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ORIGINAL ARTICLE

Efficacy of a Quebracho, Conker Tree, and *M. balsamea Willd* Blended Extract in a Randomized Study in Patients with Irritable Bowel Syndrome with Constipation

Kenneth Brown, Brandi Scott-Hoy, Linda Jennings

Kenneth Brown, Brandi Scott-Hoy, KBS Research LLC, 15660 N. Dallas Parkway, Suite 700, Dallas, TX 75248, the United States
Linda Jennings, Principal Statistician, Annette C. and Harold C. Simmons Transplant Institute, Baylor Scott & White Health, 3410 Worth Street, Suite 950, Dallas, TX 75246, the United States
Correspondence to: Brandi Scott-Hoy, KBS Research LLC, 15660 N. Dallas Parkway, Suite 700, Dallas, TX 75248, the United States.
Email: brandi@kbsresearch.com
Telephone: +1-214-770-8409
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ABSTRACT

AIM: To assess efficacy and safety of a blended Quebracho, Conker Tree and *Mentha balsamea Willd* extract in patients diagnosed with irritable bowel syndrome with constipation (IBS-C).

MATERIALS AND METHODS: This was a 2-week double-blind, randomized, placebo-controlled study of patients previously diagnosed with IBS-C (N=16). Subjects were randomized at baseline and assessed using a scoring system for symptoms of constipation, bloating, and a total constipation plus bloating score before receiving the blended herbal extract or placebo. At baseline and 2 weeks, vital signs, concomitant medications, diary entries of symptoms, and adverse events were recorded as well as assessment of constipation, bloating, and a total constipation plus bloating score. Treatment group, time of symptom scores, and the interaction between group and time were analyzed. Paired t-tests were used to assess temporal effects within each treatment group.

RESULTS: There were no baseline differences in the constipation, bloating, and total constipation plus bloating scores for the herbal extract and placebo groups. The repeated measures analysis of variance tests showed a significant time/group interaction for the herbal extract effect on improving all three scores. There were significant improvements in the average constipation (p=0.0034), bloating (p<0.001) and constipation plus bloating scores (p<0.001) for the herbal extracts group compared to no improvement for the placebo arm. There were no reports of AEs over the 2-week period.

CONCLUSION: The results from this pilot study suggest a blended extract of Quebracho, Conker Tree and *M. balsamea Willd* can safely manage symptoms in IBS-C subjects.

Key words: Herbal Extract; Supplement; Irritable Bowel Syndrome; Bloating; Constipation

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List of Abbreviations

Adverse Events (AEs); End of Study (EOS) Gastrointestinal (GI); Irritable Bowel Syndrome (IBS); IBS with Constipation (IBS-C); IBS with Diarrhea (IBS-D); IBS with Alternating Constipation and Diarrhea (IBS-M); Small Intestinal Bacterial Overgrowth (SIBO); Selective Norepinephrine-Reuptake Inhibitors (SNRIs); Selective Serotonin-Reuptake Inhibitors (SSRIs); Tricyclic Antidepressants (TCAs).

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) motility disorder characterized by the presence of abdominal pain and a change in the pattern of bowel movements in the absence of other diagnosed disease[1]. Based on population studies, the incidence of IBS is between 7% and 20% worldwide[2] with women experiencing IBS symptoms 1.5 to 2 times more frequently than men[3]. Diagnosis of IBS after excluding other diseases or pathology is categorized according abdominal pain with differing stool consistency of three main subtypes: IBS with constipation (IBS-C), with diarrhea (IBS-D), or alternating constipation and diarrhea (IBS-M)[4,5]. The incidence of each subtype, IBS-C, -D, and -M, varies according to national population analyzed. In the United States, for example, IBS-M represents about 40% of the population with IBS-C and -D relatively equally distributed among the population at ~27%[6]. More women than men are diagnosed especially with IBS-C[3]. Symptomology in these women has a huge impact on quality of life and productivity[7]. It is estimated that constipation alone results in hundreds of millions of dollars in healthcare expenditures, lost productivity to the economy and personal costs in terms of lower quality of life[8,9].

Symptoms of IBS-C according to Rome III criteria include recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with two or more of the following: 1. Improvement with defecation; 2. Onset associated with a change in frequency of stool; 3. Onset associated with constipation. The criterion must be fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis and there must be hard or lumpy stools $\geqslant$25% and loose or watery stools <25% of the time[10]. The symptoms of gas, bloating and constipation in IBS-C patients have been linked to the production of gases, particularly hydrogen and methane, in the upper small intestine as measured by lactulose breath testing[11]. The bacteria generating these gases in functional bowel patients are putatively methogenic archaebacteria[12]. There is strong evidence that methane delays intestinal transit, possibly acting through neuromuscular signals[13]. This is further supported by the finding that methane production is associated with delayed transit time in clinical studies[14,15].

Antibiotics such as rifaximin and neomycin have been shown in clinical studies to reduce symptoms in IBS-C[16], but are not currently approved for use in this condition. Other typical treatments include fiber supplements[17], laxatives such as polyethylene glycol and stimulants[18,19], prosecretory agents such as lubiprostone and linaclotide[20,21], and probiotics[22]. All of these therapies have a variable effect in patients with IBS-C. The use of tricyclic antidepressants (TCAs), selective serotonin-reuptake inhibitors (SSRIs) and selective norepinephrine-reuptake inhibitors (SNRIs) have also been found to be efficacious in IBS patients but not without side effects[23]. Antibiotics are used to treat IBS, particularly if small intestinal bacterial overgrowth (SIBO) is suspected. Rifaxmin, for example, is used as a short course treatment primarily for non-constipated IBS patients[24]. Patients with IBS-C, where bacterial overgrowth is suspected or patients with bloating, are particularly difficult to manage since the bacteria present produce methane and hydrogen, potentially inhibiting intestinal transit[25]. A diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) has been shown to reduce gas, bloating and IBS symptoms in some patients[26]. Even with all of these therapies, there is a need for safe, efficacious agents for patients with IBS-C with abdominal pain, gas, and bloating.

Quebracho extract contains tannins which are large delocalized flavonoid structures. These molecules potentially have dual function; acting as a molecular sink for excess hydrogen and methane as well as disrupting and destroying bacterial lipid bilayers[27,28]. Ruminants fed tannins show reduced emission of methane[29,30]. Conker Tree extract, which contains escins also known as saponins, have been shown to act as an antimicrobial agent to promote intestinal motility[31] and may directly reduce methane production/emission[32,33]. Finally, *M. balsamea Willd* extract contains peppermint oil which has evidence for managing abdominal discomfort[22].

Based on the activity of the molecules summarized above, a combination of these three extracts was tested in a 2-week double-blind, randomized, placebo-controlled in-office experiential study of patients previously diagnosed with IBS-C symptoms of constipation and bloating meeting Rome III criteria.

MATERIALS AND METHODS

Trial design

To test the effectiveness of a new over-the-counter dietary supplement consisting of a blended extract of Quebracho, Conker Tree and *M. balsamea Willd* (Atrantil™) with purported activity in bloating and constipation, participants (N =16) were individually randomized to one of two parallel groups, blended extract or placebo using a 1:1 construction. Concomitant medications for comorbidities were noted and recorded. Subjects were then randomized to receive extract or placebo. At baseline and 2 weeks, subjects visited the site. Vital signs were taken, there was a review of diaries and recording of any adverse events (AEs), and study product was examined for compliance. At week 2, study product and placebo were collected, unused product recorded, and the symptom questionnaire administered.

The study was conducted in accordance with ICH Guidelines on Good Clinical Practice and the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964, as revised in 2004) and approved by an internal research ethics committee. Screening was performed after a 2-week wash out period of any medications used to treat IBS-C. Subject medical history, vital signs, a urine pregnancy test and symptom questionnaire were administered prior to randomization. There were no changes to the protocol throughout the study.

Participants

Inclusion criteria were age at least 18 years, a diagnosis of IBS-C at least 6 months prior to enrollment into the study (according to Rome III criteria) and a history of uncontrolled symptoms of constipation and bloating. Participants were excluded if they had a diagnosis of IBS with diarrhea (ROME III criteria), a history of any serious GI, hepatic, renal, cardiovascular, neurological or hematological disorder, history of drug or alcohol abuse, history of psychiatric disorders, or history of allergy to study-related products. All patients signed written, informed consent prior to being randomized in the study to participate as well as to have the data published upon completion.

Study Setting

This was a single-site, randomized, double-blind, placebo-controlled 2-week study which enrolled subjects previously diagnosed with IBS-C.

Interventions

Participants, after meeting inclusion/exclusion criteria, were randomized to receive either the study product consisting of

Quebracho (150 mg), Conker Tree (470 mg) and *M. balsamea Willd* oil (0.2 mL) extracts or placebo. The Quebracho extract is standardized to 80-82% polyphenol content with 72-74% soluble tannins, primarily consisting of profisetinidin subunits as part of trimeric, tetrameric and pentameric condensed tannins (~75%) determined by MALDI-TOF and ^{1}H- and ^{13}C-NMR fingerprint analysis. The Conker Tree extract is standardized to 20% saponin content by UV-Visible spectrophotometry and High Performance Thin Layer Chromatography (HPTLC) densitometry. Finally, pure peppermint oil content from *M. balsamea Willd* was determined by specific gravity, angular rotation and refractive index (USP29). The amount of each ingredient in the study product was determined empirically based on the highest, non-toxic commercial available amount of tannins in the Quebracho, saponins in Conker Tree, and peppermint oil in *M. balsamea Willd* extracts which have been consumed as part of foods so that they could be combined in a single capsule for ease of dosing. Any other medications used to treat IBS-C as well as narcotics were not permitted and no rescue medication for IBS, constipation, or bloating was allowed for the duration of the study. Any unused study product was collected at the end of the study.

Outcomes

A 7 point Likert scale for IBS was administered at baseline and 2 weeks[25]. Questions were totaled to create subscores for constipation, bloating, and a total constipation plus bloating score.

Randomization and Blinding

Simple randomization was used for this study at a 1:1 ratio. The sample size is sufficient for the analysis to evaluate an exploratory response of the blended extract (n=8) and placebo (n=8). The blended extract and the matching placebo had a similar color and was encapsulated to assure that the participants in each group as well as the health care providers could not tell them apart. The blind was held by the statistician until completion of all data collection for all participants.

Statistical Methods

Scores for constipation, bloating, and a total constipation plus bloating were reported as means plus standard deviations. Each subject was evaluated at baseline and the end of study (EOS) at 2 weeks. These results were analyzed using a repeated measures analysis of variance model that included terms for treatment group, time of symptom scores, and the interaction between group and time. Paired t-tests were used to compare changes over time within each treatment group. Wilcoxon two-sample tests were used to compare treatment groups at each time point. Significance was defined as $p < 0.05$. All analysis was performed using SAS 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Subjects in this randomized, double-blind single-site study ranged in age from 23 to 57 years (mean=38 years). There were 13 females and 3 males initially enrolled. The subjects were primarily Caucasian in the study, with two Hispanic and one of Middle Eastern participant. These IBS-C patients had been diagnosed for several years with uncontrolled constipation and bloating. Post study results were only available for 13 of 16 participants. Two placebo and one subject administered the blended extract did not report results. All participants reporting results did not have any unused study product remaining at the end of the study suggesting that 13 of 16 participants were compliant with taking each study intervention.

The repeated measures analysis of variance tests showed a significant time x group interaction for the percent improvement of constipation, bloating and the total scores. Within group changes comparing at EOS (Post) to baseline (Pre) scores demonstrated a significant improvement in the extract group but not in the placebo group for constipation, bloating and the total score (Table 1).

Similar results were found using a Wilcoxon Two-Sample Test comparing extract to placebo at baseline and EOS. At baseline there was no statistical difference between extract and placebo, but by EOS, the extract showed significantly better symptom management (Table 2).

Table 1 Comparison of Post- vs. Pre- Scores for Extract and Placebo Groups.

Description	N	Mean	Std Dev	Median	Minimum	Maximum	Paired T-Test, *p*-value
Extract							
Post-Pre Avg Constipation	7	1.96	1.055	1.5	0.75	3.75	0.004*
Post-Pre Avg Bloating	8	4.13	1.188	4.25	2	5.5	<0.001*
Post-Pre Avg Score	7	2.62	0.886	2.5	1.17	4	<0.001*
Placebo							
Post-Pre Avg Constipation	6	0.33	0.408	0.38	-0.25	0.75	0.102
Post-Pre Avg Bloating	8	0.31	0.458	0.5	-0.5	1	0.095
Post-Pre Avg Score	6	0.28	0.39	0.33	-0.33	0.67	0.141

*Significant Response.

Table 2 Pre- and Post-Administration of Extract Compared to Placebo.

Description	Group	N	Median (25%, 75%)	Mean (SD)	Min, Max	Mean Score	*P*- Value
Pre Avg Constipation	Extract	7	2.50 (1.25, 2.50)	2.14 (0.73)	1.00, 3.00	8.57	0.104
	Placebo	6	1.25 (1.25, 1.50)	1.38 (0.21)	1.25, 1.75	5.17	
Pre Avg Bloating	Extract	8	1.25 (0.75, 2.00)	1.25 (0.76)	0.00, 2.00	8.81	0.788
	Placebo	8	1.00 (0.25, 2.00)	1.13 (0.95)	0.00, 2.50	8.19	
Pre Avg Score	Extract	7	2.17 (1.17, 2.33)	1.90 (0.57)	1.00, 2.33	8.64	0.095
	Placebo	6	1.33 (1.17, 1.83)	1.42 (0.36)	1.00, 1.83	5.08	
Post Avg Constipation	Extract	7	4.25 (4.00, 4.25)	4.11 (0.45)	3.25, 4.75	10	0.0034*
	Placebo	6	1.63 (1.50, 2.00)	1.71 (0.51)	1.00, 2.50	3.5	
Post Avg Bloating	Extract	8	5.50 (5.00, 6.00)	5.38 (0.69)	4.00, 6.00	12.5	<0.001*
	Placebo	8	1.25 (1.00, 2.00)	1.44 (0.73)	0.50, 2.50	4.5	
Post Avg Score	Extract	7	4.67 (4.50, 4.83)	4.52 (0.49)	3.50, 5.00	10	0.003*
	Placebo	6	1.58 (1.50, 1.83)	1.69 (0.45)	1.17, 2.50	3.5	

*Significant Response.

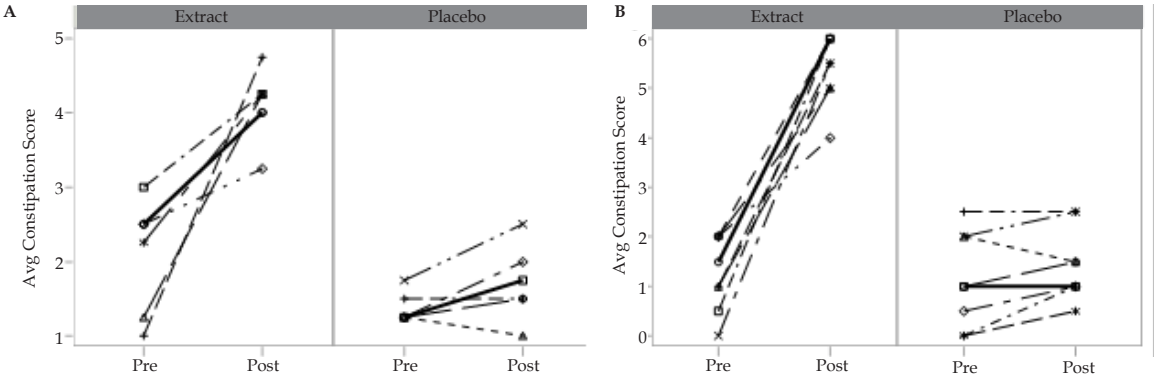

Figure 1: Percent Improvement in Constipation (A) and Bloating (B) Before and After Extract Administration Compared to Placebo.

The plot of individual subject scores for constipation and bloating before and after administration of either the extract or placebo is shown in Figure 1.

Finally, there were no dropouts or reported AEs during the course of the study or changes in concomitant medications for comorbid conditions.

Though this study has a small number of patients, the results demonstrate that a blended extract of Quebracho, Conker Tree and *M. balsamea Willd* can dramatically improve constipation and bloating in patients with IBS-C compared to placebo. This is the first report of this combination of ingredients for the management of symptoms in IBS-C patients.

DISCUSSION

Irritable bowel syndrome with constipation represents a difficult to treat, intractable problem especially in women that effects quality of life and work productivity[3,7-9]. Mönnikes has found that IBS patients have worse health-related quality of life even compared to patients with diabetes and end-stage renal disease[34]. Symptoms such as altered bowel movements, abdominal pain, bloating and distension drive this worsening effect on life functions. It is estimated that over 90% of IBS patients suffer from bloating which is directly linked to abdominal pain and distention[35]. These symptoms may be caused SIBO or dysbiosis. Better symptom management is needed, even with currently marketed FDA-approved drugs which have been shown to be safe and effective.

Like many approaches to human health which begin in animal husbandry such as probiotics[36] and oral serum-derived bovine immunoglobulin[37], the blended extract tested in this study has its origins in reducing gas emissions in ruminants[38]. Fermentation of grasses and other forage in the bovine gut leads to gas production reducing the utilization of feed sources adversely affecting meat and milk production[28-30]. Therefore, a variety of tannins have been used as feed additives to decrease gases such as hydrogen and methane in cows and other animals. In the human digestive tract, bacteria in the colon, but also those in the small intestine, can ferment certain foodstuffs to hydrogen and methane[39]. It has been found that individuals with a higher incidence of SIBO or who experience more bloating and distention seem to produce more hydrogen and methane which can lead to abdominal pain and constipation[40]. Addition of tannins in patients who have bloating, distention and constipation may help to manage these symptoms and improve quality of life for these individuals similar to the use of these agents in ruminants.

Tannins like those purified from the Quebracho tree have over 50 years of safe use in wine[41]. Tannins serve as antiradical sinks and antioxidants. The latter activity may be especially important for hydrogen binding near neutral pH found in the upper intestine. Tannins also nonspecifically bind dietary fiber which may make it less susceptible to fermentation[42]. These highly branched polyphenol molecules have been additionally found to disrupt bacteria lipid bilayers acting as bacteriostatic agents[27]. Conker Tree extract which contains the antimicrobial escins[31], also known as saponins, can also reduce the production as well as emission of methane[32,33]. Escins have further been found to increase GI motility and transit through the ileus in mice[43] and improve time to recovery of passage of gas, GI sounds and bowel movements in postoperative colorectal surgery patients[44]. Though patients were not assessed for abdominal discomfort in this study, the *M. balsamea Willd* extract which contains peppermint oil would be expected to help manage this symptom that typically accompanies bloating and constipation in IBS patients[22,45]. Peppermint oil has also been shown to act as an antispasmodic attenuating contractile responses to acetylcholine, histamine, 5-hydroxytryptamine, and substance P[46]. Further experimentation is needed to determine the additive or synergistic effect of tannins, saponins, and peppermint oil on bacterial populations in the small intestine, stimulation of motility and effects on abdominal pain.

It is possible that the blended extract could also be utilized in patients with IBS-D who have also been diagnosed by breath test with SIBO. Sachdeva *et al*[47] found that there was a statistical link between patients with IBS-D, female gender, and bloating that was also a predictor of SIBO in effected populations. Therefore, it is possible that the tannins in the blended extract could act as a sink for hydrogen ions generated by invasive bacteria in the small bowel of IBS-D patients. There is also data to support the use of peppermint oil for abdominal pain in this population[22]. It is unknown what effect, however, saponins Conker Tree Chestnut would have on diarrheal symptoms. This would have to be tested clinically in IBS-D patients with SIBO.

The results demonstrated in this small placebo-controlled study showed a statistically significant reduction of abdominal bloating and constipation (Figure 1) in two weeks for a group administered the blended extract of Quebracho, Conker Tree, and *M. balsamea Willd* compared to the placebo group which continued to experience these symptoms unabated. Limitations of this study are the small

sample size and that there were more female participants *vs* men (4:1) than normally diagnosed with IBS-C (2:1)[3]. Since this was a single-site, healthcare provider practice which recruited the participants, the number of women vs men reflected the practice composition. It is unknown whether this selection biased the results in favor of the blended extract over the placebo. Even if women respond more to the product compared to men, this would an interesting and exciting finding. This blended extract contains safe, food ingredients which also produced no reported side effects, something needed in care of IBS-C patients. Based on these results, a blended extract of Quebracho, Conker Tree, and *M. balsamea Willd* shows promise for use in IBS-C and should be considered as a reasonable approach in these difficult to treat patients. Larger studies, which meet Rome suggested criteria for study design and have the proper ratio of women to men in a multicenter format are needed to assess the efficacy of this product.

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Authors Contributions: Dr. Brown and Ms. Scott-Hoy performed the clinical study and collected the data. Dr. Brown was the principle investigator for the study. Dr. Jennings interpreted and performed statistical analysis of the study data. All authors wrote, revised for intellectual content, and approved the final manuscript. We thank Dr. Bruce P. Burnett for his writing and editorial assistance.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

REFERENCES

1 Brandt LJ, Bjorkman D, Fennerty MB, Locke GR, Olden K, Peterson W, Quigley E, Schoenfeld P, Schuster M, Talley N. Systematic review on the management of irritable bowel syndrome in North America. *Am J Gastroenterol* 2002; **97(11 Suppl)**: S7-S26 [PMID: 12425586]

2 Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol* 2012; **10(7)**: 712-721 [PMID: 22426087 doi: 10.1016/j.cgh.2012.02.029]

3 Lovell RM, Ford AC. Effect of gender on prevalence of irritable bowel syndrome in the community: systemic review and meta-analysis. *Am J Gastroenterol* 2012; **107(7)**: 991-1000 [PMID: 22613905 doi: 10.1038/ajg.2012.131]

4 Longstreth GF. Definition and classification of irritable bowel syndrome: current consensus and controversies. *Gastroenterol Clin North Am* 2005; **34(2)**: 173-187 [PMID: 15862928]

5 Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterol* 2006; **130(5)**: 1480-1491 [PMID: 16678561]

6 Su AM, Shih W, Presson AP, Chang L. Characterization of symptoms in irritable bowel syndrome with mixed bowel habit pattern. *Neurogastroenterol Motil* 2014; **26(1)**: 36-45 [PMID: 23991913 doi: 10.1111/nmo.12220]

7 Everhart JE, Ruhl CE. Burden of digestive diseases in the United States, part II: lower gastrointestinal diseases. *Gastroenterol* 2009; **136(3)**: 741-754 [PMID: 19166855 doi: 10.1053/j.gastro.2009.01.015]

8 Pekmezaris R, Aversa L, Wolf-Klein G, Cedarbaum J, Reid-Durant M. The cost of chronic constipation. *J Am Med Dir Assoc* 2002; **3(4)**: 224-228 [PMID: 12807642]

9 Dennison C, Prasad M, Lloyd A, Bhattacharyya SK, Dhawan R, Coyne K. The health-related quality of life and economic burden of constipation. *Pharmacoeconomics* 2005; **23(5)**: 461-476 [PMID: 15896098]

10 Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. *Gastroenterol* 2002; **123**: 2108-2131 [PMID: 12454866]

11 Pimentel M, Mayer AG, Park S, Chow EJ, Hasan A, Kong Y. Methane Production During Lactulose Breath Test Is Associated with Gastrointestinal Disease Presentation. *Dig Dis Sci* 2003; **48**: 86-92 [PMID: 12645795]

12 Attaluri A, Jackson M, Valestin J, Rao SS. Methanogenic flora is associated with altered colonic transit but not stool characteristics in constipation without IBS. *Am J Gastroenterol* 2010; **105**: 1407-1411 [PMID: 19953090 doi: 10.1038/ajg.2009.655]

13 Jahng J, Jung IS, Choi EJ, Concklin JL, Park H. The effects of methane and hydrogen gases produced by enteric bacteria on ileal motility and colonic transit time. *Neurogastroenterol Motil* 2012; **24**: 185-190 [PMID: 22097886 e92. doi: 10.1111/j.1365-2982.2011.01819.x]

14 Pimentel M, Lin HC, Enayati P, van den Burg B, Lee HR, Chen JH, Park S, Kong Y, Conklin J. Methane, a gas produced by enteric bacteria, slows intestinal transit and augments small intestinal contractile activity. *Am J Physiol Gastrointest Liver Physiol* 2006; **290**: G1089-G1095 [PMID: 16293652]

15 Triantafyllou K, Chang C, Pimentel M. Methanogens, methane and gastrointestinal motility. *J Neurogastroenterol Motil* 2014; 20(1): 31-40 [PMID: 24466443 doi: 10.5056/jnm.2014.20.1.31]

16 Pimentel M, Chang C, Chua KS, Mirocha J, DiBaise J, Rao S, Amichai M. Antibiotic treatment of constipation-predominant irritable bowel syndrome. *Dig Dis Sci* 2014; **59(6)**: 1278-1285 [PMID: 24788320 doi: 10.1007/s10620-014-3157-8]

17 Moayyedi P, Quigley EM, Lacy BE, Lembo AJ, Saito YA, Schiller LR, Soffer EE, Spiegel BM, Ford AC. The effect of fiber supplementation on irritable bowel syndrome: a systemic review and meta-analysis. *Am J Gastroenterol* 2014; **109(9)**: 1367-1374 [PMID: 25070054 doi: 10.1038/ajg.2014.195]

18 Chapman RW, Stanghellini V, Geraint M, Halphen M. Randomized clinical trial: macrogol/PEG 3350 plus electrolytes for treatment of patients with constipation associated with irritable bowel syndrome. *Am J Gastroenterol* 2013; **108(9)**: 1508-1515 [PMID: 23835436 doi: 10.1038/ajg.2013.197]

19 Kamm MA, Mueller-Lissner S, Wald A, Richter E, Swallow R, Gessner U. Oral bisacodyl is effective and well-tolerated in patients with chronic constipation. *Clin Gastroenterol Hepatol* 2011; 9(7): 577-583 [PMID: 21440672 doi: 10.1016/j.cgh.2011.03.026]

20 Drossman DA, Chey WD, Johanson JF, Fass R, Scott C, Panas R, Ueno R. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome-results of two randomized, placebo-controlled studies. *Aliment Pharmacol Ther* 2009; **29(3)**: 329-341 [PMID: 19006537 doi: 10.1111/j.1365-2036.2008.03881.x]

21 Vidolock EJ, Cheng V, Cremonini F. Effects of linaclotide in patients with irritable bowel syndrome with constipation or chronic constipation: a meta-analysis. *Clin Gastroenterol Hepatol* 2013; **11(9)**: 1084-1092 [PMID: 23644388 doi: 10.1016/j.cgh.2013.04.032]

22 Ford AC, Moayyedi P, Lacy BE, Lembo AJ, Saito YA, Schiller LR, Soffer EE, Spiegel BM, Quigley EM; Task Force on the Management of Functional Bowel Disorders. Task force on the management of functional bowel disorders. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. *Am J Gastroenterol* 2014; **109(suppl 1)**: S2-S26 [PMID: 25091148 doi: 10.1038/ajg.2014.187]

23 Ford AC, Quigley EM, Lacy BE, Lembo AJ, Saito YA, Schiller

LR, Soffer EE, Spiegel BM, Moayyedi P. Effect of antidepressants and psychological therapies, including hypnotherapy, in irritable bowel syndrome: systemic review and meta-analysis. *Am J Gastroenterol* 2014; **109(9)**: 1350-1365 [PMID: 24935275 doi: 10.1038/ajg.2014.148]

24 Menees S, Maneerattanaporn M, Chey W. Efficacy of rifaximin in patients with irritable bowel syndrome: A meta-analysis. *Am J Gastroenterol* 2012; **107(5)**: 28-35 [PMID: 22045120 doi: 10.1038/ajg.2011.355]

25 Pimentel M, Lin HC, Enayati P, van den Burg B, Lee HR, Chen JH, Park S, Kong Y, Conklin J. Methane, a gas produced by enteric bacteria, slows intestinal transit and augments small intestinal contractile activity. *Am J Physiol Gastrointest Liver Physiol* 2006; **290**: G1089-G1095 [PMID: 16293652]

26 Magge S, Lembo A. Low-FODMAP Diet for Treatment of Irritable Bowel Syndrome. *Gastroenterol Hepatol (N Y)* 2012; **8(11)**: 739-745 [PMID: 24672410]

27 Nakayama T, Hashimoto T, Kajiya K, Kumazawa S. Affinity of polyphenols for lipid bilayers. *Biofactors* 2000; **13(1-4)**: 147-51 [PMID: 11237174]

28 Hook SE, Wright AD, McBride BW. Methanogens: Methane producers of the rumen mitigation strategies. *Archaea* 2010; 945785 [PMID: 21253540 doi: 10.1155/2010/945785]

29 Animut G, Puchala R, Goetsch A, Patra A, Sahlu T, Varel V, Wells J. Methane emission by goats consuming different sources of condensed tannins. *Anim Feed Sci Technol* 2008; **144**: 228-241

30 Puchala R, Animut G, Patra AK, Detweiler GD, Wells JE, Varel VH, Sahlu T. Effects of different fresh-cut forages and their hays on feed intake, digestibility, heat production, and ruminal methane emission by Boer × Spanish goats. *J Anim Sci* 2015; **90**: 2754-2762 [PMID: 22408087 doi: 10.2527/jas.2011-4879]

31 Fu F, Hou Y, Jiang W, Wang R, Liu K. Escin: Inhibiting inflammation and promoting gastrointestinal transit to attenuate formation of postoperative adhesions. *World J Surg* 2005; **29(12)**: 1614-1620 [PMID: 16311848]

32 Guo YQ, Liu JX, Lu Y, Zhu WY, Denman SE, McSweeney CS. Effect of tea saponin on methanogenesis, microbial community structure and expression of mcrA gene, in cultures of rumen micro-organisms. *Lett Appl Microbiol* 2008; **47(5)**: 421-426 [PMID: 19146532 doi: 10.1111/j.1472-765X.2008.02459.x]

33 Li W. Using Saponins to Reduce Gaseous Emissions from Steers*:* Doctor of Philosophy Dissertation, Michigan State University, Department of Animal Science, 2012

34 Mönnikes H. Quality of life in patients with irritable bowel syndrome. *J Clin Gastroenterol* 2011; **45**: S98-S101 [PMID: 21666428 doi: 10.1097/MCG.0b013e31821fbf44]

35 Ringel Y, Williams RE, Kalilani L, Cook SF. Prevalence, characteristics, and impact of bloating symptoms in patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2009; **7**: 68-72 [PMID: 19124113 doi: 10.1016/j.cgh.2008.07.008]

36 Allen HK, Levine UY, Looft T, Bandrick M, Casey TA. Treatment, promotion, commotion: Antibiotic alternatives in food-producing animals. *Trends Microbiol* 2013; **21(3)**: 114-119 [PMID: 23473629 doi: 10.1016/j.tim.2012.11.001]

37 Petschow BW, Blikslager AT, Weaver EM, Campbell JM, Polo J, Shaw AL, Burnett BP, Klein GL, Rhoads JM. Bovine immunoglobulin protein isolates for the nutritional management of enteropathy. *World J Gastroenterol* 2014; **20(33)**: 11713-11726 [PMID: 25206275 doi: 10.3748/wjg.v20.i33.11713]

38 Hristov AN, Oh J, Firkins JL, Dijkstra J, Kebreab E, Waghorn G, Makkar HP, Adesogan AT, Yang W, Lee C, Gerber PJ, Henderson B, Tricarico JM. Special topics--Mitigation of methane and nitrous oxide emissions from animal operations: I. A review of I. of enteric methane mitigation options. *J Anim Sci* 2013; **91(11)**: 5045-5069 [PMID: 24045497 doi: 10.2527/jas.2013-6583]

39 Cummings JH, Macfarlane GT. The control and consequences of bacterial fermentation in the human colon. *J Applied Bacteriol* 1991; **70(6)**: 443-459 [PMID: 1938669]

40 Pimentel M, Chow EJ, Lin HC. Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. *Am J Gastroenterol* 2000; **95**: 3503-3506 [PMID: 11151884]

41 Bertoldi D, Santato A, Paolini M, Barbero A, Camin F, Nicolini G, Larcher R. Botanical traceability of commercial tannins using the mineral profile and stable isotopes. *J Mass Spectrom* 2014; **49(9)**: 792-801 [PMID: 25230175 doi: 10.1002/jms.3457]

42 Tedeschi LO, Ramírez-Restrepo CA, Muir JP. Developing a conceptual model of possible benefits of condensed tannins for ruminant production. *Animal* 2014; **May 1**: 1-11. [PMID: 24784919]

43 Matsuda H, Li Y, Yoshikawa M. Effects of escins Ia, Ib, IIa, and IIb from horse chestnuts on gastrointestinal transit and ileus in mice. *Bioorg Med Chem* 1999; **7(8)**: 1737-1741 [PMID: 10482465]

44 Xie Q, Zong X, Ge B, Wang S, Ji J, Ye Y, Pan L. Pilot postoperative ileus study of escin in cancer patients after colorectal surgery. *World J Surg* 2009; **33(2)**: 348-354 [PMID: 19052813 doi: 10.1007/s00268-008-9816-1]

45 De Sousa AA, Soares PM, de Almeida AN, Maia AR, de Souza EP, Assreuy AM. Antispasmodic effect of Mentha piperita essential oil on tracheal smooth muscle of rats. *J Ethnopharmacol* 2010; **130(2)**: 433-436 [PMID: 20488237 doi: 10.1016/j.jep.2010.05.012]

46 Khanna R, MacDonald JK, Levesque BG. Peppermint oil for the treatment of irritable bowel syndrome: a systematic review and meta-analysis. *J Clin Gastroenterol* 2014; **48(6)**: 505-512 [PMID: 24100754 doi: 10.1097/MCG.0b013e3182a88357]

47 Sachdeva S, Rawat AK, Reddy RS, Puri AS. Small intestinal bacterial overgrowth (SIBO) in irritable bowel syndrome: frequency and predictors. *J Gastroenterol Hepatol* 2011; **26 (Suppl 3)**:135-138 [PMID: 21443727 doi: 10.1111/j.1440-1746.2011.06654.x]

Peer reviewers: Zhaoxiang Bian, School of Chinese Medicine, Hong Kong Baptist University, Kowloontong, Hong Kong, HKSAR, China; Guang-Yin Xu, MD, PhD, Professor, Institute of Neuroscience, Department of Neurobiology, Soochow University, 199 Renai Road, Suzhou 215123, China; Paolo Sossai, MD, AGAF, Chief Department of Medicine, General Hospital, Viale Comandino, 70, I - 61029 Urbino,Italy.