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ORIGINAL ARTICLE

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Effect of Iberogast (STW5) on tolerance to colonic gas in patients with irritable bowel syndrome: A randomized, double-blind, placebo control clinical trial

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Abstract

Background: STW5 is an herbal medicinal product that, in previous studies, reduced abdominal pain in irritable bowel syndrome (IBS). The effect of STW5 on gas-related abdominal symptoms is unknown.

Aim: To determine the effects of STW5, compared to placebo, on the responses to colonic gas in IBS.

Methods: Using a cross-over design, two gas challenge tests were performed in 10 patients with IBS and bloating after 2-weeks treatment with (a) STW5 and (b) placebo. The challenge test consisted in continuous infusion of gas into the colon (24 mL/min for 60 min), followed by a 30-min free evacuation period. Gas evacuation, symptom perception, and abdominal distension were continuously registered.

Results: Colonic gas filling was associated to a significant rise in abdominal symptom perception, that was significantly greater when patients were on-placebo (score increment 4.0 ± 0.3) compared with on-STW5 (score increment 3.2 ± 0.4; $p = 0.035$). Gas filling was associated to a progressive abdominal distension that was similar with both treatments. Opening of the rectal cannula produced a massive gas evacuation, similar after both treatments, associated to a return of abdominal perception and distension to basal levels when patients were on-STW5 (score increment −0.1 ± 0.4; distension 0.3 ± 0.2 cm; $p = 0.399$, and $p = 0.112$ vs. basal), whereas both remained increased on-placebo (score increment 0.5 ± 0.3; distension 0.8 ± 0.3 cm; $p = 0.048$, and $p = 0.016$ vs. infusion start).

Conclusions: STW5 improves colonic gas tolerance in IBS patients with bloating without a significant effect on gas retention and evacuation. This medicinal product can be beneficious for treatment of gas-related abdominal symptoms in patients with bloating. EudraCT: 2019-003976-38.

KEYWORDS
abdominal distension, bloating, colonic gas, irritable bowel syndrome, STW-5

Abbreviations: DGBI, disorders of gut-brain interaction; IBS, irritable bowel syndrome.

1 | INTRODUCTION

Patients with disorders of gut-brain interaction (DGBI) have gastrointestinal symptoms related to a combination of disturbances including gastrointestinal motility, sensitivity, mucosal, and immune function, gut microbiota and the processing of stimuli at the central nervous system.[1] STW5 is an herbal medicinal product composed of nine different medicinal plant extracts, namely candy tuft (*Iberis amara*), extracts of lemon balm leaf (*Melissa officinalis*), chamomile flower (*Matricaria chamomilla*), caraway fruit (*Carum carvi*); peppermint leaf (*Mentha x piperita*), liquorice root (*Glycyrrhiza glabra*), Angelica root (*Angelica archangelica*), milk thistle fruit (*Silybum marianum*) and greater celandine herb (*Chelidonium majus*). In different controlled clinical trials STW5 has demonstrated a beneficial effect for management of DBGI like functional dyspepsia or IBS.[2–6] As a combination of different herbs extracts, its mechanism of action is the result of the interaction of the nine extracts and more than 350 secondary compounds of the plant extracts.[7] Different studies have shown that STW5 modifies gastric, intestinal, and colonic motility[8–10] and has effects on visceral hypersensitivity,[11] inflammation,[12,13] mucosal barrier, and permeability[14] as well as on intestinal microbiota,[15] suggesting that STW5 has a multitarget mechanism of action that can be suited to counteract different disturbances related to symptom development in patients with DGBI.[7]

One of the most common symptoms of patients with DGBI is the sensation of bloating.[16] Different studies have shown that patients with IBS have a poor tolerance to intestinal gas that may be related to a combination of impaired transit and evacuation of gas, visceral hypersensitivity, and altered viscero-visceral and viscero-somatic responses.[17–22] However, the effect of STW5 on transit and tolerance to intestinal gas in patients with DGBI has never been studied.

The primary objective of the study was to determine the effect of STW5 on clearance of colonic gas in subjects with irritable bowel syndrome (IBS), measured as mL of gas recovered by a rectal cannula. The secondary objectives were: (a) to determine the effect of STW5, compared to placebo, on subjective perception of abdominal symptoms (measured by a graded symptom scale) in response to colonic gas infusion in subjects with IBS; (b) To determine the effect of STW5, compared to placebo, on objective abdominal distension (measured in mm by a tape-measure) in response to colonic gas infusion in subjects with IBS; (c) To determine the adverse events that occur during the study. Using a previously developed and validated method of intestinal gas challenge,[18,23,24] we developed a randomized, double-blinded, cross-over study comparing, on separate days, the responses to a gas challenge performed after 14-days on-STW5 (20 drops t.i.d.) or after 14 days on-placebo.

Key points

- STW5 is an herbal medicinal product that has demonstrated a beneficial effect for management of irritable bowel syndrome. The effects of STW5 on intestinal gas, and gas related abdominal symptoms like bloating have not been previously investigated.
- Using a double blind, cross-over, placebo controlled study design, STW-5 reduced abdominal symptoms induced by colonic gas filling in patients with IBS, and improved the recovery of symptoms and objective abdominal distension following colonic gas emptying.
- The previously demonstrated positive effects of this herbal preparation on abdominal symptoms in patients with IBS, could be related to an improved tolerance to colonic gas contents, by reducing sensitivity to colonic loads.

2 | MATERIALS AND METHODS

2.1 | Participants

Twelve patients with IBS (nine women and three men; age range 22–61 years) according to Rome IV criteria were included in the study. Patients were recruited consecutively from the out-patient clinics of University Hospitals Vall d'Hebron and Germans Trias i Pujol. The diagnosis of IBS was made using the Rome questionnaires. According to Rome criteria, nine patients had diarrhea predominant IBS (IBS-D), one patient constipation predominant IBS (IBS-C) and two patients a mixed IBS (IBS-M). The protocol for the study had been previously approved by the Spanish Agency of Medicines (Agencia Española de Medicamentos y productos sanitarios) and the Ethics Committee of the University Hospital Germans Trias i Pujol and University Hospital Vall d'Hebrón. CONSORT reporting guidelines had been used.[25] All patients gave written informed consent before participating in the study. All authors had access to the study data and reviewed and approved the final manuscript. The register of the study is: EudraCT: 2019–003976-38. In the present manuscript the part one of the study (IBO-1): IBS patients treated with STW5, is presented.

2.2 | Gas challenge test

The gas challenge was divided in two periods: (a) Filling period and (b) evacuation period. The filling period consisted in a continuous gas infusion at 24 mL/min during 60 min (1440 mL final volume) via a balloon-catheter (Foley catheter 20 F; Bard, Barcelona, Spain) introduced into the rectum and hermetically connected to a volumetric pump (GIP-3000 Infusion Pump, Solfer Solutions SL, Barcelona, Spain). To prevent rectal gas leaks, the intrarectal balloon was inflated with 5 mL water. After 60 min the gas infusion was stopped, and the rectal cannula was connected to an electronic barostat to quantify the volume of gas evacuated during the following 30 min (evacuation period). The gas mixture infused (88% nitrogen, 6.5% carbon dioxide, and 5.5% oxygen) mimicked the partial pressures of venous blood gases to minimize diffusion

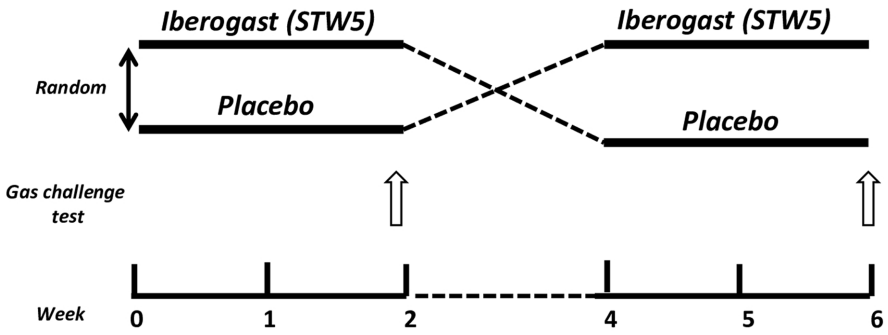

FIGURE 1 Experimental design. In each participant two gas challenge test were performed after a 2-week intervention period with the patient on placebo or Iberogast (STW5) 20 drops t.i.d. using a two-period, cross-over, randomized, double-blind study design.

across the intestinal-blood barrier. These methodology has been widely used and validated in detail in previous studies.[21,23,26]

2.3 | Perception measurements

Conscious perception was measured at 10-min intervals by means of four graphic rating scales, each graded from zero (no perception) to six (painful sensation), specifically for scoring four possible types of abdominal sensations: (a) pressure/bloating, (b) cramp/rumbling sensation, (c) puncture/stinging sensation, and (d) other type of sensation (to be specified), respectively. The questionnaire included an additional tic box (YES/NO) to signal belching. The location of the perceived sensations was marked on an abdominal diagram divided into nine regions corresponding to epigastrium, periumbilical area, hypogastrium, both hypochondria, flanks, and iliac fossae. Participants were instructed to report the sensations perceived over the preceding 10-min period in the scales. This methodology has been widely used and validated in previous studies.[17–23]

2.4 | Measurements of abdominal distension

Once the subjects were positioned in bed a non-stretch metric tape measure was adjusted around the abdomen over the umbilicus by means of two elastic bands. Girth measurements were taken at 10-min intervals, while the subjects were breathing relaxedly, as the average of inspiratory and expiratory determinations over three consecutive respiratory excursions.[23]

2.5 | Procedure

After the 2-week period on treatment with STW5 or placebo (see below), the day of the study patients came to the Motility Unit after 8-h fasting. Participants were instructed to follow a low-flatulogenic diet during the 2 days prior to each study day. The night before the study they had a light dinner that could consist of meat, fish, eggs, rice, pasta and/or white bread, but avoiding particularly dairy products, salad, fruit, and alcoholic beverages. If the patient did not pass stools 8 h before the study, a bowel movement was induced by administration of a rectal enema with 250 mL of saline (Fisioenema®, Casen Recordati. Utebo [Zaragoza], Spain).

With the patients lying in right lateral position the rectal cannula was introduced into the rectum, and the balloon was filled with 5 mL of water. Thereafter the patients were placed supine in bed at an angle of 30° to the horizontal, and the belt for measurement of abdominal distension (see above) was positioned and adjusted. The rectal tube was connected to the infusion system, and gas infusion started.

2.6 | Experimental design

A cross-over, randomized, double-blind study was designed to determine the effect of Iberogast (STW5) on colonic gas tolerance (Figure 1). Eligible patients were randomized on a 1:1 basis to receive either Iberogast or identical appearing placebo, according to centralized automated randomization. The trial was double-blind; neither the patient nor research team or treating staff knew the allocation. This was achieved by identical packaging, labeling, and organoleptic properties (liquid presentation, dark brown color, taste, and smell) of both the bottled Iberogast and matched placebo. Each bottle of Iberogast or placebo was identified by a kit code. Randomization lists containing kit allocation were generated by the supply company who produced the kit (Bayer Laboratories). Code break envelopes were also produced by the supply company. Access to the code break envelopes was restricted to designated safety team.

In each participant, two gas challenge test were performed after a 2-week intervention period with the patient on placebo or on Iberogast (STW5) 20 drops t.i.d. After 2-weeks on the allocated treatment, a gas challenge test was performed at the motility lab. Thereafter, a 2 weeks interval with no intervention was started, and followed by a new 2-weeks treatment period and a final gas challenge test (Figure 1). The gas challenge tests were performed with the investigator and patients blind for the assigned intervention. Adverse events were assessed after each 2-weeks treatment period before the start of the corresponding gas infusion test.

2.7 | Data analysis

In each subject, during each gas challenge test, we calculated the volume of gas retained within the gut as the difference between the volume of gas infused and the volume of gas recovered. Perception of abdominal sensations experienced by participants during the studies was measured by the score rated in the scales at each time

interval. When more than one sensation was referred at the same time interval, the highest score reported (the most severe sensation independently of the type) was computed for comparisons. In each subject we also counted the number of times each abdominal sensation was scored to calculate the frequency (as percent distribution) of each specific sensation.

Changes in abdominal girth during the study were referenced to girth measurement at the start of the study, before gas infusion was started.

2.8 | Statistical analysis

In previous studies using the same methodology of colonic gas infusion,[21–23] patients retained 506 mL of gas into the colon at the end of the collection period with a standard deviation of 276 mL, whereas healthy subjects retained 174 ± 163 mL. Due to the lack of previous studies on the effect of Iberogast on gas transit, we considered that a reduction of 50% of the volume of gas retained should be clinically relevant for our purposes. According to this forecast, nine subjects per group should complete the study to discriminate differences in gas retention with a power of 80% and an alpha error of 5%.

In each treatment period, mean values (±SE) of the parameters measured at 10-min intervals were calculated. The Kolmogorov–Smirnov test was used to check the normality of data distribution. Comparisons of parametric, normally distributed data were performed by the Student's *t*-test for paired data. Non-parametric data were compared using the Wilcoxon signed-rank test.

3 | RESULTS

3.1 | General aspects

Twelve IBS patients were included in the study from September 2020 to March 2022. Ten subjects completed the 4-week intervention period uneventfully. The reasons for withdrawal of the remaining two patients were patient decision in one case and laboratory test abnormalities in the screening lab test in the other (Figure S1).

Two patients reported adverse events during Iberogast intake. One patient reported respiratory infection treated with acetylcysteine and other patient reported back pain treated with conventional analgesia. Both adverse events were not related to study medication, spontaneously overcome and the protocol of the study could be completed in both cases without changes. No adverse events were reported during placebo intake.

3.2 | Effect of Iberogast (STW5) on gas transit during the gas challenge test

After the 60-min infusion period, opening of the rectal cannula was followed by a massive rectal evacuation of gas in all subjects, both when the gas infusion study was performed on-STW5 and on-placebo. Hence, 10-min after opening of the rectal cannula 834 ± 69 mL of gas had been expelled when the study was performed on-STW5, and 793 ± 95 mL when patients were on-placebo. This greater volume expelled on-STW5 was not significantly different than the volume expelled on-placebo ($p = 0.353$). Gas evacuation continued during the next 20-min of the free evacuation period, and by the end of the evacuation period, the final volume of gas retained was 359 ± 70 mL and 408 ± 99 mL, STW5 and placebo, respectively; $p = 0.309$ (Figure 2A).

3.3 | Effect of Iberogast (STW5) on abdominal symptoms during the gas challenge test

During the 60-min infusion period, subjective abdominal perception of symptoms increased progressively in parallel with colonic gas filling (Figure 2B). However, the increment in abdominal perception was significantly lower when patients were studied on-STW5 compared to placebo. Hence, by the end of the infusion period, when the colon had been filled with 1440 mL of gas, perception score increment was 3.2 ± 0.4 when infusion was performed on-STW5, and 4.0 ± 0.3 when infusion has been performed on-placebo ($p = 0.035$).

Evacuation of the infused colonic gas after opening of the rectal cannula during the evacuation period was associated to an immediate and progressive reduction in abdominal perception in both groups. However, at the end of the evacuation period, even though the differences between groups faded ($p = 0.083$ Iberogast vs. placebo), perception had returned to basal levels after 30-min gas evacuation when patients were on-STW5 (score increment −0.1 ± 0.4; $p = 0.399$ vs. infusion start), but remained significantly increased when the studies were performed on-placebo (score increment 0.5 ± 0.3; $p = 0.048$ vs. infusion start).

The type of abdominal perception referred by participants was predominantly abdominal bloating/fullness sensation, in >90% of times, either alone or associated to cramp/colicky sensation or stinging sensation, without differences whether the infusion was performed on-STW5 or on-placebo (Figure 3). Most of the symptoms were referred to the lower part of the abdomen, predominantly hypogastrium and both iliac fossae (Figure 4). When the study was performed with STW5 the location of symptoms encompassed more than one abdominal area more frequently (68 ± 8% of times) than when performed on placebo (55 ± 12% of times), but without significant differences whether the infusion was performed on-STW5 or on-placebo ($p = 0.328$).

3.4 | Effect of Iberogast (STW5) on objective abdominal distension during the gas challenge test

Alike abdominal perception, colonic gas filling during the 60-min infusion period was associated to a progressive increment in abdominal girth, that reached the maximal distension at the end of the

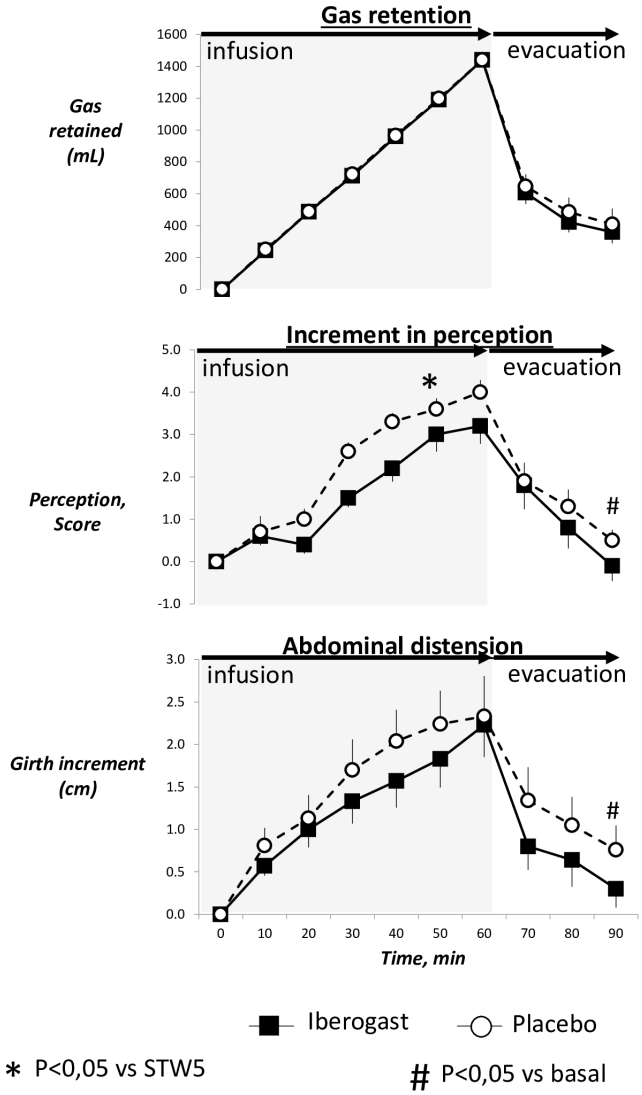

FIGURE 2 Effect of colonic gas filling on gas retention, perception, and abdominal distension. Gas infusion was associated to a progressive increment in abdominal perception that was significantly lower when the patients were on STW5 compared to placebo. Colonic gas evacuation was followed by a regression of perception and abdominal distension, that was complete (return to basal levels) when the study was performed on-STW5.

infusion period, without significant differences whether gas infusion was performed on-STW5 or on-placebo (Figure 2C). Hence, by the end of the infusion period, when the colon had been filled with 1440 mL of gas, girth increment was 2.2 ± 0.4 cm when infusion was performed on-STW5, and 2.3 ± 0.5 cm when infusion has been performed on-placebo ($p = 0.438$).

Evacuation of the infused colonic gas after opening of the rectal cannula during the evacuation period was associated to an immediate and progressive reduction in abdominal distension, that had returned to basal levels after 30-min gas evacuation when patients were on-STW5 (girth increment 0.3 ± 0.2 cm; $p = 0.112$ vs. infusion start), but remained significantly increased when the studies were performed on-placebo (girth increment 0.8 ± 0.3; $p = 0.016$ vs. infusion start).

4 | DISCUSSION

In the present study, the effect of STW5 on the responses to a colonic gas load in patients with IBS complaining of bloating, was compared to placebo by means of a double blinded, cross-over, placebo controlled clinical trial. We found that STW-5 had a positive effect on abdominal symptoms by reducing the intensity of subjective symptoms elicited by colonic gas, and improving the recovery of the objective abdominal distension elicited by colonic gas, without a significant effect on gas retention and gas evacuation.

Irritable bowel syndrome is a disorder of gut-brain interaction (DGBI) characterized by abdominal pain associated to altered defecation.[27] One of the most common and most bothersome symptoms referred by IBS patients is abdominal bloating.[19,28] The mechanism of production of bloating in IBS is not completely understood, but several alterations that are common in patients with DGBI could contribute to development of bloating. These include visceral hypersensitivity,[22] altered gas transit and evacuation,[17,18,23,29-31] increased fermentation of carbohydrates,[32,33] intestinal dysbiosis,[34] bacterial overgrowth,[35] and altered viscero-visceral and viscero-somatic reflex responses.[18,20,22]

STW5 is an herbal preparation that has been shown to reduce overall abdominal symptoms in IBS.[4] Previous studies using different experimental models have shown that STW5 can modulate motility, hypersensitivity, inflammation, and gut permeability.[4,8,10,12–14] Hence, the multi-target action of STW5 could theoretically be beneficial for patients with IBS by acting at different mechanistic targets simultaneously.[7]

In our study, we found that STW5 improved the tolerance to colonic gas, by reducing the intensity of the perception induced by filling of the colon with a fixed gas load. Previous studies using a similar methodology as we used in the present study, have shown that patients with IBS develop greater abdominal perception of symptoms in response to colonic gas filling than healthy subjects.[23,24] An effect that is probably related to the hypersensitivity that has been largely described in IBS.[36,37] Several studies have shown that STW5 reduces visceral sensitivity. Studies with animal models have shown that STW5 reduces intestinal afferent sensitivity reducing nerve discharge following chemical and mechanical stimuli.[11,38] Further in vitro studies have shown binding of STW5 to different receptors involved in pain transmission, like serotonin, muscarinic, and opioid receptors.[39] These experimental findings can be the rational for the findings in clinical trials showing a reduction of abdominal pain in IBS patients after treatment with STW5.[4]

In addition to the effects on visceral sensitivity, in different studies STW5 has been shown to modulate gastrointestinal motility by region-specific effects at different levels of the gastrointestinal tract. These includes relaxation of the gastric fundus,[8] increased contractile activity of the antrum,[40] and decrease muscle activity of the ileum in experimental animals, an effect that was similar to that obtained by the antispasmodic papaverine.[10,41] In a proof of concept study with gas infusion in healthy subjects, we found that abolition of intestinal motility with iv glucagon simulating the effect of a

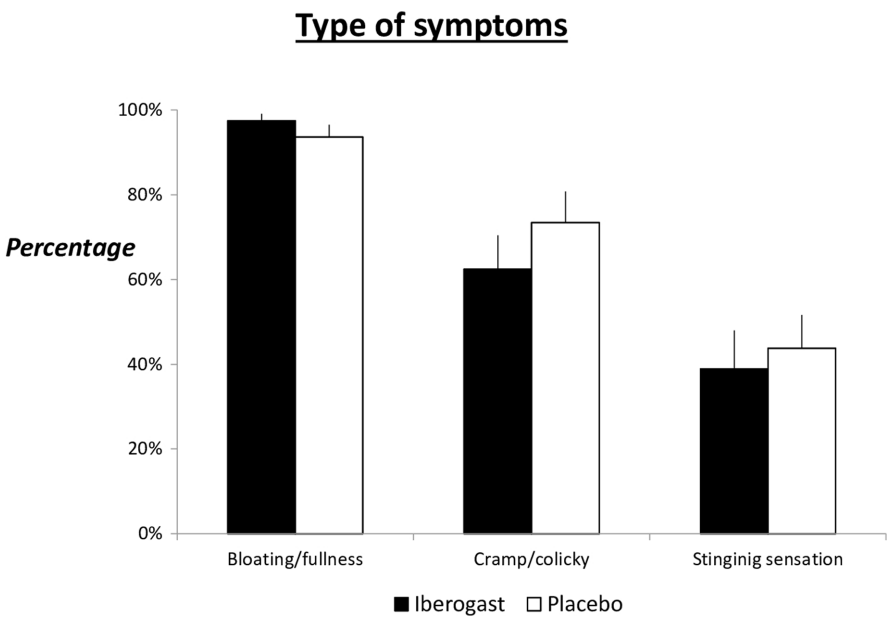

FIGURE 3 Type of abdominal symptoms elicited by colonic gas filling. Gas filling induced similar symptoms when patients were treated with STW5 and placebo, mainly sensation of bloating/fullness and cramp/colicky sensation.

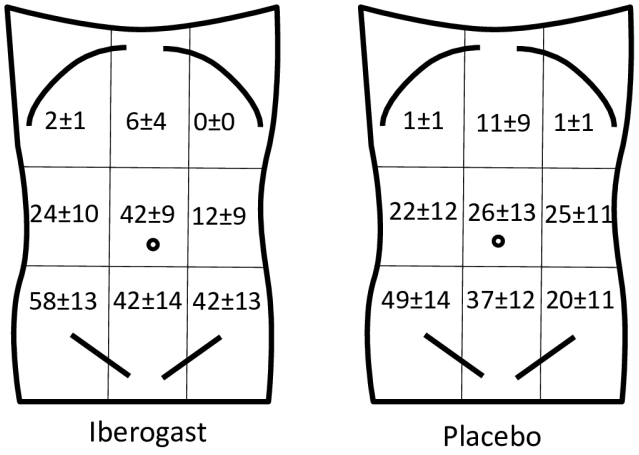

FIGURE 4 Location of abdominal sensations elicited by colonic gas filling. Most symptoms were referred to the lower regions of the abdomen, both ileal fossae and hypogastrium, and periumbilical area, without significant differences when the infusions were performed on-STW5 and on-placebo.

potent antispasmodic, increases intestinal compliance and improves tolerance to intestinal gas.[42] Hence, even though no effect of STW5 on colonic emptying was observed in our study, and the volume of gas retained into the colon was similar in all experimental conditions, we should consider that, in addition to the decreased transmission of afferent stimuli induced by STW5, the antispasmodic action of STW5 could had an add-on effect to reduce the symptoms induced by colonic gas.

By contrast to bloating sensation, which is a subjective symptom, abdominal distension describes a visible objective increment in abdominal girth. Recent studies have shown that altered abdominophenic reflex responses to small increments in colonic contents are responsible for visible abdominal distension in patients with IBS.[21,26,43] Subsequent studies have shown that these altered muscular responses may be modulated by biofeedback techniques, suggesting that some type of consciousness of abdominal sensations could lie behind abdominal distension. In our study, the STW5 group developed a similar abdominal distension than the placebo group during colonic gas load, but gas evacuation during the collection period was associated to a quicker return of abdominal distension to basal levels when patients had been pretreated with STW5, despite no differences in the rate of colonic gas evacuation. The mechanism for the quicker recovery of abdominal distension cannot be elucidated by our data. Whether the rapid decrease in abdominal perception could contribute to the more rapid decrease in abdominal distension observed in the present study, or whether STW5 may have some direct effect on abdominophrenic muscles is an issue to be studied in further studies.

In our study we used a gas challenge test to reproduce gas related abdominal symptoms in IBS patients. This method has been extensively used in previous studies, and has demonstrated to reproduce abdominal symptoms both in healthy controls and patients with IBS and bloating.[21,23,24,26] The mixture of gases infused to fill the colon is not absorbed,[44] and studies using scintigraphy of radiolabeled gas have shown that the colonic gas infusion technique produces a homogeneous and hermetic filling of the colon, without gas leakage to the small intestine or via the anus both in healthy subjects and patients with IBS.[23] In both cases, the gas is distributed along the colon without surpassing the ileocecal valve. Further studies using measurement of colonic gas with CT-scans have confirmed the reliability of this methodology.[22] A limitation of the present study is the small number of patients included. We acknowledge that inclusion of different subtypes of IBS (diarrhea, constipation, and mixed) could increase the variability of the results in our study cohort. However, in previous studies with larger groups of IBS patients, we found no differences in transit and tolerance to intestinal gas in different subtypes of IBS.[17,18] In addition, we used a cross-over design to have each patient as its own control, reducing the interpersonal variability that could have influenced the results of the study. However, we have to consider that the sample size

of the study was powered for the primary end-point (gas evacuation and retention), but nor for the secondary end-points (symptom perception and abdominal distension). A limitation of our study is inherent to the laboratory conditions. The volume of gas used to challenge the colon is within the range of normal gas production under some circumstances, like gas swallowed during meals[45,46] or fermentation of non-absorbed carbohydrates by colonic bacteria.[32] These volumes have been shown to be enough to reproduce abdominal symptoms (bloating and distension) in patients with IBS, as it has been the case in the present study. Hence, even though a direct infusion of gas into the colon is not a physiological condition, the methodology used allows to challenge the colon in a controlled way, so that the characteristics of the challenge are reproducible and comparable.

In conclusion, using a gas challenge test with colonic gas filling in patients with IBS, we have demonstrated that STW5 reduces the intensity of symptoms elicited by colonic gas, despite no effects on colonic gas emptying, and has a minor effect on abdominal distension. Hence, the previously demonstrated positive effects of this herbal preparation on abdominal symptoms in patients with IBS, could be related to an improved tolerance to colonic gas contents, by reducing sensitivity to colonic loads. Consequently, this herbal preparation may be a safe and efficacious alternative for the management of functional abdominal symptoms related to visceral hypersensitivity, like bloating and other gas-related symptoms.

AUTHOR CONTRIBUTIONS

AA: acquisition of data; analysis and interpretation of data; drafting of the manuscript, statistical analysis. BB: Acquisition of data. Monitoring of the study. JS: study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. All authors approved the final version of the article, including the authorship list.

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CONFLICT OF INTEREST STATEMENT

JS: Research Grants from Bayer and Salvat laboratories. Consulter/speaker with Menarini, Casen Recordati, Reckit Benkiser and Norgine. AA and BB: None.

DATA AVAILABILITY STATEMENT

Data will be available in EudraCT and from the authors after request.

CLINICAL TRIAL REGISTRATION

ClinicalTrials.gov ID NCT04656730; EudraCT 2019–003976-38.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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