

## Berberine helpt bij Prikkelbare Darm Syndroom

*A Randomized Clinical Trial of Berberine Hydrochloride in Patients with Diarrhea-Predominant Irritable Bowel Syndrome.*  
Chen et al. (Phytother. Res.), 2015

Het prikkelbare darm syndroom (PDS) is een erg frequente aandoening, die de levenskwaliteit van de patiënten die hieraan lijden sterk beïnvloedt. PDS komt meer voor in vrouwen dan in mannen en kent **volgens de Rome III criteria een prevalentie van tot wel 29.2% van de algemene bevolking**.

Het subtype van **PDS met diarree (PDS-D)** komt voor bij **ongeveer 23.4 procent van de patiënten**. Het ziektemechanisme in PDS-D is nog niet volledig gekend, maar verschillende factoren zoals viscerale hypersensitiviteit, ontsteking van de darmmucosa en veranderingen in het darmmicrobioom werden reeds naar voor gebracht.

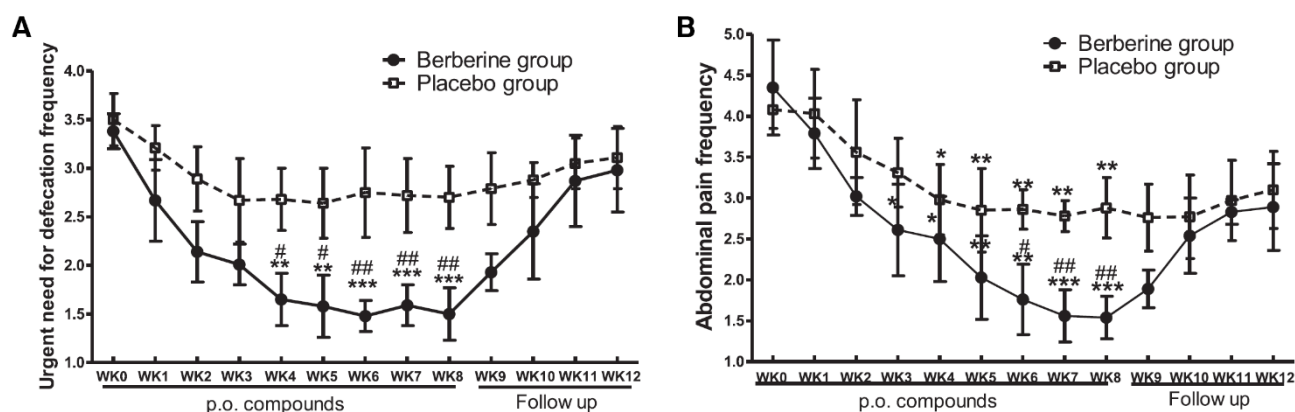
**Berberine is een erg interessante fytonutriënt** waarvan reeds werd aangetoond dat het een anti-microbiële activiteit heeft en **diarree kan verminderen en de motiliteit in de darm bidirectioneel kan reguleren**. In deze studie willen de onderzoekers bijgevolg nagaan of de orale toediening van berberine effectief de symptomen van PDS-D patiënten kan verminderen en dit in een gerandomiseerde **dubbel-blind placebo gecontroleerde studie bij 164 patiënten**.

### Resultaten en Conclusie:

De resultaten van dit onderzoek toonden aan dat in de berberine groep de **frequentie van diarree significant was gedaald na 8 weken inname van berberine** (Fig. 1A,  $p < 0.001$ ). Deze daling leidde bijgevolg tot een significant lagere frequentie van diarree in de berberine groep vergeleken met placebo ( $p = 0.032$ ). Inname van **berberine zorgde voor een daling van 64.4% in de frequentie van buikpijn**, wat een significant grotere daling betekent dan de 29.4% bij placebo (Fig. 1B,  $p < 0.01$ ).

Tenslotte werd ook aangetoond dat de **behandeling met berberine de IBS symptoom score, angst en depressie scores significant verlaagde** en zorgde voor een **significant hogere levenskwaliteit in vergelijking met placebo** (zie artikel tabel 3).

Er kan dus geconcludeerd worden dat **orale inname van berberine gunstig en effectief** is voor het verbeteren van de symptomen en de levenskwaliteit **bij patiënten met PDS-D**.



**Figuur 1 | Het effect van berberine op diarree frequentie en buikpijn.** De inname van berberine zorgt voor een significant sterkere daling in de frequentie van diarree en buikpijn, vergeleken met placebo. ##  $p < 0.01$  vs. placebo.



# A Randomized Clinical Trial of Berberine Hydrochloride in Patients with Diarrhea-Predominant Irritable Bowel Syndrome

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We aimed to evaluate clinical symptoms in diarrhea predominant irritable bowel syndrome (IBS-D) receiving berberine hydrochloride in a randomized double-blind placebo-controlled clinical trial. Overall, 196 patients with IBS-D were recruited for this study; consequently, 132 patients randomized to receive daily 400 mg of berberine hydrochloride, delivered twice daily or placebo for 8 weeks followed by a 4-week washout period. After a 2-week run-in period, diarrhea, abdominal pain, urgent need for defecation frequency and any adverse events were recorded daily. Prior to administration of the medication and after completing the treatment, assessment of IBS symptom scores, depression and anxiety scale scores and the IBS scale for quality of life (QOL) was carried out. The effects of berberine hydrochloride on IBS-D, defined by a reduction of diarrhea frequency ( $P = 0.032$ ), abdominal pain frequency ( $P < 0.01$ ) and urgent need for defecation frequency ( $P < 0.01$ ), were significantly more pronounced in the berberine group than the placebo group in the 8 weeks of treatment. A trend of improvement ( $P < 0.05$ ) was observed with berberine hydrochloride for IBS symptom score, depression score and anxiety score and the IBSQOL, compared with placebo. At last, berberine hydrochloride was well tolerated. So we concluded that berberine hydrochloride is well tolerated and reduces IBS-D symptoms, which effectively improved patients QOL. Copyright © 2015 John Wiley & Sons, Ltd.

**Keywords:** diarrhea; abdominal pain; irritable bowel syndrome; berberine hydrochloride; anti-depressant.

## INTRODUCTION

Irritable bowel syndrome (IBS) is a highly prevalent functional disorder, which reduces patients' quality of life. With a female gender predilection, the prevalence of IBS diagnosed by the Rome III criteria in the general population is 1.1–29.2%, and IBS with diarrhea (IBS-D), as a subtype, accounts for 23.4% (95% CI 8.4%–42.6%) of patients with IBS (Cirillo and Capasso, 2015; Lovell and Ford, 2012; Oshima and Miwa, 2015). Currently, the mechanism of IBS-D pathogenesis is incompletely understood. However, altered bowel motility, visceral hypersensitivity, mucosal immune activation, increased mucosal permeability, enteric neuromuscular dysfunction, abnormal brain-gut interactions, alteration in the gut microbiome and psychological disturbance have been hypothesized (Camilleri, 2013; Zheng and Tang, 2015).

Because IBS-D likely consists of several different disease states, current treatment is focused upon the patient's most bothersome symptoms. Various drug categories (antispasmodics, dopamine antagonists, 5-HT<sub>3</sub> antagonists, sedatives, antibiotics, probiotics and herbal medicines), modifications in diet and lifestyle, and complementary

and alternative therapies have been proposed as a symptomatic treatment (Lazaraki *et al.*, 2014; Teschke *et al.*, 2015). However, to date there is no definite effective cure for all of IBS-D symptoms.

Berberine, as a traditional Chinese medicine isolated from Chinese Goldthread Rhizome, has been used extensively for the treatment of diarrhea. Initially, some studies have demonstrated its significant antimicrobial activity (Sun *et al.*, 2014a). However, in the following studies, berberine has been recognized for its anti-diarrheal effect, in particular secretory diarrhea. Zhang Y *et al.* (Zhang *et al.*, 2012) found that berberine increased the expression of Na<sup>+</sup>/H<sup>+</sup> exchanger3 (NHE3) and aquaporin4 (AQP4), suggesting that berberine may exhibit its anti-diarrheal effect partially by enhancing the absorption of Na<sup>+</sup> and water from the intestinal lumen. Moreover, berberine significantly increased the nociceptive threshold in rats, partly through nitric oxide (NO)-mediated pathways (Tang *et al.*, 2013). Recently, we found (Feng *et al.*, 2013) that berberine plays an inhibiting role on gastrointestinal (GI) motility in rodents, which is supported by evidences from intestinal myoelectric activities and upper GI Transit. The mechanism of berberine action was discovered to be closely related to that of the endogenous opioid system (EOS). Finally, Chen DP (Chen *et al.*, 2013) reported that berberine induced bidirectional motility regulation on rat jejunum, which needed the presence of the enteric nervous system depending on the influx of extracellular Ca<sup>2+</sup>.

These findings provided a theoretical foundation and experimental evidence for berberine's clinical application in treating GI disorders, in particular in the treatment

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of IBS-D. Therefore the aim of this study was to investigate whether oral administration of berberine hydrochloride is effective in alleviating IBS-D symptoms in a randomized double-blind placebo-controlled clinical trial.

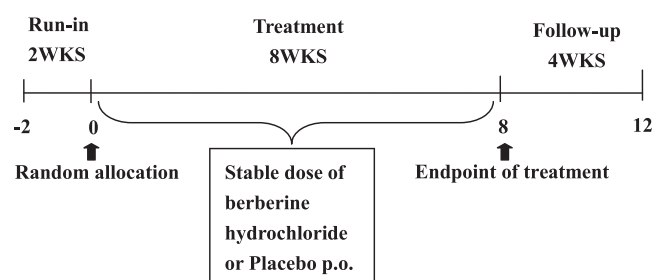
## METHODS

**Patients.** The study was conducted in accordance with the ethical principles of the 1975 Declaration of Helsinki, and the study protocol was approved by local committee of bioethics of Tenth People's Hospital of Shanghai (No. SHSY-IEC-pap-14-12). Verbal and written consent was obtained from each patient.

Between May 2011 and Jan. 2015, 196 patients with IBS-D, aged 18–65 years, were recruited for this study from the Tenth People's Hospital of Shanghai, Tongji University School of Medicine, Shanghai, China. All patients fulfilled the inclusion criteria based on the Rome III classification system (Drossman, 2006), as supervised by an experienced gastroenterologist. Age, gender, employment status, tobacco smoking, duration of IBS symptoms, family history of IBS, use of alternative therapy and symptom severity (mild: can be ignored but does not affect life style; moderate: cannot be ignored but does not affect life style; severe: affects life style; very severe: markedly affects life style) were recorded at the beginning of the study.

**Study design.** This was a 14-week single-center double blind placebo controlled clinical study. Patients were asked not to take any medications known to alter GI tract function or relieve pain conditions, and to report all psychoactive drugs, such as sedatives and antidepressants within a month before and during the study. The following patients were excluded from the study (i) pregnant or breast-feeding women; (ii) subjects with organic GI, anal, hepatic or other systemic disorders; (iii) patients with previous GI surgery history, or (iv) history of cerebral disease or surgery.

Patients who met the inclusion criteria were recruited and randomized into two groups, after 2-week run-in, to receive either berberine hydrochloride (totally 400 mg; per 200 mg oral, twice daily) or an identically appearing placebo (Vitamin C tablet, totally 400 mg; per 200 mg oral, twice daily) for 8 weeks, products both from Shanghai Sine Tianping Pharmaceutical Co., Ltd. Four week was taken to follow-up (Fig. 1).



**Figure 1.** Study design. A 14-week study including a run-in, treatment and follow-up.

During the treatment and follow-up period, subjects were asked to record diarrhea frequency, abdominal pain frequency, urgent need for defecation frequency and any adverse events, which recorded daily and assessed each week. Just prior to administration of the medication and after completing the 8-week course of the treatment, all patients were reviewed and asked to complete several questionnaires. These questionnaires had been previously validated and used to assess the frequency and severity of GI symptoms, like the Birmingham IBS symptom score, which comprised a self completed questionnaire consisted of 14 questions based on the frequency of IBS related symptoms (each question had a standard response scale with symptoms all being measured on a 6-point scale ranging from 0=never to 5=all the time) (Roalfe *et al.*, 2008). Furthermore, the hospital anxiety and depression scale (HAD) (Snaith and Zigmond, 1986) and the IBS special scale for quality of life (QOL) (IBSQOL) (Drossman *et al.*, 2000) were used. Specifically, IBSQOL consisted of 34 items, reflecting respective condition in domains of anxiety, conflict behavior, somatic character, health concerning, dietary restriction, social response, heterosexual concept and family relationship. Each item was differentiated into five grades (none=5, mild=4, moderate=3, lean to severe=2 and severe=1). The sums of symptom severities were used to compute the IBS symptom and the anxiety/depression scores.

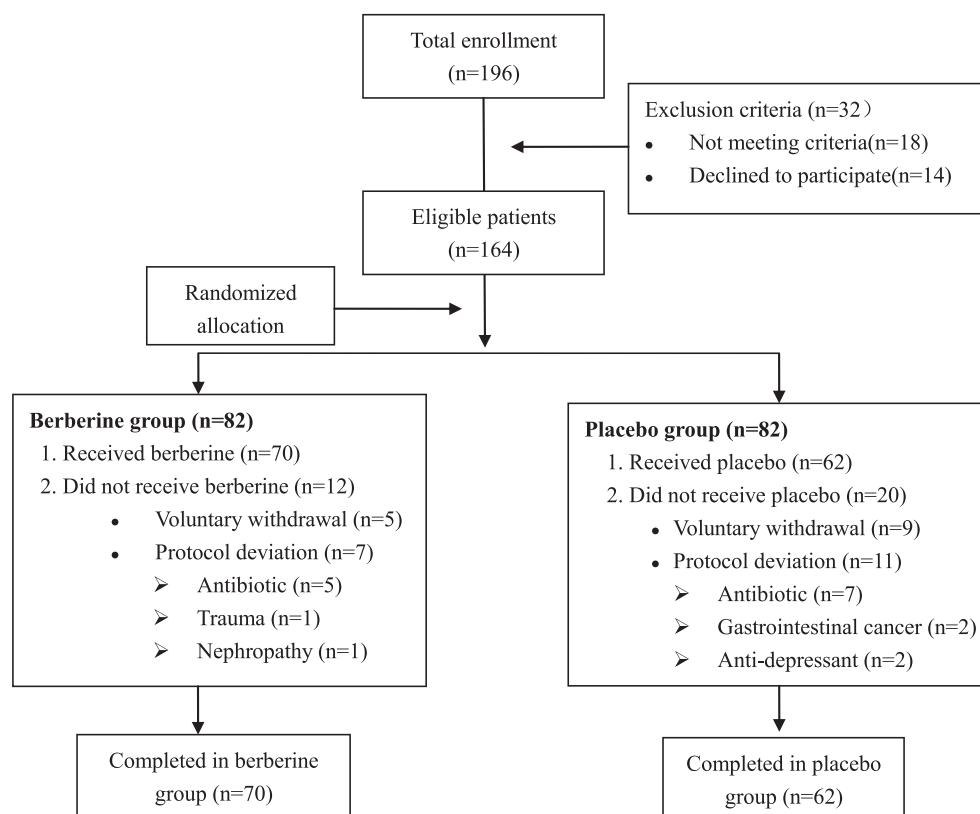
**Statistics.** PRISM 5.0 (GraphPad Software Inc., La Jolla, CA, USA) was used for statistical analyses. Intra-individual pre- and post-therapy scores for IBS symptoms, QOL, anxiety and depression were analyzed by Student's t-test and Mann–Whitney *U*-test. One-way analysis of variance (ANOVA) followed by Student–Newman–Keuls *post hoc* test was used for analysis of multiple treatment means. *P* values < 0.05 were considered significant. The data are expressed as means ± SE.

## RESULTS

### Study cohort

Out of a total of 196 enrolled patients, 32 patients were excluded, including 18 patients who did not meet the criteria, and 14 patients declined to participate. The remaining 164 patients were ultimately included in the study and received the treatment in berberine and placebo group (Fig. 2). Each group was allocated randomly with 82 patients.

Subsequently, 12 patients were excluded in berberine group: 5 patients because of voluntary withdrawal and 7 patients because of protocol deviation. In protocol deviation, 5 patients used an antibiotic, 1 patient had accidental trauma and 1 was diagnosed with nephropathy during the trial. Twenty patients were excluded in placebo group: 9 patients because of voluntary withdrawal and 11 patients because of protocol deviation, in which 7 patients used an antibiotic and 2 patients used an anti-depressant. The other 2 patients were diagnosed with carcinoma in gastrointestinal tract (both diagnosed during study time with endoscopic submucosal dissection for gastrointestinal



**Figure 2.** Flow diagram of the IBS-D patient cohort.

neoplasm). Thus, 70 patients in berberine group and 62 in placebo group completed the study.

Patients ranged in age from 19 to 61 years in berberine group and from 18 to 65 years in placebo group. No differences were observed between groups with respect to any of the baseline characteristics (Table 1).

### Effect on bowel symptoms

Table 2 shows the effect of berberine hydrochloride and placebo on diarrhea frequency in IBS-D patients. In

berberine group, diarrhea frequency was significantly reduced in patients after 8-week berberine hydrochloride treatment compared with the baseline value ( $P < 0.01$ ). On week 12, no berberine hydrochloride taken for follow-up 4 weeks, the diarrhea frequency increased compared with the week 8 ( $P < 0.05$ ). But in placebo group, no different was found among different weeks ( $P > 0.05$ ). Then, intergroup compared on week 8, the diarrhea frequency of berberine group was lower than that of placebo group ( $P = 0.032$ ).

The urgent need for defecation frequency recorded every week showed almost homogeneity on baseline of

**Table 1.** Baseline characteristics of study individuals

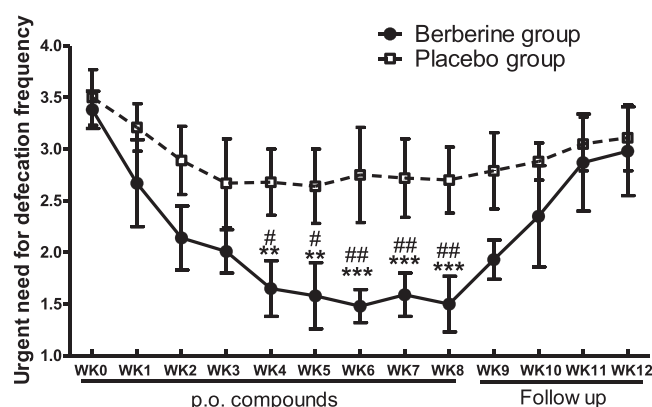
	Berberine group N = 70	Placebo group N = 62	P value
Median (range), yr	37.4 (19–61)	36.1 (18–65)	0.231
Female (%)	51(72.9)	43(69.4)	0.529
Smoker (%)	37(52.9)	32(51.6)	0.886
Family history of IBS (%)	10(14.3)	4(6.5)	0.145
Duration of IBS (%)			
1–5 yr	37(52.9)	34(54.8)	0.820
6–10 yr	18(25.7)	18(29.0)	0.669
>11 yr	15(21.4)	10(16.1)	0.438
Employment (%)			
Employed	51(72.9)	46(74.2)	0.862
Unemployed	12(17.1)	10(16.1)	0.876
Retired	7(10.0)	6(9.7)	0.951
Severity of symptoms (%)			
Mild	3(4.3)	1(1.6)	0.371
Moderate	22(31.4)	17(27.4)	0.614
Severe	36(51.4)	35(56.5)	0.563
Very severe	9(12.9)	9(14.5)	0.782
Alternative therapy for IBS (%)	65(92.9)	59(95.2)	0.580

**Table 2.** Evolution of diarrhea frequency during the study in berberine and placebo group

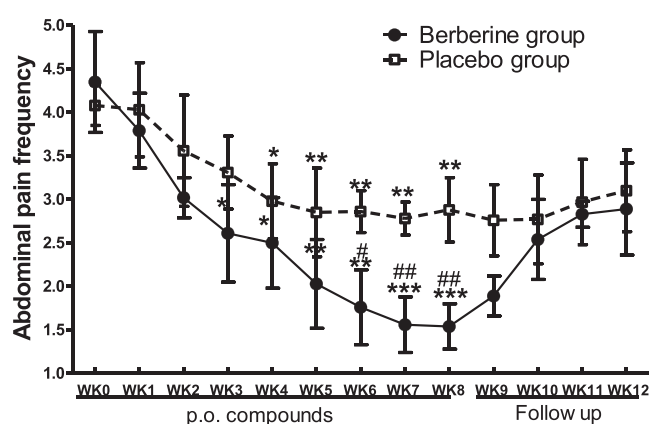
	Berberine group Mean $\pm$ SE	Placebo group Mean $\pm$ SE	<i>P</i> value intragroup
Week 0	4.67 $\pm$ 0.52	4.19 $\pm$ 0.89	0.606
Week 8 (end point of treatment)	1.39 $\pm$ 0.80	3.55 $\pm$ 0.66	0.032
Week 12 (end point of follow-up)	3.58 $\pm$ 0.73	3.81 $\pm$ 0.54	0.805
<i>P</i> value (WK0 vs. WK8)	<i>P</i> < 0.01	<i>P</i> > 0.05	
<i>P</i> value (WK8 vs. WK12)	<i>P</i> < 0.05	<i>P</i> > 0.05	

two-group in Fig. 3. Berberine hydrochloride not placebo led to significant reduction of urgent need for defecation frequency. Compared with baseline value, berberine hydrochloride significantly decreased the urgent need for defecation frequency on WK4 ( $P < 0.01$ ), WK5 ( $P < 0.01$ ), WK6 ( $P < 0.001$ ), WK7 ( $P < 0.001$ ) and WK8 ( $P < 0.001$ ). While intergroup, berberine hydrochloride effectively reduced the urgent need for defecation frequency compared with placebo on WK4 ( $P < 0.05$ ), WK5 ( $P < 0.05$ ), WK6 ( $P < 0.01$ ), WK7 ( $P < 0.01$ ) and WK8 ( $P < 0.01$ ).

As shown in Fig. 4, abdominal pain revealed a reduction of the frequency in both groups throughout the 8 weeks of treatment (WK0–WK8). In berberine group, significant difference were found on pain frequency compared with baseline on WK3 ( $P < 0.05$ ), WK4 ( $P < 0.05$ ), WK5 ( $P < 0.01$ ), WK6 ( $P < 0.01$ ), WK7 ( $P < 0.001$ ) and WK8 ( $P < 0.001$ ). While in placebo group, significant difference was also shown compared with baseline on WK4 ( $P < 0.05$ ), WK5 ( $P < 0.01$ ), WK6 ( $P < 0.01$ ), WK7 ( $P < 0.01$ ) and WK8 ( $P < 0.01$ ). Furthermore, the decrease of abdominal pain frequency on WK8 in berberine group represented a mean 64.6% ( $1.54 \pm 0.26$  vs.  $4.35 \pm 0.58$ ) reduction compared with the initial WK0 abdominal pain frequency. While in placebo group, the reduction of pain frequency was 29.4% ( $2.88 \pm 0.37$  vs.  $4.08 \pm 0.23$ ). Finally, in the intergroup analysis of the reduction pain frequency, berberine hydrochloride was significantly stronger than placebo on WK6 ( $P < 0.05$ ), WK7 ( $P < 0.01$ ) and WK8 ( $P < 0.01$ ).



**Figure 3.** Urgent need for defecation frequency analyzed in berberine and placebo groups. Berberine, but not placebo group, significantly decreased the urgent need for defecation frequency compared with baseline (WK0) on WK4 ( $^*P < 0.01$ ), WK5 ( $^{**}P < 0.01$ ), WK6 ( $^{***}P < 0.001$ ), WK7 ( $^{***}P < 0.001$ ) and WK8 ( $^{***}P < 0.001$ ). Berberine hydrochloride effectively reduced the urgent need for defecation frequency compared with placebo group on WK4 ( $^{\#}P < 0.05$ ), WK5 ( $^{\#}P < 0.05$ ), WK6 ( $^{\#}P < 0.01$ ), WK7 ( $^{\#}P < 0.01$ ) and WK8 ( $^{\#}P < 0.01$ ).



**Figure 4.** Abdominal pain frequency analyzed in berberine and placebo groups. Abdominal pain recordings revealed a reduction of frequency in both groups throughout the 8 weeks of treatment period. Significant differences were observed when the pain frequency in different week ( $^*P < 0.01$ ,  $^{**}P < 0.01$ ,  $^{***}P < 0.001$ ) compared with baseline (WK0). Intergroup analysis, berberine group vs. placebo WK6 ( $^{\#}P < 0.05$ ), WK7 and WK8 ( $^{\#}P < 0.01$ ).

### Quality of life

As shown in Table 3, after 8-week treatment, berberine hydrochloride not only significantly decreased overall IBS symptom score, anxiety score and depression score ( $P < 0.01$ ), but also increased QOL score ( $P < 0.05$ ), compared with baseline values. In placebo group, all assessed scores did not change after the treatment ( $P > 0.05$ ). Furthermore, intergroup overall IBS symptoms score, anxiety score and depression score were significantly lower after berberine hydrochloride treatment than placebo ( $P < 0.05$ ), while the QOL score was higher compared berberine hydrochloride treatment with placebo ( $P < 0.05$ ).

Of note, eight patients reported slightly upset stomach after oral berberine hydrochloride. However, all these patients recovered about one or two weeks follow-up. No other adverse side effects were observed.

### DISCUSSION

The present randomized double-blind placebo-controlled study demonstrates that berberine hydrochloride is a safe traditional Chinese herb medicine that can relieve symptoms in IBS-D patients fulfilling the Rome III criteria. This 14-week clinical trial was performed according to the recommended design of trials for IBS (Miller, 2014).

Based on our data, 164 IBS-D patients were randomized and treated for 8 weeks with either berberine

**Table 3.** Pre-treatment and post-treatment scores for IBS symptoms of patient in both the berberine and placebo groups (mean  $\pm$  SE)

	Berberine (n = 70)			Placebo (n = 62)		
	Before (0WK)	After (8WK)	P	Before (0WK)	After (8WK)	P
Overall IBS score	46.63 $\pm$ 5.33	30.13 $\pm$ 5.02*#	* < 0.01 # < 0.05	47.75 $\pm$ 3.49	41.00 $\pm$ 10.13	> 0.05
Anxiety score	9.88 $\pm$ 0.72	6.63 $\pm$ 0.60*#	* < 0.01 # < 0.05	10.25 $\pm$ 1.03	9.66 $\pm$ 0.75	> 0.05
Depression score	11.38 $\pm$ 0.94	6.75 $\pm$ 0.59*#	* < 0.01 # < 0.05	11.50 $\pm$ 0.98	10.13 $\pm$ 1.22	> 0.05
QOL score	122.20 $\pm$ 12.36	158.47 $\pm$ 6.29*#	* < 0.05 # < 0.05	126.63 $\pm$ 15.52	131.57 $\pm$ 11.58	> 0.05

\* $P < 0.01$  or  $P > 0.05$  when compared with baseline values.

# $P < 0.05$  when compared between groups.

hydrochloride at a daily dose of 400 mg, or placebo; only 70 cases in berberine group and 62 in placebo group completed the study because of patients withdrawal and protocol deviation. Because the berberine hydrochloride optimal dose on IBS-D remains to be unclearly established, our dose choice was absolutely based on the known active concentrations safely used in human. One study reported the effective dose of berberine hydrochloride patient daily intake to anti-diarrhea on *Vibrio cholerae* and *Escherichia coli* infection was 400 mg (Rabbani, 1996).

For centuries, berberine has been used to treat diarrhea and gastroenteritis in East Asian countries because of its antimicrobial, antimotility, anti-permeability and antisecretory properties (Chen et al., 2014; Menees et al., 2012). Therefore diarrhea and urgent need for defecation frequency were chosen as the primary end-point in the present study. The 2-week prospective baseline observation period ensured that patients were currently symptomatic, with a comparable diarrhea and urgent need for defecation frequency in both the active and placebo groups. After 8 weeks of treatment, the reduction of diarrhea and urgent need defecation frequency was more significant in patients receiving berberine hydrochloride than in the placebo group. However, the improved action of placebo on IBS-D symptom was also found in our clinical trial. Of note, literature reported that a significant proportion of IBS patients receiving placebo also respond to therapy. According to a study by Ford and Moayyedi, the placebo response rate in randomized clinical trials conducted in Europe may vary from 0 to 91.7%, with a mean value of 43% (Ford and Moayyedi, 2010).

In our research, the reduction of abdominal pain frequency in the berberine group represented about 64.6% after 8-week treatment, compared with the baseline value. During the 8 weeks of treatment, changes in the abdominal pain frequency had similar tendency in two groups. However, the effect of berberine hydrochloride was significantly stronger than that of placebo. It supports a potential action of berberine on visceral analgesia. This hypothesis is consistent with previous findings obtained in rats where the antinociceptive effect of berberine on visceral hypersensitivity appeared after the treatment (Tang et al., 2013). Of note, the analgesic action of berberine may be associated with, at least in part, nitric oxide (NO) pathway,

antioxidative effects and antiinflammatory (Kim, 2015; Kim and Kim, 2013).

Relatively recently, Kulkarni (Kulkarni and Dhir, 2010) has reviewed that berberine had protective effect in Alzheimer's, cerebral ischemia, mental depression, schizophrenia and anxiety. In our study, therapeutic efficacy of berberine was associated with decreased IBS symptoms scores, lower anxiety and depression scores, suggesting that the beneficial effects of berberine hydrochloride in IBS-D may be related to its action not only in the gut, but also in the central nervous system. Studies have shown that berberine has antidepressant-like effect in forced swim and tail-suspension test, and anxiolytic effect in black and white test and the elevated plus-maze test. Evidence from the literature outlined that berberine has inhibitory action on monoamine oxidase enzyme (Kong et al., 2001; Peng et al., 2007). Then it was well documented that monoamine oxidase inhibitors increase the concentrations of norepinephrine, serotonin (5-HT) and dopamine in the brain and have antidepressant and anxiolytic effects (Peng et al., 2004). Moreover, nitric oxide pathway and/or sigma receptors may be involved in mediating berberine antidepressant-like activity in mouse forced swim test (Kulkarni and Dhir, 2008). Lee et al. (2012) reported that berberine administration significantly reduced morphine withdrawal-associated depression- and anxiety-like behavior following discontinuation of repeated morphine administration in rats, possibly through modulation of hypothalamic corticotrophin-releasing factor and the central noradrenergic system. Recently, one of the reports (Sun et al., 2014b) deduced that the inhibition of organic cation transporter 2 (OCT2) and 3 (OCT3) was possibly implicated in the mechanism of antidepressant-like action of berberine.

Finally, it is known that IBS-D has a severe impact on the quality of life (QOL), which is in turn correlated with the appearance of IBS symptoms. The improvement of QOL score by berberine hydrochloride observed in this trial was significant. However, the mechanism of action of berberine on IBS-D patients' quality of life still needs further investigation.

In conclusion, berberine hydrochloride, conveniently delivered, is well tolerated and reduces diarrhea frequency, abdominal pain frequency, and overall IBS-D symptoms score as well as anxiety and depression scores; consequently, berberine improves the quality of

life of IBS-D patients. Further studies should be warranted to confirm that berberine hydrochloride is a new promising candidate to improve the symptom of discomfort in IBS-D.

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## AUTHOR CONTRIBUTIONS

Chen C and Tao C both did the most clinical trial and wrote the manuscript. Liu Z designed this research. Liu Z, Lu M and Pan Q helped to collect subject documents and clinical data. Zheng L and Li Q helped to do data analysis. Song Z and Fichna J revised the research and manuscript.

## Conflict of Interest

The authors have declared that there is no conflict of interest.

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