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Treatment of irritable bowel syndrome with herbal preparations: results of a double-blind, randomized, placebo-controlled, multi-centre trial

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SUMMARY

Background: Herbal medications have been used in many countries for the treatment of patients with irritable bowel syndrome. Controlled data supporting the efficacy of these treatments in patients with irritable bowel syndrome are lacking.

Aim: To assess the efficacy and safety of a commercially available herbal preparation (STW 5) (nine plant extracts), the research herbal preparation STW 5-II (six plant extracts) and the bitter candytuft mono-extract in patients with irritable bowel syndrome.

Methods: Two hundred and eight patients with irritable bowel syndrome were recruited after standardized diagnostic work-up into a double-blind, placebo-controlled, multi-centre trial and were randomly assigned to receive one of four treatments: commercially available herbal preparation STW 5 ($n = 51$), research herbal preparation STW 5-II ($n = 52$), bitter candytuft mono-extract ($n = 53$) or placebo ($n = 52$). The main outcome variables were the changes in total abdominal pain and irritable bowel syndrome symptom scores.

Results: Two hundred and three patients completed the trial. STW 5 and STW 5-II were significantly better than placebo in reducing the total abdominal pain score (intention-to-treat: STW 5, $P = 0.0009$; STW 5-II, $P = 0.0005$) and the irritable bowel syndrome symptom score (intention-to-treat: STW 5, $P = 0.001$; STW 5-II, $P = 0.0003$) at 4 weeks. There were no statistically significant differences between the bitter candytuft mono-extract group and the placebo group ($P = 0.1473$, $P = 0.1207$).

Conclusions: The commercially available herbal preparation STW 5 and its research preparation STW 5-II are both effective in alleviating irritable bowel syndrome symptoms.

INTRODUCTION

Irritable bowel syndrome is one of the most common functional gastrointestinal disorders, with a prevalence rate estimated to be between 3% and 22%.[1–3] Approximately 12% of primary care patient visits are due to irritable bowel syndrome, and irritable bowel syndrome is the major reason for general practice referrals to gastroenterologists.[4–7] Repeated consultations with extensive diagnostic work-up, expenses for medication and time lost from the workplace represent a significant burden on the health system.

Recently, revised diagnostic criteria for irritable bowel syndrome (Rome II guidelines) have included the presence of abdominal pain or discomfort for at least 12 consecutive or non-consecutive weeks in the preceding 12 months, which is relieved by defecation

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and/or is associated with a change in stool frequency and/or stool consistency.[2] The pathophysiology of irritable bowel syndrome remains poorly understood, although various mechanisms are thought to play a role in the development of symptoms.[1] As yet, there is no cure for this disorder and available treatments are targeted at symptom relief.[8] The efficacy of some currently established treatments has been investigated in placebo-controlled trials. However, these treatments yield sufficient relief of symptoms only in a small proportion of patients.[9, 10] Thus, there have been many efforts to identify and develop new effective treatments. Herbal medications have been used in many countries for the treatment of patients with irritable bowel syndrome. However, controlled data supporting the efficacy of these treatments are lacking.

Thus, we aimed to evaluate the efficacy and safety of the commercially available herbal preparation STW 5 and its research preparations for the treatment of patients with irritable bowel syndrome in a placebo-controlled, randomized clinical trial.

PATIENTS AND METHODS

Study design and recruitment of patients

The clinical trial was completed as a randomized, placebo-controlled, double-blind, multi-centre study. The study protocol and consent form were approved by an independent ethics committee in accordance with the revised Declaration of Helsinki. Written informed consent was obtained from all patients prior to inclusion in the trial.

Two hundred and eight out-patients (124 females; mean age, 43.6 ± 12.9 years) with persistent irritable bowel syndrome (defined by abdominal pain or discomfort of at least 3 months' duration during the last 12 months and associated with disturbances of bowel habit, i.e. constipation, diarrhoea or alternating bowel habit) were recruited consecutively by physicians in private practice. Structural lesions and other organic diseases were eliminated by clinical evaluation, including colonoscopy, abdominal sonography, blood counts and serum chemistries. All patients with a history of and/or current organic or gastrointestinal disease were excluded from participation in the study.

As a baseline, physicians assessed the patients' predominant disturbances of bowel function as constipation-predominant, alternating or diarrhoea-predominant.

Treatment schedule

After a standardized diagnostic work-up, patients were asked to discontinue current medications that affected the gastrointestinal tract 1 week prior to randomization. At the end of this 1-week run-in period, patients who fulfilled the selection criteria were randomly assigned to one of four treatment groups: commercially available herbal preparation (STW 5), the research preparation (STW 5-II), bitter candytuft mono-extract (BCT) or placebo. The trial medication was taken three times daily (20 drops) for 4 weeks.

Primary outcome variables of efficacy

The primary outcome variables used in this study were an irritable bowel syndrome symptom scale (sum score grading minimum as 0 and maximum as 12) and abdominal pain scale (sum score grading minimum as 0 and maximum as 21). These two parameters were assessed at each visit: prior to randomization (day − 7), on the day of randomization (day 0), after 2 weeks of treatment (day 14) and after 4 weeks of treatment (day 28). The intensity of symptoms and pain was evaluated using a four-point Likert scale (0, absent; 1, mild; 2, moderate; 3, severe) and the above-mentioned sum scores were calculated. The sum scores are based on a composite score with a high face validity as required by the new guidelines of ICH Biostatistics (Guideline E9).[11]

Irritable bowel syndrome symptom scale. This scale consists of the following symptoms: flatulence/meteorism, sensation of tension or fullness, sensation of incomplete evacuation and changes in bowel habit (constipation, diarrhoea or alternating constipation and diarrhoea).

Abdominal pain scale. The following symptoms were included in the abdominal pain scale: upper abdominal pain, right and left, and lower abdominal pain, right and left.

Secondary outcome variables

Diary cards. Beginning at baseline, patients recorded the intensity of discomfort caused by irritable bowel syndrome each day on diary cards using a visual analogue scale (0–100 mm; 0, no discomfort; 100, most intense discomfort). Patients were also asked to ascertain and

document the day of first substantial improvement (complete relief or a clear improvement in irritable bowel syndrome symptoms).

Patients' and investigators' judgements of treatment efficacy and tolerability. Investigators and patients were asked to judge the efficacy and tolerability of treatment on days 14 and 28 on six-point Likert scales as 'very good', 'good', 'satisfactory', 'sufficient', 'unsatisfactory' or 'poor'.

Tolerability and adverse events

In addition to the subjective assessment of tolerability by patients and physicians, the tolerability was demonstrated by checking vital parameters at each visit and laboratory parameters on days − 7, 0 and 28. In cases in which there was a deviation of up to 20% in laboratory values, treatment was interrupted. Furthermore, the occurrence of adverse events was recorded over the whole duration of the study.

Preparations used in this study

The three herbal preparations used in the trial contained the following extracts.

(a) Commercially available herbal preparation (STW 5): bitter candytuft, chamomile flower, peppermint leaves, caraway fruit, licorice root, lemon balm leaves, celandine herbs, angelica root and milk thistle fruit.
(b) Research herbal preparation (STW 5-II): bitter candytuft, chamomile flower, peppermint leaves, caraway fruit, licorice root and lemon balm leaves.
(c) Bitter candytuft mono-extract (BCT): bitter candytuft.

A placebo of similar appearance and taste was used. In order to ensure that the patients were not able to discriminate between placebo and active treatment, 12 healthy volunteers participated in a randomized taste and visual assessment of the placebo and active medication. Five volunteers correctly identified the active compound as active, and seven volunteers considered the placebo preparation to be the active compound. Thus, it is reasonable to assume that the medication was given in an appropriately blind and controlled manner.

Randomization and blinding

The patients were allocated to one of the four treatment groups according to a randomization code list in a randomly permuted block design generated using the computer program RANCODE-PLUS V3.1 (Gauting, Germany 1992). The test drugs were labelled in numerical order according to this random list. Patients were included in the study in sequential order. Investigators and patients were unaware of the treatment groups. The investigator received a sealed coded envelope containing the identification of the patient's study medication. This envelope was to be opened only in an emergency.

Sample size

Due to three confirmatory group comparisons, a Bonferroni adjustment with $\alpha/3 = 0.017$ (one-sided) was applied. The β error was fixed at 0.2, corresponding to a power of 0.8. For the sum score of abdominal pain, a range from 0 to 21 units was possible. A range of 16 units after treatment was assumed, with a standard deviation of $16/4 = 4$. The relevant difference was considered to be 2.5 units, the effect size being $2.5/4 = 0.625$ ('medium-sized' difference according to Cohen). This leads to a sample size of 47 patients per group (calculated using 'N 2.0' software from Data Analysis and Study Planning, Gauting, Germany). In order to compensate for dropouts, it was planned to recruit 200 patients (50 patients per group).

Statistical methods

The primary confirmatory analysis was the one-sided test for superiority of the test treatments (STW 5, STW 5-II and BCT) compared with placebo. Two primary target variables (sum scores of irritable bowel syndrome symptoms and abdominal pain) on days 14 and 28 were used. Analysis was performed by adjusting for the two outcome variables and two time points by four criteria with the directional multivariate test of Wei and Lachin.[12] This test procedure is the one-sided directional test of stochastic ordered alternatives, a generalization of the Wilcoxon test. The confirmatory analysis was based on the intention-to-treat population as defined by Gillings and Koch,[13] including all patients who had at least one observation after the start of treatment, with missing values replaced by the 'last value carried forward' method.

Potential baseline differences were taken into account by evaluating the main efficacy criteria as changes from baseline (differences) for day 14 and day 28. For an arbitrary point in time, the hypothesis may be defined using the general Mann–Whitney superiority measure

as: H_O, $MW_{TP} \leq 0.5$; H_A, $MW_{TP} > 0.5$ (T, test preparation; P, placebo; MW, Mann–Whitney statistic). The multiple level α for the primary analysis was controlled by applying a Bonferroni–Holm adjustment to the three criteria, with the ordered P values of $\alpha/3$, $\alpha/2$ and α. All other tests were interpreted in a descriptive sense only.

Test results are presented as P values and as the Mann–Whitney superiority measure, together with the 95% confidence intervals (CI). The Mann–Whitney superiority measure of relevance shows the probability that a randomly selected patient from the test group will be better off than a randomly selected patient from the reference group.[14]

For the evaluation of 'time until first substantial improvement', the log rank test for group differences (Cox–Mantel test) was applied. For the 'presence of substantial improvement' on day 28, an r by 2 table was used. A Kruskal–Wallis test was applied as a multigroup test for data with ordered categories.

RESULTS

Study design and patient randomization

The study design and patient allocation are depicted in Figure 1. All 208 randomized patients received study medication and were eligible for the safety evaluation (safety population: STW 5, $n = 51$ patients; STW 5-II, $n = 52$ patients; BCT, $n = 53$ patients; placebo, $n = 52$ patients). In one patient (STW 5-II group), no efficacy assessment was performed. This patient was excluded from the efficacy evaluation according to the intention-to-treat principle. Thus, the confirmatory efficacy evaluation was performed with 207 patients.

Four patients (three in the STW 5 group and one in the BCT group) discontinued the study after the first efficacy assessment on day 14 because of the inefficacy of the treatment. In these cases, missing values were replaced by the 'last value carried forward' method.

Demographic and baseline characteristics

The demographic and baseline characteristics are summarized in Table 1. Analyses for homogeneity showed no relevant differences. In addition, there were no differences in the baseline parameters (Figures 2 and 3).

Primary outcome variables

Irritable bowel syndrome symptom scale. The mean sum scores of the irritable bowel syndrome symptoms are shown in Figure 2. After 2 weeks of treatment, the symptom score was significantly better for STW 5 and STW 5-II than for placebo ($P = 0.0085$ and $P = 0.0006$ vs. placebo, respectively). After 4 weeks, the difference between STW 5/STW 5-II and placebo increased further ($P = 0.001$ and $P = 0.0003$ vs. placebo, respectively). In contrast, the improvement of the irritable bowel syndrome symptom score was not significant compared with placebo during treatment with BCT after 14 and 28 days ($P = 0.0781$ and $P = 0.1207$, respectively).

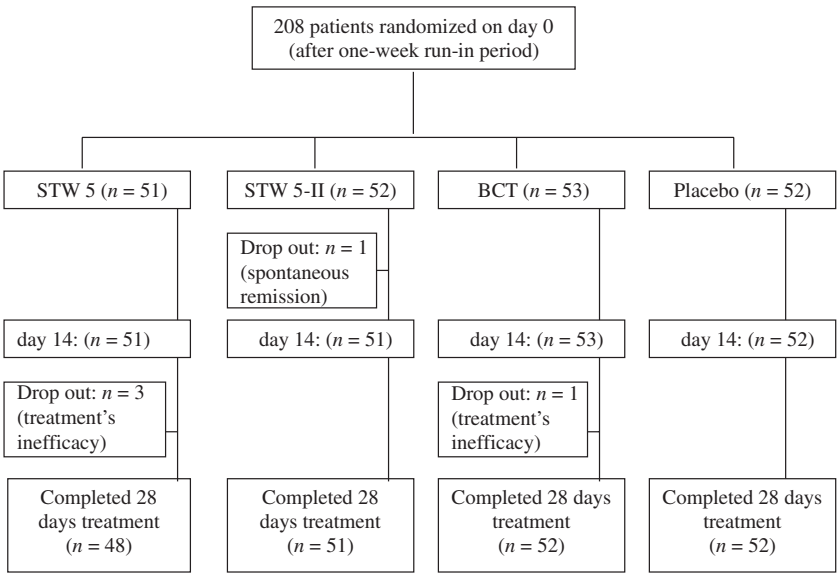

Figure 1. Study design and patient allocation. STW 5, commercially available herbal preparation (nine plant extracts); STW 5-II, research herbal preparation (six plant extracts); BCT, bitter candytuft mono-extract.

Table 1. Demographic and baseline characteristics

Characteristic	STW 5 ($n = 51$)	STW 5-II ($n = 52$)	BCT ($n = 53$)	Placebo ($n = 52$)
Female gender (n)	35	30	29	30
Age (years), mean (s.d.)	43.6 (12.9)	49.2 (10.6)	47.5 (11.2)	46.1 (10.4)
Weight (kg), mean (s.d.)	71.3 (11.8)	71.8 (11)	70.5 (12.5)	69.4 (10.8)
Height (cm), mean (s.d.)	170 (8)	170 (8)	170 (7)	169 (7)
Duration of symptoms				
< 3 months	0	0	0	0
3–6 months	22	21	19	26
6–12 months	20	20	18	14
> 12 months	9	11	16	12
Predominance of symptoms				
Diarrhoea	19	13	12	13
Constipation	14	22	13	16
Alternating	18	17	28	23
Pain severity				
Mild	3	4	2	4
Moderate	32	31	32	27
Severe	15	17	19	20
Very severe	1	0	0	1
Alcohol consumption	23	21	29	23
Smoking	16	7	13	18

STW 5, commercially available herbal preparation; STW 5-II, research herbal preparation; BCT, bitter candytuft mono-extract.

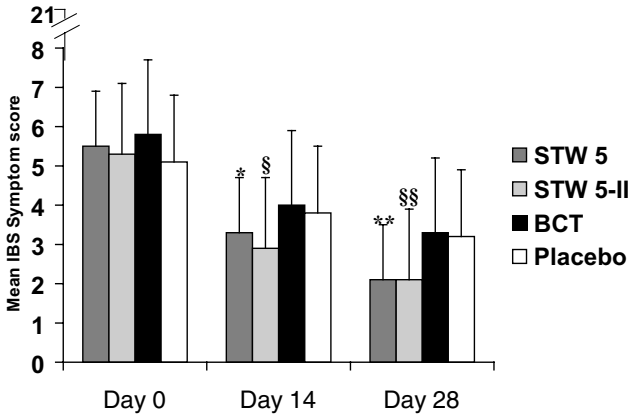

Figure 2. Irritable bowel syndrome (IBS) symptom sum score (± s.d.) for the various treatment groups at baseline and after 2 and 4 weeks of treatment. Intention-to-treat population. *$P = 0.0085$, §$P = 0.0006$, **$P = 0.001$ and §§$P = 0.0003$ vs. placebo. STW 5, commercially available herbal preparation (nine plant extracts); STW 5-II, research herbal preparation (six plant extracts); BCT, bitter candytuft mono-extract.

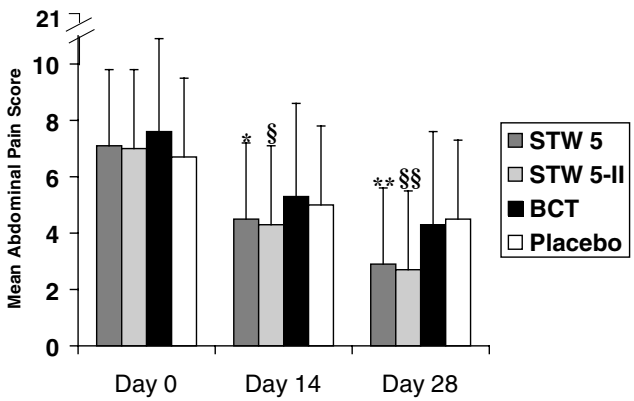

Figure 3. Abdominal pain sum score (± s.d.) for the various treatment groups at baseline and after 2 and 4 weeks of treatment. Intention-to-treat population. *$P = 0.0033$, §$P = 0.0035$, **$P = 0.0009$ and §§$P = 0.0005$ vs. placebo. STW 5, commercially available herbal preparation (nine plant extracts); STW 5-II, research herbal preparation (six plant extracts); BCT, bitter candytuft mono-extract.

Abdominal pain scale. The mean sum scores of abdominal pain are depicted in Figure 3. The commercially available herbal preparation STW 5 and the research preparation STW 5-II were statistically superior to placebo in reducing abdominal pain after 2 weeks ($P = 0.0033$ and $P = 0.0035$ vs. placebo, respectively) and 4 weeks ($P = 0.0009$ and $P = 0.0005$ vs. placebo, respectively) of treatment. The differences between BCT and placebo after 2 and 4 weeks were not statistically significant ($P = 0.1166$ and $P = 0.1473$, respectively).

The efficacy of treatment with regard to irritable bowel syndrome and abdominal pain symptoms is summarized in Table 2. For the majority of symptoms, the improvement during treatment with STW 5-II and STW 5 was substantially better than with placebo.

Table 2. Complete relief or absence of specific irritable bowel syndrome (IBS) symptoms (% of patients)

	Absence of symptoms at baseline, *n* (%)	Complete relief of IBS symptoms, *n* (%, total patients)	
		After 14 days	After 28 days
Flatulence/meteorism			
STW 5	3 (5.8)	9 (18.8, 48)	21 (45.7, 46)
STW 5-II	2 (3.9)	14 (28.6, 49)	22 (44.9, 49)
BCT	6 (11.3)	4 (8.5, 47)	13 (28.3, 46)
Placebo	3 (5.7)	5 (10.2, 49)	10 (20.4, 49)
Sensation of incomplete evacuation			
STW 5	32 (62.8)	12 (63.2, 19)	13 (72.2, 18)
STW 5-II	32 (62.8)	10 (52.6, 19)	14 (73.7, 19)
BCT	32 (62.3)	8 (40, 20)	10 (50, 20)
Placebo	38 (73.08)	5 (35.7, 14)	7 (50, 14)
Changes in bowel habit (constipation, diarrhoea or alternating)			
STW 5	3 (5.8)	3 (6.3, 48)	8 (17.8, 45)
STW 5-II	0 (0)	2 (3.9, 51)	9 (18, 50)
BCT	2 (3.8)	1 (1.9, 51)	8 (16, 50)
Placebo	3 (5.7)	1 (2.1, 49)	1 (2.1, 49)
Sensation of tension or fullness			
STW 5	3 (5.8)	14 (29.2, 48)	25 (52.1, 48)
STW 5-II	9 (17.7)	16 (37.2, 43)	25 (58.1, 43)
BCT	4 (7.6)	10 (20.4, 49)	13 (26.5, 49)
Placebo	8 (15.4)	9 (20.5, 44)	15 (34.1, 44)
Upper abdominal pain, left			
STW 5	3 (5.8)	9 (26.5, 34)	16 (50, 32)
STW 5-II	2 (3.9)	3 (11.5, 26)	7 (26.9, 26)
BCT	6 (11.3)	5 (15.6, 32)	10 (32.3, 31)
Placebo	3 (5.7)	2 (6.1, 33)	9 (27.3, 33)
Upper abdominal pain, right			
STW 5	25 (49)	8 (30.8, 26)	11 (45.8, 24)
STW 5-II	28 (55)	11 (47.8, 23)	12 (52.2, 23)
BCT	27 (51)	7 (26.9, 26)	10 (40, 25)
Placebo	25 (48.1)	4 (14.8, 27)	7 (25.9, 27)
Lower abdominal pain, left			
STW 5	12 (23.5)	7 (17.9, 39)	11 (29.7, 37)
STW 5-II	12 (23.5)	4 (10.3, 39)	15 (38.5, 39)
BCT	11 (20.8)	8 (19.1, 42)	11 (26.8, 41)
Placebo	13 (25)	4 (10.3, 39)	6 (15.4, 39)
Lower abdominal pain, right			
STW 5	21 (41.2)	7 (23.3, 30)	11 (39.3, 28)
STW 5-II	14 (27.5)	9 (24.3, 37)	16 (43.2, 37)
BCT	18 (34.0)	8 (22.9, 35)	11 (32.4, 34)
Placebo	22 (43.1)	5 (17.2, 29)	7 (24.1, 29)

STW 5, commercially available herbal preparation; STW 5-II, research herbal preparation; BCT, bitter candytuft mono-extract.

Secondary efficacy criteria

Global judgement of efficacy. The physicians judged the efficacy to be 'very good' or 'good' in 64.7% of patients treated with STW 5 and in 72.6% of patients treated with STW 5-II, but less so in the BCT group (47.2%) and in the placebo group (38.5%). The Kruskal–Wallis analysis for the presence of substantial improvement showed hints of group differences ($P = 0.0001$). Superiority in comparison with placebo was found for STW 5 ($P_{exact} = 0.010$) and for STW 5-II ($P_{exact} < 0.0001$), but not for BCT ($P_{exact} = 0.2754$). There were no significant differences between the physicians' judgements and the patients' judgements.

Diary cards. The evaluation of diary cards showed that the intensity of discomfort caused by irritable bowel syndrome in the STW 5 and STW 5-II groups decreased more impressively than in the other groups. The mean values are depicted in Table 3.

For the evaluation of the 'time until first substantial improvement', the log rank test for group differences (Cox–Mantel test) showed superiority for STW 5 ($P = 0.0039$) and STW 5-II ($P = 0.0003$), when compared with placebo, but not for BCT ($P = 0.5720$).

Efficacy based on the predominance of symptoms

The improvement of the sum scores of irritable bowel syndrome symptoms and abdominal pain in the STW 5 and STW 5-II groups occurred regardless of the predominance of symptoms.

Safety results

The evaluation of the global judgement of tolerability showed no substantial group differences. Throughout all

Table 3. Visual analogue scale of global abdominal symptoms (mean/s.d., intention-to-treat population)

	STW 5	STW 5-II	BCT	Placebo
Day 0	59.1/18.9	60.3/16.1	62.4/17.7	62.0/19.6
Day 14	36.4/18.4*†	35.3/16.5*†	46.3/19.7*	46.8/21.4*
Day 28	27.3/19.3*†	26.1/17.7*†	33.9/24.6*	45.2/22.6*

STW 5, commercially available herbal preparation; STW 5-II, research herbal preparation; BCT, bitter candytuft mono-extract.
* $P < 0.05$ vs. baseline.
† $P < 0.05$ vs. placebo.

groups, tolerability was most often considered to be either 'very good' or 'good' (investigator's judgement on day 28: STW 5, 97.9%; STW 5-II, 90.2%; BCT, 83.0%; placebo, 88.5%). There were no essential differences between the physicians' judgements and the patients' judgements.

No serious adverse events were reported. Two minor adverse events were noted: one in the BCT group (headache, therapy was continued) and one in the STW 5 group (constipation, therapy was continued). Blood chemistry before and after treatment showed only minor and clinically irrelevant variations.

DISCUSSION

This multi-centre, randomized, double-blind, placebo-controlled study indicates that both the well-tolerated commercially available herbal preparation STW 5 and the research preparation STW 5-II are effective in patients with irritable bowel syndrome. In contrast, BCT failed to improve irritable bowel syndrome symptoms in this study. Although only partly explored, the effect of STW 5 and STW 5-II potentially may be mediated via their influence on gastrointestinal motility,[15] possibly via 5-hydroxytryptamine (5-HT) pathways.[16]

The management of patients with irritable bowel syndrome is difficult. Many therapeutic agents, including prokinetics, anticholinergics, laxatives, antispasmodics and other drugs, have limited effects. New treatment modalities, such as 5-HT_3 antagonists or 5-HT_4 agonists, have been shown to be effective for either diarrhoea-predominant or constipation-predominant irritable bowel syndrome, but not for both.[17, 18] In contrast, the results of the present study indicate that the investigated herbal preparations STW 5 and STW 5-II might be effective in the treatment of irritable bowel syndrome regardless of the predominance of irritable bowel syndrome symptoms. This is a clear advantage as the predominance of irritable bowel syndrome symptoms often fluctuates. The overall improvement of the symptom scores with STW 5 and STW 5-II was significant and was of the order of 15–25% better than that obtained with placebo. With regard to the magnitude of effects, it is noteworthy that the proportion of patients with complete relief of symptoms was considerably higher in the STW 5 and STW 5-II groups. For example, there was complete relief of the sensation of tension or fullness in 52% and 58% of patients treated with active STW 5 and STW 5-II, respectively, compared with 34% of placebo-treated subjects. Thus, the proportion of patients with complete relief was more than 50% greater than that obtained with placebo, and this held true for virtually all symptoms.

The evaluation of treatment effects in irritable bowel syndrome is difficult and there is currently no gold standard. In our study, we used two different parameters as the main target variables. The irritable bowel syndrome symptom scale includes symptoms associated with abdominal discomfort and changes in bowel habit. The abdominal pain scale includes information about pain sensation in irritable bowel syndrome patients. Both STW 5 and STW 5-II were significantly better than placebo for both variables. Another difficulty in clinical trials of irritable bowel syndrome patients is the remarkable placebo response. This has been described to vary from 40% to 70% in short-term trials,[19–21] and may even be higher in long-term studies. Despite this well-known possible high placebo response rate in irritable bowel syndrome, a clear, statistically significant improvement in irritable bowel syndrome symptoms was assessed for treatment with the herbal preparations STW 5 and STW 5-II when compared with placebo.

Although herbal preparations have already been used in many countries for the treatment of irritable bowel syndrome, few clinical studies have been performed with these preparations. To our knowledge, this is one of the first randomized trials to test a herbal preparation in patients with irritable bowel syndrome. Our findings are in good accordance with a recently published double-blind, placebo-controlled study that demonstrated a significant improvement of symptoms in patients with irritable bowel syndrome after treatment with a traditional Chinese herbal medicine.[22]

Herbal preparations are complex and contain a number of active ingredients possibly working together, rather than one specific active substance. The multiple effects of different active ingredients may be of benefit for the variety of different symptoms that occur in functional gastrointestinal disorders. Indeed, STW 5 and STW 5-II, tested in this trial, have also been shown to be effective in reducing the symptoms of functional dyspepsia.[23–25] As functional dyspepsia is often combined with irritable bowel syndrome,[26] and the differentiation between these two functional disorders is often unclear, an advantageous profile might exist for preparations with different mechanisms of action. Pharmacological experiments support the synergistic effect of the different herbal ingredients of STW 5.[15, 27] By combining the effects of extracts of *Iberis amara* on smooth muscle tone with the

spasmolytic effects of extracts from other plants, STW 5 displays a dual action principle on the smooth muscles of the gastrointestinal tract. Depending on the baseline pathophysiological condition, either the motility stimulating effect or the spasmolytic effect is predominant. In addition to the influence on gastrointestinal smooth muscles, some of the STW 5 plant extracts have anti-inflammatory, anti-ulcerogenic, carminative and antibacterial properties.[15] *In vitro* studies have shown a > 10-fold higher affinity of STW 5 to both M_3 and 5-HT_4 receptors than to 5-HT_3 receptors. Of the nine herbal extracts, *Iberis amara* selectively inhibits binding to M_3 receptors, while celandine herb and chamomile flowers are selective to 5-HT_4 and liquorice root to 5-HT_3 receptors.[16] Experimental studies on patients suffering from irritable bowel syndrome have demonstrated the spasmolytic effect of peppermint oil and a pain-reducing effect in these patients.[28–33] However, a meta-analysis of peppermint oil in the treatment of irritable bowel syndrome has shown that its role is far from established.[34] There is no doubt that further well-designed studies are needed to elucidate the exact mechanisms of action of herbal preparations in patients with functional gastrointestinal disorders.

The tested herbal preparations were well tolerated with minimal adverse events, none of which were serious. No significant abnormal blood values were observed during the study period. Laboratory values concerning liver function are of special interest because some herbal preparations have hepatotoxic effects.[35, 36] Moreover, alkaloids from celandine herbs, one of the nine constituents in STW 5, have been shown to be hepatotoxic in a few patients. However, this hepatotoxicity seems to be dose dependent and was described in patients taking more than 10 mg/day alkaloids. The amount of alkaloids from celandine herbs in a daily dose of STW 5 is approximately 0.35 mg. Such a low dose of alkaloids could explain the absence of hepatotoxic effects of STW 5. Thus, although STW 5 has been available on the market for more than four decades, no cases of hepatotoxicity have been noted. Furthermore, the results from other studies with STW 5 have shown its very good tolerability profile.[23, 25] In contrast, some synthetic preparations with influence on the gastrointestinal motility have had to be withdrawn from the market due to their serious adverse effects.[17, 37, 38] A good tolerability profile of a preparation used for the treatment of irritable bowel syndrome is of particular importance because of the chronic nature of the disease, which often requires long-term use of the medication.

In conclusion, the results of this randomized, double-blind, multi-centre study indicate that the herbal preparations STW 5 and STW 5-II are highly effective for the treatment of patients with irritable bowel syndrome. The precise mechanism of action needs to be elucidated.

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