions such as nausea, vomiting, diarrhea and loose stools.

Aucklandiae Radix, its taste is spicy, bitter, and warm attributed to the spleen, stomach, large intestine, three jiao, and bile meridian, has the effect of relieving pain, strengthening the spleen and eliminating

food. It is used for chest and flank, abdominal distention and pain, diarrhea after heaviness, food accumulation, and lack of diet. Costunolide and Dehydrocostus Lactone are biologically active sesquiterpene lactones extracted from *Aucklandiae Radix*, and modern pharmacological studies [21, 22] show that sesquiterpene lactones have antitumor, antimalarial, antibacterial and anti-inflammatory activities.

Poria [23], sweet, light, flat, belonging to the Heart, Lung, Spleen, and Kidney meridians, has the effect of promoting water seepage, benefiting the Spleen, and calming the mind. Traditional Chinese medicine believes that *Poria* "reinforces water without harming the righteous, and replenishes but does not help evil"; Modern medical studies have shown that the pharmacological effects of *Poria* are mainly manifested in diuresis, sedation, anti-tumor, and immune enhancement. *Poria* has the effect of reducing swelling with water, and long-term use may cause urinary system damage, frequent urination, polyuria and other symptoms; *Poria*, can reduce gastric juice secretion, long-term use may cause abnormal digestive function, abdominal discomfort, cause indigestion and other symptoms [24–26].

Alismatis Rhizoma sweet, light, cold, back to the kidney, bladder meridian, conducive to water infiltration, heat release, turbidity and lipid reduction effect. The chemical components of *Alismatis Rhizoma* mainly include triterpenoids, diterpenoids, sesquiterpenes, polysaccharides, phenols, amino acids and various trace elements, of which triterpenoids are its main pharmacodynamic components, Dai Mengxiang [27] et al. found that in addition to the diuretic effect, *Alismatis Rhizoma* also has a variety of effects such as regulating blood lipids, lowering glucose, anti-tumor, anti-virus, anti-inflammatory and so on [28–30]. After taking a large amount, it can cause nausea, vomiting, abdominal pain, increased frequency of stools, abnormal liver function and other adverse reactions.

Polyporus, sweet, light, and flat attributed to the kidney, and bladder meridian, conducive to the effect of water seepage. Jiang Kaiyun [31] et al. investigated the functions of *Polyporus* recorded in the Materia Medica and found that *Polyporus* has potential functions such as tonifying weakness and strengthening, clearing heat and detoxification, relieving moisture and yellowing, and so on. Modern medicine [32] shows that *Polyporus* has diuretic, antitumor, immunomodulating, liver protective, anti-radiation, anti-mutagenic, antibacterial and other pharmacological effects. The water-relieving effect of pork not only increases urine output, but also promotes the release of sodium, potassium, chlorine and other electrolytes. When using *Polyporus* for a long time, attention should be paid to whether there are adverse reactions such as water-electrolyte imbalance and whether *Polyporus* are not toxic.

Modern pharmacological study on the improvement of bacterial flora status of SPS

The main extracts of SPS are soysterols, catechinic acid, licorice chalcone, proanthocyanidin B1, etc.

Soysterols

Soysterol is a phytosterol and is an important extracted ingredient in SPS. The anti-inflammatory and antioxidant pharmacological effects of soy sterol are significant and can effectively reduce the release of inflammatory cytokines. Clinical studies have found that the number and diversity of oral and intestinal flora in patients with cirrhotic ascites decreases as the disease progresses [33]. Through APP/PS1 mice, Jiefan [34] found that stigmasterol could improve the diversity of intestinal flora, dysregulation of microbiota structure and intestinal inflammation of mice A, reduce the relative abundance of pro-inflammatory bacteria *Alloprevotella*, *Parasutterella* and *Desulfovibrio fairfieldensis*, and increase the content of anti-inflammatory *Lactobacillus reuteri*. Flegastrol can act on the NF- κ B signaling pathway, hinder the transcription of inflammatory factors IL-1, IL-6, monocyte chemotactic protein-1 and COX2, play an anti-inflammatory and improve the macrobiotic environment.

Licochalcone

As an important extract of SPS, Licochalcone has anti-inflammatory, antitumor, anti-microbial, anti-HIV, anti-allergic and other effects, and can effectively regulate the distribution of intestinal flora and reduce the probability of ascites. Jia Yongxin [35] reported that licochalcone can gradually increase the abundance of intestinal flora in mice. The richness of the intestinal flora of mice increases with the measurement, and studies have confirmed that licochalcone can affect the phyla *P. icutiella* and *Bacteroides* to varying degrees, and improve the intestinal flora structure of mice. Liu Yining [36] and other studies have found that licochalcone can inhibit bacterial growth by destroying the bacterial cell wall (*Staphylococcus aureus*). The results showed that licorice chalcone inhibited the growth of bacteria, had anti-inflammatory effects, and could destroy part of the bacterial cell wall.

Catechins acid

Catechins acid are phenolic compounds with anti-inflammatory, antibacterial, antiviral and antioxidant properties. Modern pharmacological studies have found that [37] Catechins can lower blood lipid levels, regulate flora balance and improve the richness and diversity of human intestinal flora. Catechins are tea polyphenols, Zou Yan et al. [38] have found that, on the one hand, tea polyphenols can promote the growth of various probiotics in the host intestine, including *bifidobacteria* and *lactobacilli*, thereby increasing the number of beneficial flora; On the other hand, tea polyphenols can inhibit the number of various harmful bacteria such as *Clostridium* and *E. coli* in the host gut, thereby reducing the number of harmful flora [39]. Tea polyphenols interact with the digestive tract flora to maintain a healthy and homeostatic intestinal environment, and can also prevent various metabolic syndromes and avoid the effects caused by metabolic disorders.

According to the modern pharmacological analysis of SPS, it is proven to have various biological activities and pharmacological effects in the treatment of cirrhotic ascites, which is not only widely used in Chinese traditional medicine, but also further confirmed and applied in modern pharmacological research, and is gradually becoming a research hotspot. SPS is capable of anti-inflammatory, regulating the body's immunity, inhibiting the growth and reproduction of bacteria, viruses, fungi and other microorganisms, and has a positive effect on improving the balance of intestinal flora and regulating the diversity of intestinal flora in the treatment of cirrhotic ascites (Table 2).

The link between SPS and the pathogenesis of ascites

The earliest record of SPS is from the "*Pu Ji Zhan Fang*" written by Xu Shu Wei, a famous physician of the Northern Song Dynasty: "To treat the deficiency and swelling of the spleen, SPS is used. Two taels of each of the two herbs are used to treat the deficiency of the spleen. These medicines can strengthen the spleen and earth, warm the kidney and water, and promote the recovery of the spleen's function of transporting water and fluids. In the formula, *Radix Aconiti* is good at warming kidney yang and helping Qi to move water, while dry ginger can warm spleen yang and help it to move and transform water. The combination of papaya tonifies the spleen and harmonizes the middle, and the combination of *Tsaoko Fructus* strengthens the efficacy of moving Qi and inducing stagnation, so that when Qi is moved, the edema will disappear [40]. This formula can harmonize the herbs,

benefit the spleen and harmonize the middle. This formula can harmonize Qi and Blood and harmonize Yin and Yang, which is in line with the pathology of ascites in liver cirrhosis.

Yan's SPS is the first formula in Yan's Jisheng Fang-*Treatment of Oedema*, written by Yan Youhe in the Southern Song Dynasty, and since then Yan's formula has been used clinically and less often than Xu's [41]. Since then, Yan's formula has been used in clinical practice and Xu's less frequently. In the treatment of oedema, Yan added Mu Xiang (*Magnoliae Officinalis Cortex*) and Hou Pu (*Aucklandiae Radix*) to strengthen the function of moving Qi and inducing stagnation, so that when the Qi dissolves, the dampness dissolves, and when the Qi is smooth, the swelling disappears. This formula is in line with the pathogenesis of ascites caused by deficiency of the spleen and kidney. Zhuling (*Polyporus*), *Atractylodes macrocephala* and *Poria* are the main drugs used in the formula of SPS to treat ascites. Chen Liang [42–44] et al. found that *Poria* can increase the level of *bifidobacteria* in the intestinal tract and has the function of intestinal regulating intestinal flora, while *Poria* polysaccharide and *Atractylodes macrocephala* can regulate intestinal flora and protect the intestinal tract by increasing the level of *bifidobacteria* and *lactobacilli*. Meanwhile, YAN Weilun [45] et al. found that *Atractylodes macrocephala* could also improve intestinal mucosal permeability, restore the balance between intestinal water secretion and absorption, and achieve the purpose of repairing damaged intestinal mucosa. The combination of these drugs can improve the status of the body's flora, promote the elimination of body water and fluid, and effectively treat cirrhotic ascites.

Study on the mechanism of SPS in the treatment of ascites in liver cirrhosis

Improving intestinal flora

As the first organ to receive intestinal flora, the liver's pathogenesis is closely linked to dysbiosis. Jiang Zhongwei [46] Through the clinical treatment of 36 patients with cirrhotic decompensation, it was found that patients with cirrhotic ascites are prone to various infections, including but not limited to spontaneous peritonitis, and through 3 months of clinical treatment it was found that regulating the growth of the flora can have an adjunctive effect on cirrhotic ascites. The main ingredients are *Atractylodes Macrocephala*, *Radix et Rhizoma Pseudostellariae*, *Radix Ginger*, *Magnoliae Officinalis Cortex*, *Aucklandiae Radix*, *Fuling*, *Zexie*, *Tsaoko Fructus* and *Ginger Bark*. It is recognized as "the first product to return Yang to save the rebellion". It can effectively help Yang to replenish fire, dispel cold and relieve pain, and has cardiopulmonary, immunomodulatory and anti-inflammatory effects. *Radix et Rhizoma Pseudostellariae* is a warming component of SPS. Tang Zhidan et al [47]. studied the fecal flora of mice with *Radix et Rhizoma Polygoni* and Red Ginseng and proved that *Radix et Rhizoma Polygoni* improved the micro-ecological environment of the intestinal tract to a certain extent, inhibiting pathogenic bacteria and promoting the growth of beneficial bacteria. Dried ginger is the active ingredient of SPS, and Yu Lingying [48]. The relative abundance of the *Phylum Aspergillus* was significantly reduced and that of the *Phylum Bacteroides* was significantly increased, which had an inhibitory effect on the pathogenic flora of the small intestine. Grzanna R's [49] research has found that the *Fuling*, *Muxiang*, dry ginger, *poria*, and spleen seeds in SPS have good therapeutic effects in inhibiting the production of pathogenic bacteria and regulating intestinal flora.

Table 2 Modern pharmacological study on the improvement of bacterial flora status by SPS

Types of extracts	Effects	Mechanism	References
Soysterol	Anti-inflammatory and antioxidant, improve micro-ecological environment of bacterial flora	Acts on NF-κB signaling pathway, blocking transcription of inflammatory factors IL-1, IL-6, monocyte chemotactic protein-1, and COX2	[33][34]
Licorice Chalcone	Anti-inflammatory, anti-tumor, anti-microbial, anti-HIV, anti-allergy	Increasing the abundance of intestinal flora can differentially affect the phylum <i>Bacillus thicckus</i> , <i>Bacillus mimicus</i>	[35][36]
Catechins	Anti-inflammatory, antibacterial, antiviral and antioxidant	Lowering blood lipid levels and regulating the balance of bacterial flora	[37–39]

Inhibition of inflammatory factor expression

Modern research has shown that a variety of drugs in SPS have the effect of inhibiting the expression of inflammatory factors, which can effectively improve the microenvironment of the body. Inflammatory exudate enters the interstitial tissue space and tends to cause inflammatory oedema. Soysterol is an important extract ingredient of SPS, which has anti-inflammatory and antioxidant pharmacological activities in mammals. It can effectively inhibit the release of inflammatory cytokines, reduce the inflammatory state, slow down the rate of glomerulosclerosis and reduce the development of inflammatory oedema [50]. It can also slow down the development of inflammatory oedema. Zheng Jiamei [51] the extract of *Mucuna pruriens* in SPS can inhibit inflammatory cell infiltration and synovial membrane proliferation, reduce serum C-reactive protein, interleukin-1- β , interleukin-6 and tumor necrosis factor- α , and improve the inflammatory response in rats; Ji Minyou et al. [52] reported that *Glycyrrhiza glabra* extracts not only showed protective effects in a tert-butyl hydroperoxide-induced acute liver injury mouse model, but also inhibited the production of inflammatory factors such as NO and inducible NO nitrogen synthase, COX-2, TNF- α , interleukin-1 β and interleukin-6 in LPS-stimulated microglia. The above study shows that SPS can relieve the pain and discomfort caused by inflammation and regulate the levels of inflammatory factors to achieve therapeutic purposes. It is highly effective in inflammation treatment and can effectively reduce inflammatory oedema and alleviate the deterioration of ascites in cirrhosis.

Inhibition of the renin-angiotensin-aldosterone system

Poria is an important component of SPS that exerts a diuretic effect on swelling. *Poria* can act as a diuretic by activating Na⁺-K⁺-ATPase on the cell membrane, which is a novel aldosterone receptor antagonist as the primary active component of *Poria*, competing for aldosterone receptors in vitro and effectively reversing the aldosterone effect in vivo to promote urination, facilitate recovery of renal function and clear proteinuria. The main active ingredient of *Atractylodes macrocephala*, which has diuretic effect, can strongly inhibit the activity of Na⁺, K⁺-ATPase, thus reducing the intracellular exchange of Na⁺ and K⁺ by this transport function [53]. The active ingredient is caryophyllone, which strongly inhibits the activity of Na⁺, K⁺-ATPase, thereby reducing the intracellular Na⁺, K⁺-ATPase function. Wei Wei [53]. It was found that *Poria* can significantly reduce the lipid level and fat accumulation in the liver of rats, reduce the fat factor, and also increase the relative abundance of *Prevotella* spp., *Bacillus* spp. and *Sartorius* spp., indicating that *Poria* polysaccharide can significantly increase the diversity of intestinal flora in the feces of rats, alleviate the structural changes of intestinal flora and improve the dysbiosis of the intestinal flora of rats.

In summary, SPS can effectively inhibit glomerular secretion of renin, reduce the content of aldosterone by interfering with the RAAS system, further weaken the reabsorption of tubular fluid by the renal tubules and collecting ducts in rats, and increase urine discharge. At the same time, it can reduce ascites status by lowering blood lipid level, regulating intestinal flora structure and increasing intestinal flora diversity.

Cardioplegia and vasodilation

Modern medicine believes that improving cardiovascular function can be an important tool in the treatment of oedema [54, 55]. It has been shown in a number of experimental studies that the herbs in SPS have a significant cardiogenic effect. A number of experimental studies have shown that *Radix et Rhizoma Polygoni* in SPS has a significant cardiogenic effect, which is particularly effective in cardiac insufficiency and vasodilatation, and is very effective in improving cardiogenic oedema. Shi Qin [56] the combination of Dried Ginger and *Radix et Rhizoma Pinelliae* in SPS can effectively counteract the damage caused by myocardial ischemia and reperfusion in rats, and reduce the serum levels of creatine isoenzyme as well as myocardial TN-I and LDH activities. Wang Suna [57] et al. found that the herb can

alleviate the inflammatory state of the body by regulating the levels of anti-inflammatory and pro-inflammatory factors and correcting the disorder of intestinal flora in mice.

In summary, SPS can regulate the metabolism of flora and improve the microcirculatory status, inhibit the expression of inflammatory factors and the renin-angiotensin-aldosterone system, and treat cirrhotic ascites; *Poria* can reduce the burden on the liver by lowering the blood lipid level and fat accumulation in the liver, and delay the occurrence of cirrhotic ascites, and *Radix et Rhizoma* can improve the cardiogenic ascites and inhibit the growth of pathogenic flora through its cardiogenic effect.

Comparison of ascites in the treatment of cirrhosis by traditional Chinese medicine and Western medicine

The traditional treatment of ascites in cirrhosis is a direct infusion of ascites, diuresis, and sodium intake. As the main method of treating ascites in cirrhosis, diuresis may cause adverse reactions compared with traditional Chinese medicine treatment. Tan Runner [58] It was found that the urine Na⁺ of patients treated with spironolactone every day was significantly increased, the symptoms of water retention and sodium retention were also relieved, and the water used was significantly reduced, which showed that spironolactone could effectively reduce serum aldosterone, reduce water and sodium retention, and effectively reduce ascites; Patients with furosemide injection and intravenous albumin injection have also been significantly treated. Spironolactone is a commonly used potassium-sparing diuretic, and its structure is similar to aldosterone, which can achieve the role of potassium-sparing diuretic by competing to inhibit the binding site of aldosterone to the receptor, especially during sodium-potassium exchange. Spironolactone [59] may cause serious adverse effects, such as gynecomastia, vaginal bleeding, etc., during treatment and may cause hyperkalemia. Williams [60] found that after treatment, 762 patients had hyperkalemia (5.3%), gynecomastia (1.8%), and gastritis (2%). As long as the patient is monitored for a long time while receiving drug therapy, spironolactone can have acceptable side effects, but caution against its use without careful, long-term monitoring for hyperkalemia and vigilance for factors that may decrease a patient's renal function and result in hyperkalemia.

Based on the possible adverse reactions caused by Western medicine treatment, traditional Chinese medicine provides new ideas for the treatment of ascites in liver cirrhosis. Traditional Chinese medicine believes that liver ascites is mainly formed by emotions, unclean diet, jaundice accumulation, etc., that hurt the spleen and stomach, resulting in abnormal water transport. Clinically, SPS is commonly used.

Study on the clinical application of SPS in the treatment of ascites in liver cirrhosis

Poria cocos, as a medicine to strengthen the spleen and promote water retention in SPS, can be used to regulate intestinal flora and improve ascites in liver cirrhosis. Song Keyulian [61]. After 14 days of continuous administration, the intestinal contents of the mice were cultured and found that the high dose of *Poria* can increase the level of intestinal bifidobacteria, which is effective in regulating intestinal flora. *Poria* is a traditional tonic medicine, which has the effect of diuresis and dampness to improve ascites. It was found that *Poria* has an inhibitory effect on *Staphylococcus aureus* and *Escherichia coli*, which can improve ascites by regulating the intestinal flora status. *Poria*, as one of the main ingredients in SPS, has been shown to be effective in the treatment of ascites in liver cirrhosis. Liang Chao [62] 106 patients with liver cirrhosis were randomly divided into a control group and an experimental group, the control group was treated with conventional western medicine and the experimental group was treated with *Fu Ling* medicine, the results showed that the proportion of positive stool flora in the experimental group was lower than that in

Table 3 Study on the clinical application of SPS in the treatment of ascites in liver cirrhosis

Author	Research Content	Research findings	Literature
Song Keyu	Poria has inhibitory effect on Staphylococcus aureus and Escherichia coli	Regulating the status of intestinal flora can improve ascites	[61]
Liang Chao	The effect of conventional western drug treatment and Porphyrin drug treatment on the proportion of positive stool flora	Poria drug can reduce the proportion of positive stool flora	[62]
Chen Daolei	Spleen San warms the kidneys and helps the yang, strengthens the spleen and helps the water to support the right qi, regulates the flow and distribution of qi, and improves the microcirculatory state.	Real Spleen San can enhance strength and improve ascites	[63]
Wu Junsong	Acts on PI3K-Akt, Ras, Rap1, MAPK and other signaling pathways to exert anti-inflammatory and bacterial growth inhibiting effects	External application of real spleen powder to Shen Que acupoint can increase the levels of peripheral blood CD4 ⁺ , CD8 ⁺ , T cells and peripheral blood NK cells and inhibit inflammatory factors	[64]
Meng Aijun	The combination of Spleen Drink and Wu Ling San with Western medicine treatment showed significant improvement in spleen thickness, ALT, AST, TBil, ALb, and portal vein internal diameter.	Real Spleen San has obvious advantages in treating spleen-kidney Yang deficiency type ascites	[66]
Chu Liang	Clinical efficacy of Spleen San combined with western medicine in the treatment of ascites compared with the efficiency of western medicine alone	Chinese herb Atractylodes macrocephala in Solid Spleen San has the effect of drying dampness and promoting water	[67]

the control group, suggesting that the treatment was effective. Chen Daolei [63] randomly divided 60 patients with ascites into a control group and an experimental group, with the control group receiving needle treatment, and the experimental group receiving SPS combined with needle treatment. The control group was treated with acupuncture, and the experimental group was treated with SPS and water-dispersing powder combined with acupuncture. The study effectively proved that SPS Dispersing Powder could exert the effect of warming the kidney and helping Yang, strengthen the spleen and promote water to support the righteousness, regulate the flow and distribution of Qi, unblock the Qi and improve the microcirculatory status, enhance physical strength and improve ascites. Wu Junsong [64]. The study by Wu Junsong et al. found that SPS can act on PI3K-Akt, Ras, Rap1, MAPK and other signalling pathways to exert anti-inflammatory effects and inhibit bacterial growth. Wang Fuyou [65] et al. observed the efficacy of combining Western medicine with the external application of SPS and water dispersant in the treatment of malignant ascites. 20 patients with ascites were treated with the external application of SPS and water dispersant combined with Western medicine, which proved that the external application of SPS and water dispersant combined with Western medicine in the treatment of malignant ascites could effectively reduce the symptoms of ascites and improve the quality of life of patients, and the accumulation of TCM symptoms such as weakness, nausea, chest tightness, abdominal distension and shortness of breath were effectively improved compared with those before treatment, which has the promotion It has the value of promotion. It has been proved that external application of SPS to Shen Que acupoint can increase the level of peripheral blood CD4⁺, CD8⁺, T cells and peripheral blood NK cells, inhibit inflammatory factors and improve the intestinal flora environment, which has an important role in improving the immune function of patients with malignant ascites. Meng Aijun [66]. The treatment of 72 patients with ascites using traditional Chinese medicine (ShiShanDrink combined with Wu LingShan plus reduction) together with western medicine showed significant improvement in spleen thickness, ALT, AST, TBil, ALb and portal vein internal diameter, which proved the obvious advantage of ShiShanDrink in the

treatment of ascites with spleen and kidney yang deficiency. It proved that SPS Drink has the efficacy of diuresis and dampness, dampness and yang to transform Qi, which can strengthen the spleen, move qi and diuresis, and can treat dropsy of Qi, dropsy of water and dropsy of blood, which is caused by the deficiency of the original but the actual symptoms, and can improve the therapeutic effect of ascites caused by liver cirrhosis with deficiency of spleen and kidney. Chu Liang [67]. The total effective rate of the treatment group was found to be significantly better than that of the control group after one course of treatment, confirming that the clinical efficacy of the combination of SPS with western medicine in the treatment of ascites was significantly better than that of western medicine alone. The study showed that SPS is good at warming kidney yang, helping Qi and chemistry to move water, and also warming spleen Yang, helping transportation and chemistry to control water, warming kidney and spleen, helping Yang and suppressing Yin, and can permeate dampness, making water-dampness flow from the stool. In this formula, Radix et Rhizoma Pseudostellariae and Radix ginger can warm the Spleen-Yang (It refers to clammy extremities, cold pain in the abdomen, indigestion, and water cessation.), inhibit the reproduction of pathogenic bacteria in the intestinal tract and improve the balance of intestinal flora. The Chinese herb Atractylodes macrocephala is used in the treatment of ascites, as it has the effect of drying dampness and inducing diuresis. Yan Weilun [45]. The results showed that Atractylodes macrocephala could promote the proliferation of Bifidobacterium and Lactobacillus in the intestinal flora of mice in both the low, medium and high-dose groups, and the promotion effect was more significant in the high-dose group (Table 3).

Summary and reflection

In summary, the gut microbiota plays an important role in host metabolism and immune regulation, and the liver is the organ in closest contact with the gut, exposed to a large number of bacterial components and their metabolites. Changes in the intestinal flora predispose to liver disease and prevention and anti-infective treatment

of cirrhotic ascites due to dysbiosis is essential. It is common in clinical practice, but there is no specific medicine for it, and it is difficult to treat because it is difficult to heal and prone to recurrence. Although Western medicine can reduce the symptoms, it is easy to have recurrent attacks after the medicine is stopped. The drugs in SPS can not only diuretic and reduce ascites, but also improve the state of flora, regulate the structure of flora, protect the liver to a certain extent, and enhance the non-specific immune function of the body and improve the immunity of the body. It can prolong the survival time of patients and improve the quality of life of patients with ascites. Laboratory studies by the above-mentioned investigators as well as clinical practice have shown that SPS can significantly improve the clinical symptoms of patients and has better long-term efficacy. However, toxic side effects have not been extensively investigated in the clinical setting. Further clinical and laboratory studies are needed to determine the dose and route of administration to achieve maximum therapeutic effect.

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