Review Article

Research Progress of Qiweibaizhu Powder in Treating Digestive System Diseases

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Abstract

Diarrhea is a common clinical problem that can lead to health complications, including death. It is the second-most common cause of death in children. The World Health Organization introduced a program to encourage the development and use of traditional herbal medicines in the treatment of diarrhea. Qiweibaizhu Powder (QWBZP) is a well-known pediatric prescription in China that is commonly used to treat digestive system diseases, such as diarrhea, which is also a type of syndrome in traditional Chinese medicine. Many studies have examined the clinical effects and mechanisms of QWBZP, and innovative and improved formulations have been developed. Recent studies on the effects of QWBZP on diarrhea caused by human rotavirus, antibiotic-associated diarrhea, and mesenteric lymphadenitis in experimental models and clinical trials with diarrhea patients have been reviewed. We conducted a literature search of several databases, including PubMed, China National Knowledge Infrastructure, Chongqing VIP Information Co., Ltd., and Wanfang. A short background of the QWBZP is also provided. The collective findings highlight the curative effects of QWBZP on diarrhea caused by viral infection, antibiotic use, and mesenteric lymphadenitis. Furthermore, QWBZP can regulate the balance of the gastrointestinal microbiota and protect and repair the intestinal mucosal barrier. This review will provide a reference for further studies on QWBZP.

Keywords: Antibiotic-associated diarrhea, intestinal microbiota, mesenteric lymphadenitis, spleen deficiency, viral diarrhea

Introduction

Diarrhea is a frequent clinical problem in hospitalized patients, including those who are critically ill in the intensive care unit. Complications of diarrhea include skin damage, dehydration and electrolyte abnormalities, nutritional deficiencies, and kidney problems. Strategies that prevent or treat diarrhea could, in turn, decrease these complications.[1] Antibiotics, antifungal therapy, prokinetics, and enteral nutrition may predispose critically ill patients to diarrhea.[2]

According to the World Health Organization (WHO), the emphasis in treating diarrhea is to prevent dehydration and continue oral feeding. The sole intervention recommended is zinc, which is frequently used in low-income and middle-income countries.[3,4] In high-income countries, additional interventions have been used to reduce the disease duration. Some clinical practice guidelines commonly recommend probiotics, racecadotril, and smectite as adjuvants in the management of diarrhea.[5,6] Enteral nutrition is often considered the culprit, and feeding is discontinued.[7]

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Herbs have been used in the treatment of diarrhea since ancient times. *Myrtus communis* L (*Myrtaceae*) is a remedy in folklore for several diseases, including diarrhea and gastric ulcers.[8] The seed and husk of *Plantago ovata* Forsk are used to treat diarrhea.[9] *Pomegranate* (*Punica granatum* L.), a fruit native to countries in the Middle East and North Africa, such as Tunisia, can help control diabetes.[10] *Apium leptophyllum* Pers. (Family-Umbelliferae), which is also known as Ajamoda, is also used to treat diarrhea. The annual herb is distributed in India, Sri Lanka, Pakistan, South America, Queensland, and some tropical areas.[11]

Globally, diarrhea affects approximately 2.2 million individuals. The majority are infants and children less than 5 years of age.

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Diarrhea is the second most common cause of death in children. The WHO has introduced a program to encourage the use of traditional herbal medicines in the prevention and treatment of diarrhea.[12]

In China, Qiweibaizhu Powder (QWBZP) is used for the treatment of diarrhea in children. QWBZP comprises seven herbs: Radix Ginseng, Poria, Rhizoma Atractylodis Macrocephalae (fried), Herba Pogostemonis leaves, Radix Aucklandiae, liquorice, Radix Glycyrrhizae, and Radix Puerariae. QWBZP (formerly known as Baizhu powder) was created by renowned doctor Qian Yi during the Northern Song Dynasty. The original prescription was recorded in the *Key to Therapeutics of Children's Diseases Part II*. A description in that volume notes that "QWBZP can be used for spleen and stomach deficiency, vomiting, diarrhea, shock, and all people are suitable to take regardless of whether the Yin or Yang is deficient or not."[13]

Many clinical studies have examined the treatment of diarrhea in children using QWBZP. A meta-analysis including 11 clinical studies involving a total of 2216 patients in the treatment group and the control group were analyzed using the R project. The conclusion was that QWBZP and its modified formula were significantly better in the treatment of diarrhea in children than routine treatment.[14]

Historically, physicians in China have also efficaciously used QWBZP and its modified prescription for the treatment of diabetes and malnutrition in children, summer heat, and anorexia. QWBZP is used for the treatment of diseases and syndromes that are often related to spleen and stomach deficiencies, which also serves as a clinical indication for the use of the QWBZP from the perspective of traditional Chinese medicine (TCM). QWBZP is widely used to treat diarrhea caused by virus infection and antibiotic use. It has been proven to shorten the duration of treatment and reduce the adverse effects of antibiotic abuse in children.

To provide further clarity of the benefits of QWBZP, we reviewed the literature concerning the effects of QWBZP on diarrhea due to human rotavirus (HRV), antibiotic-associated diarrhea (AAD), and mesenteric lymphadenitis in experimental models and clinical trials with diarrhea patients. The databases included PubMed, China National Knowledge Infrastructure (CNKI; http://www.cnki.net/), Chongqing VIP Information Co., Ltd. (VIP; http://www.cqvip.com/), and Wanfang (http://www.wanfangdata.com.cn/). "Qiwei Baizhu Powder and diarrhea" and "Qiwei Baizhu San and diarrhea" were used as subject headings for the databases search of studies published from 2010 to 2020. Seventy-three articles were obtained. These articles were further selected for inclusion in this review using "HRV," "AAD," and "mesenteric lymphadenitis" as keywords.

Effects and Mechanism of Qiweibaizhu Powder in the Treatment of Diarrhea of Different Causes

Diarrhea due to human rotavirus

Clinical studies have confirmed the effectiveness of QWBZP against diarrhea caused by HRV infection. In a clinical trial investigating the effect of QWBZP in the treatment of enteritis caused by HRV infection, 66 patients in the treatment group were administered QWBZP. The recorded outcomes, including stool frequency, stool characteristics, and laboratory examinations, revealed that 32 of the 66 cases were cured, 19 cases were obviously improved, 10 cases were improved, and only 5 cases showed no effect, representing a total effective rate of 92.4%.[15]

In another study, the efficacy rate in the treatment group was 96.2% after oral treatment with QWBZP added as a supplement to the routine treatment of HRV diarrhea.[16] Other authors described that compared with montmorillonite powder, modified QWBZP had a significantly higher total efficacy rate and benefits in reduction of the number of stools, improved stool characteristics, relief of abdominal pain and vomiting, and alleviation of dehydration.[17] In addition, no adverse reactions occurred during the treatment. The study highlighted the advantages of the integrated use of TCM and modern medicine in treating HRV diarrhea.[17]

Diarrhea caused by HRV infection in children is common, especially in the autumn and winter.[18] An efficacy rate of 93.33% was reported for the treatment of HRV diarrhea in children with diosmectite powder. Significantly reduced symptoms included diarrhea, vomiting, and shortened duration of fever. After treatment, Bifidobacteria and Lactobacillus counts increased significantly, and the intestinal flora improved.[19] Other authors described the positive effect of QWBZP on the recovery of bacterial lactase gene diversity, and the increased abundance of Lysobacter and Eukaryota.[20]

After HRV invades the intestinal tract, it replicates in the columnar epithelial cells of the small intestine, leading to degeneration and necrosis of the cells and swelling, irregularity, and shortening of the hair. These events result in the shedding of intestinal mucosal epithelial cells and impaired absorption of electrolytes and water, which causes diarrhea.[21] A study showed that QWBZP reduces the number of plaque-forming units of HRV and viral production, inhibits viral RNA synthesis *in vitro*, prolongs the survival time of HRV-infected cells, and promotes cell regeneration.[22]

The clinical indications for QWBZP are consistent with the main symptoms of diarrhea. Research on the mechanisms of QWBZP in the treatment of diarrhea has been based mainly on intestinal microbial metabolism. The treatment of HRV enteritis in suckling mice with QWBZP reportedly produced significant changes in multiple functional genes related to intestinal microbial metabolism (particularly the genes related to carbohydrate metabolism).[23,24] In particular, the production of pyruvate acetic acid was increased due to the enhancement

of glycolysis and the increased acetic acid produced by anaerobic fermentation. These metabolic changes can release more energy, which supplies the metabolic needs of intestinal microbial and mucous membrane epithelial cells. In addition, the changes can stimulate colonic epithelial cells, which are conducive to colonic reabsorption to water and electrolytes, which can reduce diarrhea symptoms.[23,24]

QWBZP also has protective and restorative effects on the intestinal mucosal barrier. Two studies have shown that QWBZP can enhance the immune function of suckling mice infected with HRV, by increasing the serum levels of interferon-gamma (IFN-γ) and immunoglobulin A (sIgA), and the level of sIgA in the intestinal mucosa (xx, yy). QWBZP can also promote the expression of antiviral proteins such as protein kinase R, eukaryotic translation initiation factor 2 alpha, oligoadenylate synthase, and RNase L in the nucleus of intestinal mucosa intraepithelial lymphocyte (iEL) CD^3+ T cells of infected mice, which can facilitate the clearance of HRV.[25] Alleviation of the pathological changes in the intestinal villi in mice and restoration of the barrier functions have been described. Therefore, QWBZP can effectively alleviate diarrhea and dehydration symptoms of HRV-infected suckling mice, accelerate virus clearance from the small intestine, and reduce the duration of the disease.[26,27]

Several studies have shown that after QWBZP intervention in suckling mice infected with HRV, the expressions of interleukin (IL)-10, IFN-α, IFN-γ, IFN regulatory transcription factor (IRF) 3, and IRF7 were upregulated, and the expression of Toll-like receptor 3, myeloid differentiation factor 88, IL-6, and IL-1 β was downregulated. Specifically, QWBZP can regulate IRF3 and IRF7, and IRF3 and IRF7 could increase the serum levels of IFN-α/β in HRV-infected mice. The expression of CD44 was downregulated, and CD69 was upregulated to promote the response of γ/δ T cells, thereby clearing HRV and reducing the inflammatory response of the infected intestinal mucosa.[28-30]

Effect on antibiotic-associated diarrhea

AAD occurs when pathogenic bacteria multiply in a short period because of gastrointestinal microbiota imbalance caused by antibiotic-mediated killing or inhibition of normal, antibiotic-sensitive bacteria.[31] In another study, the incidence of AAD in children was 6.2%, and QWBZP has curative effects on AAD.[32]

The intestinal microbial metabolism of mice is affected by the use of antibiotics, and QWBZP can gradually restore the metabolic diversity of intestinal microorganisms in mice.[33,34] In another study, QWBZP increased the viable counts of intestinal yeast in a mouse model of AAD, and the combination of QWBZP and yeast had a synergistic effect on the treatment of AAD.[35] This study demonstrated that QWBZP can promote the proliferation of probiotics and inhibit the growth of harmful bacteria, with a regulatory effect on the balance of gastrointestinal microbiota. QWBZP can also affect the level of intestinal lactase by regulating enzyme activity and enzyme-producing bacteria.[36]

The mechanisms underlying the restoration of the healthy and balanced intestinal microbiota of QWBZP may be related to the downregulation of IFN-α expression and upregulation of IL-4 and IL-10 expression, thereby inhibiting intestinal pathological responses.[37] QWBZP can reduce the expression of IL-8 in mice with gastrointestinal microbiota imbalance, which inhibits the intestinal inflammatory response and reduces damage to the intestinal mucosal barrier.[38] When QWBZP was used to treat a mouse model of AAD (produced by combining gentamicin sulfate with cefradine), the symptoms of diarrhea resolved and the lactase activity in the intestinal mucosa recovered and improved.[39,40] Therefore, the mechanisms of the curative effects are also related to the recovery of lactase and sucrase activity in the intestinal mucosa.

The use of QWBZP and the intervention of lactase activity by dysbacteriosis diarrhea modeling with antibiotics did not correlate with the polymorphism of the lactase gene in mice. Thus, there may be other sanger-pathogen sites or other regulatory mechanisms.[41]

Blood analyses of a mouse model of AAD revealed that QWBZP can promote the production of platelets and white blood cells, improve the mean corpuscular volume, and regulate the immune function of the model of AAD.[42] Figure 1 provides a summary of the effects of QWBZP on diarrhea caused by HRV receptors and AAD receptors.

Effects on mesenteric lymphadenitis

Mesenteric lymphadenitis is a nonspecific inflammation of the mesenteric lymph nodes. It is a common disease in children and adolescents, and one of the leading causes of abdominal pain in children. Symptoms include abdominal pain, diarrhea, and vomiting. No clear cause has been found.[43] In TCM, mesenteric lymphadenitis in children is in the "abdominal pain" category. The curative effects of TCM have been described for this disease.[44] In TCM, symptoms of abdominal pain in children are mostly caused by deficiency and weakness. These can be cured using tonifying and warming methods.[45]

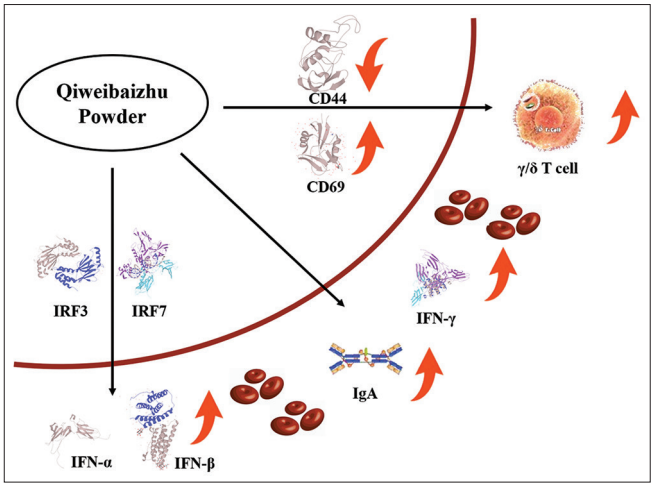

Figure 1: A schematic overview of diarrhea due to human rotavirus receptors, antibiotic-associated diarrhea receptors

According to TCM theory, deficiency of the spleen is the root cause of this disease; phlegm, dampness, and qi stagnation are the crux of the disease; and deficiency in origin and enrichment in symptoms hinders healing.[46] Therefore, modified QWBZP has been administered to therapeutically address both the symptoms and the root causes and to invigorate the spleen to eliminate dampness and regulate qi to disperse stagnation.[47]

In one study, modified QWBZP was used to treat children with mesenteric lymphadenitis. The scores for abdominal pain and other secondary symptoms were significantly reduced in 36 patients after treatment. Among these 36 patients, 33 (91.7%) had diminished or absent abdominal lymph node involvement. According to the criteria of the curative effect of the disease, 28 (77.8%) cases were cured, 5 (13.9%) improved, and 3 (8.3%) showed no improvement. According to the criteria of the curative effect of TCM syndromes, the total efficacy rate was 97.2%. Modified QWBZP can reportedly alleviate abdominal pain and other symptoms of mesenteric lymphadenitis in children with spleen and stomach deficiency and coldness, and reduce the size of enlarged lymph nodes.[45]

In another study, a multi-centered, randomized controlled design was adopted to study the therapeutic effect of QWBZP for mesenteric lymphadenitis treatment in children with spleen deficiency and dampness.[46] The total efficacy and recovery rates were higher and the transverse and longitudinal diameters of the mesenteric lymph nodes were significantly shorter than those of the cefaclor suspension group, with no obvious adverse effects observed.[46] The study revealed the benefit of QWBZP in treating mesenteric lymphadenitis with spleen deficiency and dampness

In another clinical trial, QWBZP alleviated the symptoms of abdominal pain and improved symptoms of spleen deficiency, such as yellow face, mental fatigue, dullness, and irregular stool, in children with dampness. Six months after treatment, there was no obvious recurrence, and the long-term efficacy was stable, indicating the potential value of the treatment.[47]

Other clinical studies demonstrated the significant effects of QWBZP on improved appetite, lack of luster in the complexion, thin sloppy stool of children with anorexia of spleen and stomach qi deficiency, and the increases in body weight and contents of hemoglobin, zinc, and iron in the blood.[48-50]

Effects and Mechanisms of New Preparations of Qiweibaizhu Powder on Diarrhea

Effects of ultrafine Qiweibaizhu Powder preparation

Ultra-micro grinding is a recently developed technology in which Chinese medicinal materials or decoction pieces are crushed into an ultrafine powder (1–75 μm) followed by preparation into granulated decoction pieces. This method saves on material, allows quality control, has flexible compatibility, and is convenient.[51]

A comparison of several indicators revealed that the effect of ultrafine QWBZP on diarrhea was better than that of the traditional decoction pieces. In a mouse model of AAD, QWBZP gradually restored the metabolic diversity of intestinal microbiota.[39,40] Regulatory effects on the immune function were also apparent in a mouse model of AAD.[42] Compared with the full-dose traditional decoction, the gene library and diversity of intestinal microbiota in the group treated with 50% ultrafine QWBZP was closer to the normal control group.[52] The recovery of the mucosal thickness of the intestinal segment and the mucosal lymphocyte count in each segment of the intestine of the AAD mouse model was better in the QWBZP group.[53]

Effects of probiotics

"Fourth-generation probiotics" refer to Chinese medicine probiotic compounds. These are active microbial agents made by adding lactic acid bacteria, yeast, and other probiotics to Chinese herbal medicine or its extracts for fermentation. The combination of Chinese medicine and probiotics technology can enhance the efficacy of TCM, reduce its toxic and side effects, and save on the use of medicinal materials. Therefore, research and application of Chinese medicine probiotics compounds have promising outlooks.[54] In Chinese medicine, yeast is widely used as a probiotic, as it can inhibit the growth of pathogenic bacteria and improve the balance of gastrointestinal microbiota.[55]

A Chinese medicine probiotic compound made with yeast and ultrafine QWBZP has a significant effect on the treatment of AAD. Its efficacy is superior to that of ultrafine QWBZP alone or traditional decoction in many respects.[32] Chinese medicine probiotic compounds comprising 25% ultrafine QWBZP with 25% yeast effectively treated a mouse model of AAD produced with mixed antibiotics of cefradine and gentamycin sulfate. Its effect was not different from that of 50% ultrafine QWBZP or the full-dose traditional decoction.[56] After the treatment, intestinal contents of the ileum were extracted and amplified by PCR with Lactobacillus specific primers for amplified ribosomal DNA restriction analysis. The intestinal microbiota of the group that used QWBZP with yeast was closer to that of the normal control group, proving that the QWBZP probiotic compound could alleviate AAD by adjusting the balance of intestinal microbiota.[56]

Conclusions

QWBZP has obvious curative effects on diarrhea caused by various factors that include HRV infection, AAD, and mesenteric lymphadenitis. Clinically, the curative effect of QWBZP is even more significant when combined with montmorillonite powder, cefaclor suspension, or other Western medicines. Contemporary research on the therapeutic mechanism of QWBZP has revealed that it can promote the antiviral effect of the immune system, eliminate HRV, and reduce the inflammatory reaction of intestinal mucosa infected by HRV. QWBZP can also correct the gastrointestinal flora imbalance caused by AAD.

The mechanism of QWBZP in diarrhea caused by mesenteric lymphadenitis requires further study

QWBZP is a representative and simple prescription with evidence-based ability to strengthen the spleen.[57] In clinical practice, when applied reasonably according to the patients' symptoms, QWBZP is beneficial as a TCM treatment. Investigations of the mechanisms of QWBZP have mainly focused on the mucosa, microbiota, and microbial metabolism of the intestine. With the increased application of biological technologies in TCM research, the study of the mechanisms of QWBZP will be more thorough, to provide more theoretical evidence for its clinical applications.

Commentary

According to the WHO, diarrhea is the second most common cause of death in children. Herbs are obviously effective in treating diarrhea. QWBZP consists of seven Chinese herbal medicines that can be used as food or health food in China. Its efficacy in the treatment of infantile diarrhea due to viral infection and AAD is significantly better than that of conventional treatments. Other advantages include shortened duration of the treatment course, excellent safety, and low cost.

Further in-depth studies of QWBZP need to address the mechanisms and crucial basis of the effects of QWBZP and improved preparation. The related mechanisms of QWBZP in treating diarrhea could be further investigated through metabolomics and proteomics and by using tools such as mass spectrometry combined with gas or liquid chromatography and nuclear magnetic resonance. With the improved analytical capacity of the research tools, the basis of QWBZP will be discovered. In addition, preparations of QWBZP could be further developed to improve their convenience for clinical use, especially for children.

The WHO is actively engaged in establishing herbal medicine in the treatment of diarrhea in children. Chinese herbal medicines, including QWBZP, are well-positioned for this role. The implementation of improved preparations of QWBZP in countries in need will reduce child mortality caused by diarrhea

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Conflicts of interest

There are no conflicts of interest.

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