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CASE REPORT

Response of irritable bowel syndrome with constipation patients administered a combined quebracho/conker tree/ *M. balsamea Willd* extract

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Institutional review board statement: The study is exempt from IRB review and oversight pursuant to the terms of the United States Department of Health and Human Service's Policy for Protection of Human Research Subjects at 45 CFR and 46.101(b) since the data already exists in patient medical charts and this data was accumulated retrospectively. There was no experimentation on patients. The botanical extract was recommended to patients who chose to take the formulation.

Informed consent statement: All patients gave their verbal consent for publication of their anonymous medical chart data.

Conflict-of-interest statement: No potential conflicts of interest relevant to this article were reported.

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Abstract

The aim of this case series was to retrospectively examine the symptom response of irritable bowel syndrome with constipation (IBS-C) patients administered an herbal extract in a real-world setting. Twenty-four IBS-C patients in a community office practice were provided a combination over-the-counter dietary supplement composed of quebracho (150 mg), conker tree (470 mg) and *M. balsamea Willd* (0.2 mL) extracts (Atrantil™) and chose to take the formulation for a minimum of 2 wk in an attempt to manage their symptoms. Patient responses to the supplement were assessed by visual analogue scale (VAS) for abdominal pain, constipation and bloating at baseline and at 2 wk as part of standard-of-care. Patient scores from VAS assessments recorded in medical chart data were retrospectively compiled and assessed for the effects of the combined extract on symptoms. Sign tests were used to compare changes from baseline to 2 wk of taking the extract. Significance was defined as $P < 0.05$. Twenty-one of 24 patients (88%) responded to the dietary supplement as measured by individual improvements in VAS scores for abdominal pain, bloating and constipation symptoms comparing scores prior to administration of the extract against those reported after 2 wk. There were also significant improvements in individual as well as mean VAS scores after 2 wk of administration of the combined

extract compared to baseline for abdominal pain [8.0 (6.5, 9.0) *vs* 2.0 (1.0, 3.0), $P < 0.001$], bloating [8.0 (7.0, 9.0) *vs* 1.0 (1.0, 2.0), $P < 0.001$] and constipation [6.0 (3.0, 8.0) *vs* 2.0 (1.0, 3.0), $P < 0.001$], respectively. In addition, 21 of 24 patients expressed improved quality of life while taking the formulation. There were no reported side effects to administration of the dietary supplement in this practice population suggesting excellent tolerance of the formulation. This pilot retrospective analysis of symptom scores from patients before and after consuming a quebracho/conker tree/*M. balsamea Willd* extract may support the formulation's use in IBS-C.

Key words: Irritable bowel syndrome; Constipation; Abdominal pain; Bloating; Dietary supplement; Herbal; Botanical; Extract; Peppermint

Core tip: Irritable bowel syndrome with constipation (IBS-C) is a diagnosis by exclusion which is defined by abdominal pain accompanied by reduced stool frequency and painful, hard bowel movements. Gas and bloating may also be present in many patients with this condition suggesting a role in fermentation of food producing gas by bacteria in the gut. Safe tannin byproducts from wineries used in cows to reduce gas that can impair milk and meat production are combined with saponins, shown to be antibacterial and promote intestinal motility, and peppermint oil for abdominal pain in this combination extract (Atrantil™) to manage key IBS-C symptoms.

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INTRODUCTION

One third of diagnosed irritable bowel syndrome (IBS) in the United States is constipation predominant and includes symptoms of abdominal pain, bloating, and constipation[1]. Women experience IBS symptoms about twice as frequently as men[2]. Irritable bowel syndrome with constipation (IBS-C) has a huge impact on quality of life and productivity especially in women[3] with one investigator suggesting that IBS patients have worse health-related quality of life compared to patients with diabetes and end-stage renal disease[4]. The symptom-driven quality of life altering condition can be due to the production of gas (hydrogen, methane) which causes bloating and contributes to alterations in motility in IBS-C patients. Gas production has been linked to the presence of methanogenic archaebacteria[5,6]. Methane production has been found to be associated with delayed transit time[7,8]. Individuals diagnosed with small intestinal bacterial overgrowth (SIBO) also produce more hydrogen and methane which can lead to abdominal pain and constipation[9]. Fiber supplements[10] and probiotics[11] as well as drugs like rifaximin, neomycin[12], laxatives[13,14], lubiprostone[15], and linaclotide[16] all have variable effects in patients with IBS-C. There is still a need for safe agents to support GI health in patients with IBS-C.

Atrantil™, a dietary supplement composed of Quebracho, Conker Tree and *M. balsamea Willd* extracts, has been shown against placebo to statistically improve constipation and bloating in IBS-C subjects[17]. Quebracho extract contains tannins which are large delocalized flavonoid structures that have been used safely in wine for decades[18]. Tannins potentially have dual function[19]: They act as molecular "sponges" for excess hydrogen and methane[20] as well as disrupt and destroy bacterial lipid bilayers. Conker tree extract contains escins, also known as saponins. Saponins act as an antimicrobial agents, promote intestinal motility[21] and directly reduce methane production/emission[22,23]. *M. balsamea Willd* extract contains peppermint oil which has been shown to reduce abdominal pain and discomfort[11].

Patients from a single, community physician practice, who had failed to respond to conventional therapy, chose to take a recommended over-the-counter dietary supplement composed of quebracho, conker tree and *M. balsamea Willd* extracts in attempt to manage symptoms of abdominal pain, bloating and constipation associated with IBS-C. Their medical chart responses were retrospectively analyzed for improvement in symptomology.

CASE REPORT

Patient charts were retrospectively examined from a single physician's practice in this case report of 24 IBS-C patients who took the dietary supplement, Atrantil™ [quebracho (150 mg), conker tree (470 mg) and *M. balsamea Willd* (0.2 mL) extracts], after experiencing incomplete management of symptoms with other therapies. The quebracho extract has a 80%-82% polyphenol content with 72%-74% soluble tannins, primarily consisting by of profisetinidin subunits as part of trimeric, tetrameric and pentameric condensed tannins (about 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).

No IRB review or oversight was required in this analysis according to the terms of the United States Department of Health and Human Service's Policy for Protection of Human Research Subjects at 45 CFR and 46.101(b) since the data already existed in patient medical charts and this data was accumulated retrospectively. There was

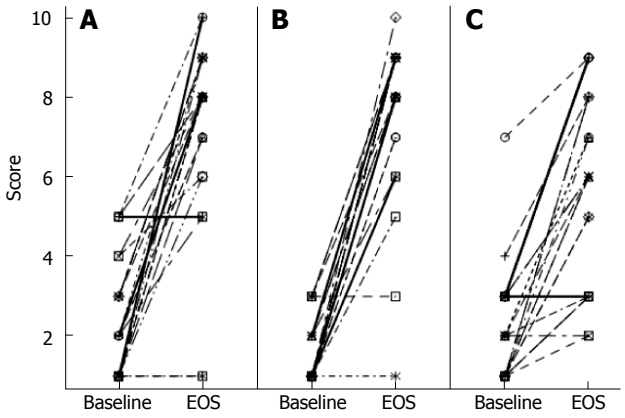

Figure 1 Visual Analogue Scores (0 = worst symptoms, 10 = no symptoms) were taken prior to administration of the dietary supplement (baseline) and at 2 wk end of analysis (end of analysis) for abdominal pain (A), bloating (B), and constipation (C). Each symbol represents a different, individual patient in the analysis.

no experimentation on patients. The dietary supplement was recommended to patients who chose to take the formulation after failing to respond to other treatments. The patients in this analysis were diagnosis with IBS-C for at least 6 mo prior to enrollment into the study (according to Rome Ⅲ criteria) and had a history of uncontrolled symptoms of abdominal pain, bloating and constipation. Patients were previously on the FODMAP diet, probiotics and/or traditional drug treatments. The combined extract was administered for two weeks. Patient response to the combined extract was assessed by visual analogue scale (VAS) at baseline (before administration) and after 2 wk [End of Analysis (EOA)] for abdominal pain, bloating, and constipation as part of standard-of-care. The median and the 25th and 75th percentiles, the interquartile range (IQR), were used to summarize the scores. Sign tests, which make no assumptions about the shape of the distribution, were used to compare changes over time. Significance was defined as $P < 0.05$. Changes in therapy for rescue due to increased symptoms and side effects were also noted. All patients consented to have their data published.

The patients in this retrospective chart analysis (n = 24) ranged in age from 18 to 58. The population consisted of 2 men and 22 women with a racial composition of 21 Caucasian, 2 Hispanic or Latino, as well as 1 African American. There were also various co-morbidities of gastroesophageal reflux disease, rosacea, hypertension and fatigue, which did not contribute to their gastrointestinal condition. Patients were not taking any other therapies for IBS-C or SIBO when they were first administered the combined extract. By EOA, 21 out of 24 patients had responded with improved VAS scores for abdominal pain (Figure 1A), bloating (Figure 1B), and constipation (Figure 1C).

Overall, 88% of this gastroenterology practice population which had incomplete relief with traditional therapies responded to the combined herbal extract in the dietary supplement. A comparison of mean VAS scores for abdominal pain, bloating and constipation from baseline and EOA showed a significant improvement in all three symptoms over time for the entire population while on the combined extract (Table 1).

Table 1 Symptom response of irritable bowel syndrome with constipation patient population to combined herbal extract

Symptom	Baseline median (IQR)	EOA median (IQR)	EOA-baseline median (IQR)	*P* value
Abdominal pain	2.0 (1.0, 3.0)	8.0 (6.5, 9.0)	5.5 (3.5, 7.0)	< 0.001
Bloating	1.0 (1.0, 2.0)	8.0 (7.0, 9.0)	6.5 (5.5, 8.0)	< 0.001
Constipation	2.0 (1.0, 3.0)	6.0 (3.0, 8.0)	4.0 (2.0, 5.5)	< 0.001

EOA: End of Analysis (2 wk); IQR: Interquartile range (25%, 75%).

A response rate of 88% in IBS-C patients with a significant reduction in abdominal pain, bloating, and constipation suggests very good efficacy in this difficult to treat population. No rescue medication was needed during the 2 wk course of the observation and there were no reported adverse events suggesting excellent tolerance of the herbal extract.

DISCUSSION

Over 90% of IBS patients suffer from bloating which is directly linked to abdominal pain and distention[24]. These symptoms may be caused by SIBO or dysbiosis. No matter the cause, current therapeutics may not meet the needs of all patients. In a 10 wk study of rifaximin (550 mg TID) *vs* placebo in IBS patients, for example, the overall response rate was 40.8% *vs* 31.2% for placebo (P = 0.01)[25]. Using a similar retrospective medical chart analysis to the one utilized in this study, Yang *et al*[26] found a 69% response rate to rifaximin and 44% to neomycin in 98 lactulose breath test positive IBS patients. Another study found that patients who had an abnormal lactulose breath test with follow up testing (n = 47) when treated with neomycin had a 75% response rate[9]. Even with the success of antibiotic treatment, relapse remains a significant problem in SIBO patients[27].

Other agents are also used for constipated patients. In an open-label extension study of lubiprostone (n = 522), a locally acting chloride channel activator, demonstrated a response rate of about 40%, but about 32% of participants in the extension part of the study required a rescue medication[28]. Adverse effects for lubiprostone include dose-related nausea and dyspnea with chest tightness. For idiopathic constipation, lanaclotide demonstrated about 50% response rate for pain and increase in stool frequency compared to placebo responses of about 35% and about 25%, respectively[29,30]. About 20% of patients on linaclotide experienced diarrhea compared to about 3% in the placebo groups.

Nutritional approaches to IBS-C and SIBO include dietary fiber, the FODMAP (Fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet

and probiotics. Fiber can be effective in managing constipation, but bloating, distension, flatulence and cramping may limit the use of insoluble fiber. Water intake with fiber is very important. In patients with IBS, soluble fiber, such as psyllium may be effective, but insoluble fiber can exacerbate symptoms[10,31]. The FODMAP diet has been found to decrease abdominal pain and bloating, but adherence to the diet can be difficult[32]. Probiotics containing *Bifidobacterium lactis* DN-173 010, *Lactobacillus casei* Shirota, and *Escherichia coli* Nissle 1917 demonstrate favorable data on defecation frequency and stool consistency[33]. Other approaches are still needed for patients with IBS-C and SIBO.

In a 2 wk randomized, double-blind placebo-controlled study of patients previously diagnosed with IBS-C (n = 16), there were significant improvements in the average constipation (P = 0.0034), bloating (P < 0.001) and constipation plus bloating scores (P < 0.001) in the Atrantil™ group compared to no improvement for the placebo arm[17]. There were also no reports of AEs over the 2 wk period. In this retrospective chart analysis of 24 patients administered Atrantil™, there was a 3.2-fold average improvement in abdominal pain, a 5.1-fold improvement in bloating, and a 2.7-fold improvement in constipation. Twenty-one of 24 patients responded to therapy for an overall response rate of 88%. There were also no reported side effects to therapy. These consistent data suggest that the combined herbal extracts of quebracho, conker tree and *M. balsamea Willd* present in Atrantil™ decreases symptoms associated with IBS-C.

The quebracho extract consists primarily of tannins, the same used in for over 50 years to change the taste and texture of wine[18]. Tannins are highly delocalized structures which are able to act as antiradical sinks or antioxidants[34]. Tannins also directly limit methanogenesis by inhibiting the growth of methane producing bacteria by reducing the availability of hydrogen[35]. Conker Tree extract contains the antimicrobial saponins[21] which can also reduce the production as well as emission of methane presumably by limiting hydrogen availability[22,23]. Saponins have also been found to improve intestinal motility in mice[36] and improve passage of gas, GI sounds and bowel movements in postoperative colorectal surgery patients[37]. The *M. balsamea Willd* extract contains peppermint oil which has been found to help reduce abdominal pain[11]. Peppermint oil has also been shown to act as an antispasmodic attenuating contractile responses to acetylcholine, histamine, 5-hydroxytryptamine, and substance P[38,39]. The combination of these extracts in Atrantil™ may have limited the availability of hydrogen by preventing growth of microorganisms which produce methane that contributes to abdominal pain, bloating and constipationin this IBS-C patient population. In addition, the combination extracts may also improve motility and intestinal transit time.

Though this pilot medical chart analysis was performed in a relatively small number of patients (n = 24) with IBS-C, the response rate was very high (88%). The small number of patients, the fact that they were drawn from a single site and the uncontrolled nature of the analysis with only therapy adherent individuals being evaluated are limitations for this study. Still, the statistical improvement in symptoms of abdominal pain, bloating and constipation found in this retrospective study are consistent with a previous placebo-controlled clinical trial[17]. Therefore, the results of this small open-label study of Atrantil™ may be a useful intervention for patients with IBS-C and SIBO. Further, larger double-blind, placebo-controlled studies are needed to confirm these results.

COMMENTS

Case characteristics

The primary symptoms experienced by this clinical practice cohort of patients were abdominal pain, bloating and constipation.

Clinical diagnosis

Significant improvements in abdominal pain, bloating and constipation were found after a 2 wk administration of the mixed quebracho/conker Tree/*M. balsamea Willd* extracts in Atrantil™ in irritable bowel syndrome with constipation (IBS-C) patients.

Differential diagnosis

Organic causes of constipation were excluded first for all patients in this practice cohort which were then diagnosed with IBS-C according to Rome III criteria for functional constipation including at least two of the following: (1) two or fewer defecations in the toilet per week; (2) At least one episode of fecal incontinence per week; (3) History of retentive posturing or excessive volitional stool retention; (4) History of painful or hard bowel movements; (5) Presence of a large fecal mass in the rectum; and (6) History of large diameter stools which may obstruct the toilet.

Laboratory diagnosis

Since there is no tissue or blood marker for IBS-C, no laboratory testing was performed in this case series.

Treatment

Twenty-four IBS-C patients in a single clinical practice were provided a combination over-the-counter dietary supplement composed of quebracho (150 mg), conker tree (470 mg) and *M. balsamea Willd* (0.2 mL) extracts (Atrantil™) and chose to take the formulation for a minimum of 2 wk in an attempt to manage abdominal pain, bloating and constipation.

Related reports

This case series is a follow up to a well-controlled pilot clinical study in IBS-C patients (Brown *et al*, 2015) testing the same dietary supplement in IBS-C patients composed of quebracho (150 mg), conker tree (470 mg) and *M. balsamea Willd* (0.2 mL) extracts (Atrantil™).

Term explanation

All terms in this case series are standard and used in the field of gastroenterology.

Experiences and lessons

This case series shows the utility of a dietary supplement in drug refractory IBS-C patients formulated to act as a molecular sink for gas ions in the intestine, a bacteriostatic agent to inhibit the impact of bacteria in the small bowel and a component to aid in abdominal discomfort.

Peer-review

The limitations of this case series were that it was in a relatively small cohort of patients biased for compliance in consuming the therapeutic agent in an uncontrolled setting. This case series in combination with the previously

published pilot clinical trial suggests promise for Atrantil™ in IBS-C patients with the caveat that a larger, well-controlled study is needed.

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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

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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.

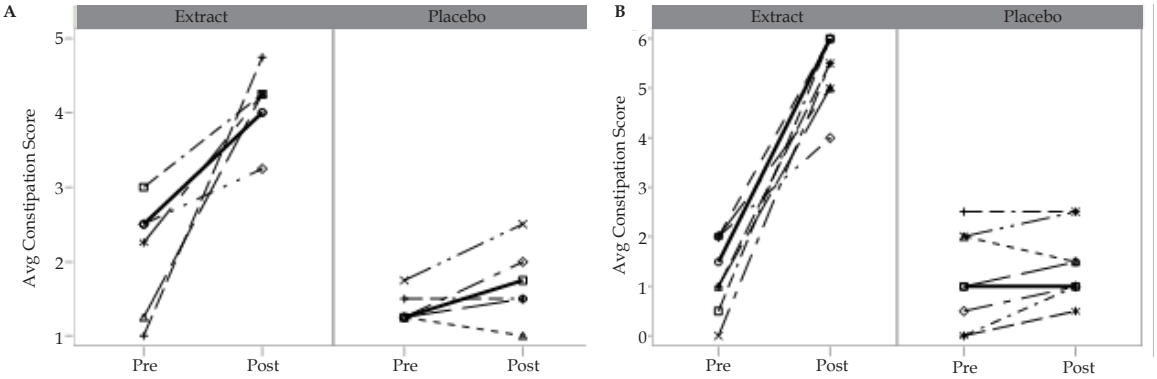

Figure 1: Percent Improvement in Constipation (A) and Bloating (B) Before and After Extract Administration Compared to Placebo.

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.

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