

A Pilot Study of the Effect of *Aloe barbadensis* Mill. Extract (AVH200®) in Patients with Irritable Bowel Syndrome: a Randomized, Double-Blind, Placebo-Controlled Study

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ABSTRACT

Background & Aims: Few effective treatment options exist for patients with irritable bowel syndrome (IBS), and many patients state the use of aloe vera products reduce their symptoms. The aim of this pilot study was to investigate the effect of *Aloe barbadensis* Mill. Extract (AVH200®) in adult patients with IBS in a randomized, double-blind, placebo controlled study.

Methods: Sixty-eight adult patients diagnosed with IBS according to the Rome III criteria were randomized to receive AVH200® or matching placebo for four weeks. Symptom questionnaires were completed on a weekly basis and the patients were asked if they had had adequate relief of their gastrointestinal symptoms.

Results: A tendency towards a higher proportion of responders in the aloe vera group (55%) vs. placebo (31%), ($p=0.09$) was observed, and the proportion of subjects who reported adequate relief at least 50% of the weeks during the treatment period tended to be larger in the aloe vera vs. placebo group (33% vs. 14%; $p=0.12$). The overall severity of the gastrointestinal symptoms was reduced in the aloe vera group (314 ± 83 vs. 257 ± 107 ; $p=0.003$) but not the placebo group (276 ± 88 vs. 253 ± 100 ; NS), without difference between the groups ($p=0.10$). AVH200® was well tolerated and no serious adverse events were observed.

Conclusion: Even though the primary endpoint was not met, AVH200® seems to be a promising treatment option for patients with IBS owing to the positive results seen within the secondary endpoints. This study may have been underpowered to detect a clinically meaningful difference between the treatment groups, and therefore larger randomized, controlled studies are required to confirm these results and to elucidate potential mechanisms explaining its effect.

Key words: aloe vera – aloe barbadensis mill. – gastrointestinal symptoms – irritable bowel syndrome.

Abbreviations. GI: gastrointestinal; HAD: Hospital Anxiety and Depression scale; IBS: Irritable Bowel Syndrome; IBS-SSS: IBS-Symptom Severity Scoring; OATT: OroAnal Transit Time; VAS: Visual Analogue Scale

INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal (GI) disorders, characterized by abdominal pain and/or discomfort related to disturbed bowel habits, and the patients also often suffer from bloating, flatulence, and overlapping GI symptoms [1, 2]. The pathophysiology of IBS is only partly understood and there are no biological markers, which contributes to difficulties in the management of the patients [3-5].

The available pharmacological treatment options have limited efficacy [6], and instead many patients use complementary or alternative therapies, such as dietary interventions, herbal preparations and psychological treatment options, e.g. gut-directed hypnotherapy or cognitive behavioral therapy [7, 8]. However, blinded, randomized, controlled studies are often lacking to support superiority of many of the complementary and alternative treatment options relative to placebo.

Aloe barbadensis Mill. or more commonly known as aloe vera has a long-standing tradition within herbal medicine. It is alleged to be effective in treatment of wounds [9], genital herpes, psoriasis vulgaris [10], and it may reduce symptoms and inflammation in patients with ulcerative colitis [11]. Evidence of the effects of aloe vera in IBS is however limited and contradictory. In a previous study of aloe vera juice there was no clear evidence that aloe vera was beneficial for patients with IBS, although a slight benefit was seen in the diarrhea

predominant group [12]. There was also no positive effect of aloe vera on the quality of life in IBS patients in a study by Hutchings et al., but problems with drop outs and other confounding factors may have affected the possibility of the study to detect a clinically important difference [13]. Despite the lack of convincing data supporting positive effects of aloe vera on IBS symptoms, many patients still state that they use aloe vera products successfully in order to reduce their symptoms. Therefore, our aim was to perform a pilot study to assess the effect of a commercially available aloe vera product on IBS symptoms. In case of trends/non-significant results, our plan was to calculate the sample size needed to demonstrate a potentially clinically significant effect in subsequent studies. In order to achieve this, we undertook a randomized, double-blind placebo controlled study in a limited IBS population, where the effect of *Aloe barbadensis* Mill. Extract (AVH200[®]) on IBS symptom severity was evaluated.

METHOD

Adult patients (18-65 years) were recruited for inclusion in the study from referrals to our gastroenterology outpatient clinic, as well as through advertisements in local newspapers. All subjects had IBS according to the Rome III criteria [1], and were evaluated by a gastroenterologist. The first patient entered the trial in August 2007 and the trial was completed in January 2008.

The study was a randomized, double-blind, placebo controlled study, with the patients being randomized to either an aloe vera group or the placebo group receiving *Aloe barbadensis* Mill. Extract (AVH200[®], Calmino group AB, Sweden) effervescent tablets (250 mg AVH200[®], 60 mg ascorbic acid and excipients) or matching placebo (60 mg ascorbic acid and excipients) respectively, dissolved in water twice a day, before breakfast and late in the evening for four weeks. The patients who agreed to participate were evaluated at a screening visit, and inclusion and exclusion criteria were checked (Table I). If the patients were found eligible to participate in the study, they entered a run in period of two weeks, during which GI symptoms were evaluated (Fig.

Table I. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Signed written informed consent	Other gastrointestinal disease(s) explaining the symptoms
Age ≥ 18 and ≤ 65	Food allergy or intolerance other than lactose intolerance*
IBS according to the Rome III criteria	Other severe disease(s) such as malignancy, severe heart disease, kidney disease neurological disease
Ability to understand and willingness to comply to the study procedures	Symptoms indicating other severe disease(s) such as weight loss, gastrointestinal bleeding or fever
	Severe psychiatric disease
	Use of aloe vera products
	Pregnant or lactating

* Lactose intolerance not accepted if symptoms remained when the patient was on a lactose restricted diet

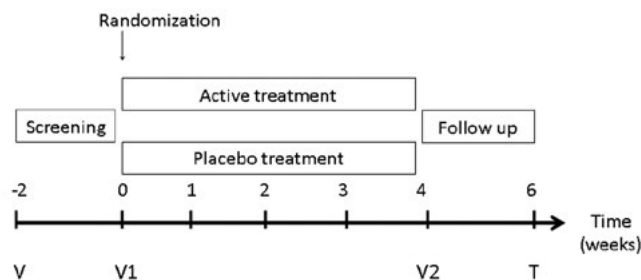


Fig. 1. Schematic presentation of the study design; for details, see text.

1). Thereafter, the patients returned for a randomization visit (visit 1) and if they still were eligible to participate and fulfilled the randomization criteria (see below), they were randomized to receive aloe vera or placebo. At the randomization visit the patients also underwent an oroanal transit time (OATT) measurement, completed questionnaires to assess severity of psychological symptom severity and blood samples for routine biochemistry and hematology were taken (see below). During the four-week treatment period the patients completed questionnaires to assess GI symptom severity weekly. After the four-week treatment period a similar evaluation was done as at the randomization visit (visit 2), i.e. OATT, blood samples and gastrointestinal and psychological symptom questionnaires, and the presence of adverse events was evaluated. Two weeks after the end of treatment period a telephone contact was used as a follow-up, asking the participants for the current symptom level, possible side effects of the treatment, and the patients were reminded to return their GI symptom questionnaires completed during the follow-up period on a weekly basis.

Signed informed consent was obtained from each of the subjects before entering the study and the study protocol was approved by the Regional Ethical Review Board of the University of Gothenburg and by the Radiation Safety Committee.

Questionnaires

Gastrointestinal symptoms: During the study the patients were instructed to evaluate their current IBS symptom severity by completing the IBS-Symptom Severity Scoring System (IBS-SSS) [14]. The IBS-SSS is a questionnaire developed to rate severity of IBS symptoms scored on a visual analogue scale (VAS) (0-100 mm). The overall IBS symptom severity score was calculated from the five items; pain severity, pain frequency, bloating severity, bowel habit dissatisfaction and life interference, ranging from 0-500. Moreover on a weekly basis, the participants were also asked if they had had adequate relief of their IBS symptoms during the preceding week.

Psychological symptoms: Before and after the treatment period (at visit 1 and 2) the patients completed the Hospital Anxiety and Depression scale (HAD) [15]. HAD is a self-assessment mood and anxiety scale, extensively validated, developed to identify patients with psychiatric distress. There are seven items each for anxiety and depression and it uses a 4-point Likert scale (0-3) which provides a minimum score of 0 and a maximum score of 21 on each sub-scale.

Investigations

Before and after the treatment period (at visit 1 and 2) OATT was measured since aloe vera previously has been shown to cause diarrhea due to induced bowel movements [16]. Prior to the investigation the patients ingested 10 radiopaque markers/ day during six consecutive days and returned to the hospital on day seven, i.e. at the planned visits where this was measured (visit 1 and 2). The number of remaining markers was evaluated with fluoroscopy (Exposcop 700 Compact, Ziehm GmbH, Nürnberg, Germany) as described elsewhere [17]. OATT, which mainly is determined by colonic transit time, can be expressed in days by dividing the number of retained markers by 10.

Randomization and blinding

At visit 1, i.e. the randomization visit, the inclusion and exclusion criteria were once again reviewed by one of the investigators (IP) and in order to be randomized, the subjects were not allowed to report adequate relief of their IBS symptoms during the screening period and at least one of the five subscores of IBS-SSS had to be ≥ 25 [14]. Eligible subjects were thereafter randomly assigned to either the aloe vera group or the placebo group for four weeks according to a randomization list produced at the unit. Concealed allocation was assured by the distribution of investigational products by a nurse at the unit, otherwise not involved in the conduct of the study. The randomization schedule was kept in a locked cabinet until the completion of the trial and all data had been entered into a computer database. Both the investigators and the participants were blinded to treatment arm assignments.

Data analysis

The primary endpoint was the proportion of responders in the two groups. A responder was defined as a subject with a reduction of ≥ 50 points on the IBS-SSS questionnaire at visit 2 (end of treatment; corresponding to the last week of the treatment period) relative to visit 1 (randomization). We also used an alternative responder definition: a patient reporting adequate relief at least 50% of the weeks during the treatment

period. As secondary endpoints the change in IBS-SSS, HAD and OATT between visit 1 and 2 was compared between the groups, and for exploratory reasons the within-group differences in IBS-SSS subscores were evaluated in the two treatment groups separately. All analyses were performed using an intention-to-treat paradigm, with drop-outs counted as non-responders and missing data were imputed from the previous assessment using the last observation carried forward technique, and included in the analysis. The data are presented as mean \pm SD or as proportions (%) and all statistical analysis were made with the SPSS version 19.0. Means were compared between two groups using the Students *t*-test, whereas nominal data were compared by use of the Pearson's χ^2 test. Significance was accepted at the 5% level ($p < 0.05$). No power calculations were performed before the start of this study, but instead we planned to perform sample size calculations for future studies based on the results obtained in this pilot study.

RESULTS

Subjects

Ninety-six patients with IBS were assessed for eligibility for the study, and of these 72 patients were screened. Of the patients assessed for eligibility, four patients did not meet the inclusion criteria and 22 did not provide informed consent after receiving written and verbal information about the study. Of the 72 patients who entered the run-in period, 68 patients were randomized (43 IBS mixed type, 20 IBS with diarrhea and 5 IBS with constipation (Fig. 2). Of the four screening failures, three subjects had too mild symptoms during the run-in period or reported adequate relief of their IBS symptoms, and one patient was excluded at the randomization visit due to concurrent use of aloe vera product not disclosed until at the randomization visit. Thirty-three subjects were randomized to the aloe vera group and 35 to the placebo group. For patient characteristics at entry, see Table II. There were no statistically significant differences between the groups at baseline. However, there was a trend towards higher IBS-SSS score in the aloe vera group ($p = 0.067$). Five subjects discontinued the study

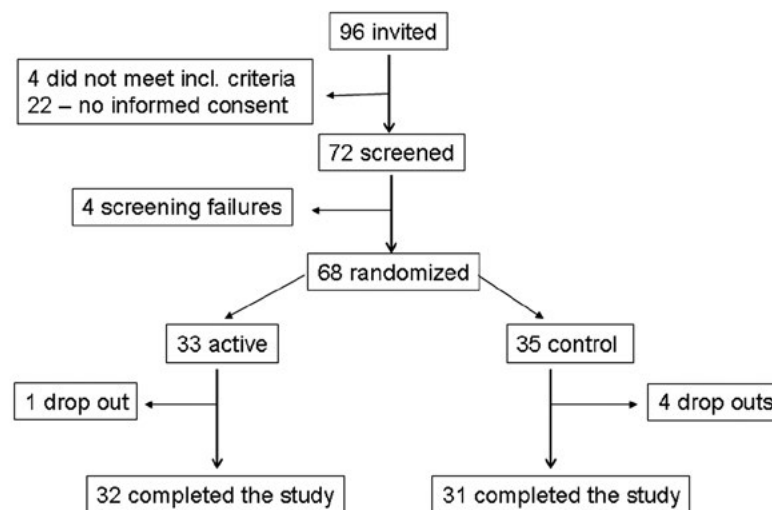


Fig. 2. Flow chart demonstrating the number of patients in the different phases of the study.

during the treatment period, four in the placebo group and one in the aloe vera group. In the placebo group one subject reported worsening of nausea, and the other three withdrew their consent because of inadequate effect of the study drug. In the aloe vera group one subject withdrew due to minor hemorrhoidal rectal bleeding. After the study, this subject reported that he had had rectal bleedings occasionally during five years prior to the study and the current bleeding stopped after three days and was not different from previous bleeding episodes. The study products were well tolerated and except for the above mentioned adverse effects, no side effects were reported and no clinically significant effects on routine biochemistry or hematology, including liver tests, were noted.

Table II. Patients' characteristics at baseline, mean (SD)

Characteristic	Aloe vera group (n=33)	Placebo group (n=35)	P-value
Female/Male ratio (% females)	24/9 (72)	27/8 (77)	0.89
Age, years	43.9 (13.3)	44.2 (14.5)	0.94
IBS-SSS (max 500)	315 (83.4)	276 (88.0)	0.07
OATT (days)	1.9 (1.0)	1.7 (1.1)	0.24
HAD depression	4.8 (3.4)	3.9 (3.7)	0.35
HAD anxiety	6.2 (3.6)	5.9 (4.0)	0.70

IBS-SSS: IBS-Symptom Severity Scoring; OATT: oro anal transit time; HAD: Hospital Anxiety and Depression scale

Primary and secondary endpoints

The primary endpoint in our study was not met; however, a tendency towards a higher proportion of responders (defined as a reduction in IBS-SSS ≥ 50 points at the end of the treatment period relative to baseline) was seen in the aloe vera group (n=18; 54.5%) vs. placebo (n=11; 31.4%) (p=0.093) (Fig. 3a). Based on this responder definition, a power calculation demonstrated that a sample size of 71 patients in each treatment group would be necessary to detect a 23.1% difference in the proportion of responders with 80% power at $\alpha=0.05$. There was also a trend towards a higher proportion of responders using our alternative definition (adequate relief $\geq 50\%$ of the weeks during the treatment period) in the aloe vera group (n=11; 33%) vs. placebo (n=5; 14%) (p=0.12) (Fig. 3b). Although the primary endpoint was not met, when comparing the change in IBS-SSS between patients receiving aloe vera and placebo, a significantly greater improvement was seen in the aloe vera group in the pain severity subscale of IBS-SSS (p=0.030) and a trend in the same direction for the total score (p=0.10) at the end of the treatment period (Fig. 4). Within the aloe vera group, the IBS symptoms were reduced at the end of the treatment vs placebo (315 \pm 83 vs. 257 \pm 107; p=0.003) but not in the placebo group (276 \pm 88 vs. 253 \pm 100; ns). Moreover, there were significant improvements in IBS-SSS subscales in the aloe vera group for pain severity (p=0.011), pain frequency (p=0.010) and bloating (p=0.032) at the end of the treatment period compared to baseline (Fig. 5). No such changes were seen in the placebo group (data not shown). At follow-up, IBS symptom severity remained unchanged compared with visit 2 in both groups (aloe vera: 257 \pm 108; placebo: 255 \pm 111). Psychological symptom severity remained unaltered after

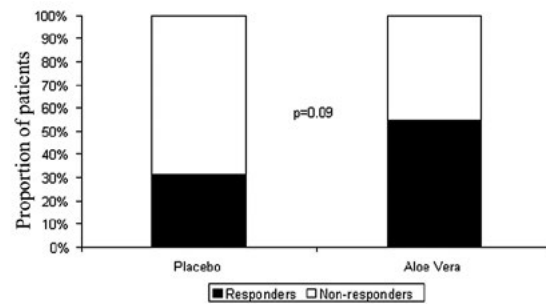


Fig. 3a. Proportion of responders in each group, i.e. of subjects with a reduction of IBS-SSS ≥ 50 points at the end of treatment vs. baseline.

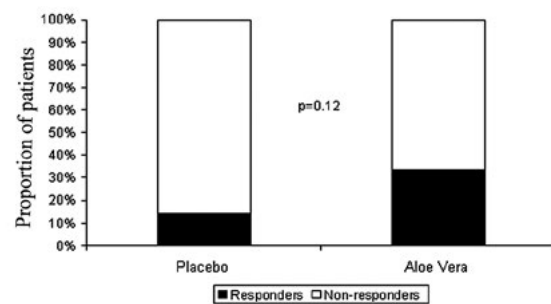


Fig. 3b. Proportion of subjects with adequate relief of IBS symptoms at least 50% of the weeks during the treatment period.

the end of the treatment in the aloe vera (anxiety: 6.2 \pm 3.6 vs. 5.3 \pm 3.4; p=0.34; depression: 4.8 \pm 3.4 vs. 4.5 \pm 3.2; p=0.84) and the placebo group (anxiety: 5.9 \pm 4.0 vs. 4.9 \pm 2.9; p=0.23; depression: 3.9 \pm 3.7 vs. 3.1 \pm 2.7; p=0.13) with no differences between the groups, and the same was true for OATT (aloe vera: 1.9 \pm 1.0 vs. 2.0 \pm 1.0 days; p=0.56; placebo: 1.7 \pm 1.1 vs. 1.9 \pm 1.2 days; p=0.16).

DISCUSSION

In this randomized double blind, placebo controlled pilot study the primary endpoint was not met. However, we found some positive results within the secondary endpoints such as pain severity, pain frequency and bloating, which although they should be interpreted with caution, support that *Aloe barbadensis* Mill. Extract (AVH200®) may be a promising treatment option for patients with IBS. However, larger studies are now needed to confirm these results and to elucidate potential mechanisms behind the tendency towards improvement in IBS symptom severity.

Even though the results may seem promising, there are several limitations with our study. First of all it has to be recognized that this was a pilot study with the aim to find tendencies towards group differences to detect potentially clinically meaningful differences, and to plan future studies based on this. A larger study is now underway with a sample size based on the observed effect size in this study. Moreover, despite the randomization procedure, the aloe vera group had a tendency towards higher IBS symptom severity at baseline, and some of the results could theoretically be due to regression towards the mean. However, also when using the adequate

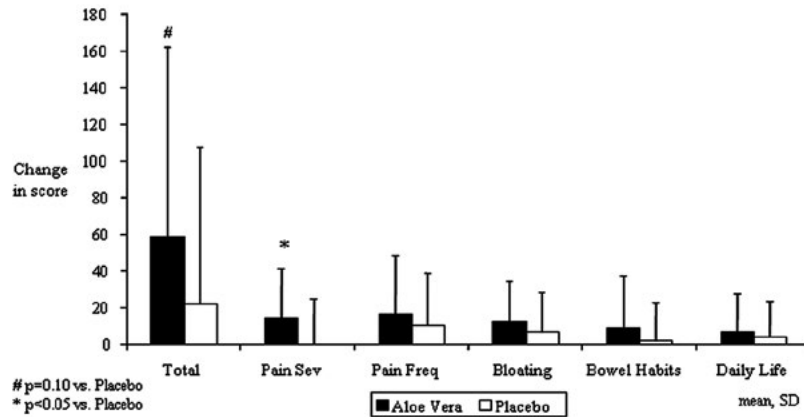


Fig. 4. Changes in IBS-SSS subscores and total score at the end of treatment period relative to baseline.

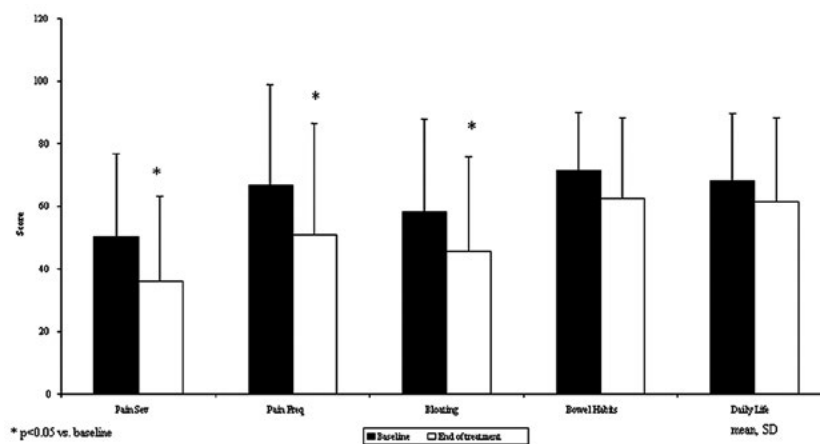


Fig. 5. IBS-SSS subscores at baseline and end of the treatment period in the aloe vera group.

relief endpoint, a trend in the same direction was observed as was seen when defining a responder based on IBS-SSS reduction. These limitations will likely be overcome in our ongoing larger study.

The potential mechanism of action of aloe vera in IBS is not evident. Aloe vera gel has proven to be anti-oxidative and anti-inflammatory *in vitro* in the colon [18], indirectly implicating that aloe vera could be beneficial in other inflammatory conditions of the gastrointestinal tract. In line with this, one randomized controlled trial in patients with ulcerative colitis lends support to this suggestion [11]. Recent evidence suggests that a subset of IBS patients demonstrate altered mucosal immune function and low-grade inflammation [18-20]. Therefore, one potential explanation behind the observed effect could be an anti-inflammatory effect, but this remains to be proven, and assessment of immune markers will be included in our larger study. Another potential mechanism could be an effect on GI motility, given the fact that some aloe vera products affect the bowel habit [16]. However, no effect on colonic transit was observed in this study. Moreover, psychological symptom severity, another important predictor of GI symptom severity in functional GI disorders [21], were also unaffected in our trial. So, to summarize, at this stage, the mechanism(s) underlying the potentially positive effect of this aloe vera product on IBS symptoms remain(s) to be elucidated.

Whether or not the content of ascorbic acid in both the Aloe barbadensis Mill Extract (AVH200[®]) and the placebo

effervescent tablet affects the results is not clear. Another ingredient, a sweetener (sodium saccharine), together with carbonating effect of the effervescent tablet is known to cause symptoms in IBS patients [22]. This effect could possibly hide an even more positive effect of the Aloe barbadensis Mill Extract (AVH200[®]). This could therefore be a potential confounder, but the effect should theoretically be similar in both groups, and will not change the overall conclusion.

Compared to other studies with the same definition of a responder (adequate relief of IBS symptoms at least 50% of the time) [23, 24] the ratio of responders in the active group vs. the placebo group was higher in the present study (19%). However, the total proportion of responders was lower in the present study. Based on these comparisons we consider it clinically relevant to continue evaluating this product in further and larger studies.

Contrary to the widespread belief that aloe vera is non-toxic, excess ingestion of aloe vera has been associated with a range of symptoms and conditions including diarrhea, and some case reports of hepatitis [25-27]. Aloin is the compound known to cause diarrhea, due to induced bowel movements, as well as decreased re-absorption of water from the GI tract [16]. However, the Aloe barbadensis Mill Extract (AVH200[®]) effervescent tablets used in the present study did not contain aloin. Moreover, the extract AVH200[®] used in the present study did not affect liver enzymes, and no other abnormal laboratory values or severe adverse events were observed.

CONCLUSION

We therefore conclude that Aloe barbadensis Mill Extract (AVH200®) is well tolerated, safe and seems to be a promising treatment option for patients with IBS. However, further larger studies are warranted to assess the efficacy of aloe vera products in IBS patients, before these treatment regimens can be recommended for clinical use.

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Authors contribution: S.S. enrolled, randomized patients to the study, analyzed the data. was also responsible for drafting and writing the manuscript. I. P. was involved in data collected and analysis. M.S. was involved in study planning, provided a critical revision of the manuscript and intellectual know-how, and obtained funding for this study. All authors approved the manuscript.

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REFERENCES

- Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology* 2006;130:1480-1491. doi: [10.1053/j.gastro.2005.11.061](https://doi.org/10.1053/j.gastro.2005.11.061)
- Gunnarsson J, Simren M. Efficient diagnosis of suspected functional bowel disorders. *Nat Clin Pract Gastroenterol Hepatol* 2008; 5: 498-507. doi: [10.1038/ncpgasthep1203](https://doi.org/10.1038/ncpgasthep1203)
- Spiller R, Aziz Q, Creed F, et al. Guidelines on the irritable bowel syndrome: mechanisms and practical management. *Gut* 2007; 56: 1770-1798. doi: [10.1136/gut.2007.119446](https://doi.org/10.1136/gut.2007.119446)
- Dixon-Woods M, Critchley S. Medical and lay views of irritable bowel syndrome. *Fam Pract* 2000; 17: 108-113. doi: [10.1093/fampra/17.2.108](https://doi.org/10.1093/fampra/17.2.108)
- Longstreth GF, Burchette RJ. Family practitioners' attitudes and knowledge about irritable bowel syndrome: effect of a trial of physician education. *Fam Pract* 2003; 20: 670-674. doi: [10.1093/fampra/cm608](https://doi.org/10.1093/fampra/cm608)
- Suares NC, Ford AC. Diagnosis and treatment of irritable bowel syndrome. *Discov Med* 2011; 11: 425-433.
- Kearney DJ, Brown-Chang J. Complementary and alternative medicine for IBS in adults: mind-body interventions. *Nat Clin Pract Gastroenterol Hepatol*. 2008; 5: 624-636. doi: [10.1038/ncpgasthep1257](https://doi.org/10.1038/ncpgasthep1257)
- Spanier JA, Howden CW, Jones MP. A systematic review of alternative therapies in the irritable bowel syndrome. *Arch Intern Med* 2003; 163: 265-274. doi: [10.1001/archinte.163.3.265](https://doi.org/10.1001/archinte.163.3.265)
- Maenthaisong R, Chaiyakunapruk N, Niruntraporn S, Kongkaew C. The efficacy of aloe vera used for burn wound healing: a systematic review. *Burns*. 2007; 33: 713-718. doi: [10.1016/j.burns.2006.10.384](https://doi.org/10.1016/j.burns.2006.10.384)
- Ulbricht C, Armstrong J, Basch E, et al. An evidence-based systematic review of Aloe vera by the natural standard research collaboration. *J Herb Pharmacother* 2007; 7: 279-323. doi: [10.1080/15228940802153339](https://doi.org/10.1080/15228940802153339)
- Langmead L, Feakins RM, Goldthorpe S, et al. Randomized, double-blind, placebo-controlled trial of oral aloe vera gel for active ulcerative colitis. *Aliment Pharmacol Ther* 2004; 19: 739-747. doi: [10.1111/j.1365-2036.2004.01902.x](https://doi.org/10.1111/j.1365-2036.2004.01902.x)
- Davis K, Philpott S, Kumar D, Mendall M. Randomised double-blind placebo-controlled trial of aloe vera for irritable bowel syndrome. *Int J Clin Pract* 2006; 60: 1080-1086. doi: [10.1111/j.1742-1241.2006.00980.x](https://doi.org/10.1111/j.1742-1241.2006.00980.x)
- Hutchings HA, Wareham K, Baxter JN, et al. A Randomised, Cross-Over, Placebo-Controlled Study of Aloe vera in Patients with Irritable Bowel Syndrome: Effects on Patient Quality of Life. *ISRN Gastroenterol* 2011; 2011: 206103. doi: [10.5402/2011/206103](https://doi.org/10.5402/2011/206103)
- Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. *Aliment Pharmacol Ther* 1997; 11: 395-402. doi: [10.1046/j.1365-2036.1997.142318000.x](https://doi.org/10.1046/j.1365-2036.1997.142318000.x)
- Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; 67: 361-370. doi: [10.1111/j.1600-0447.1983.tb09716.x](https://doi.org/10.1111/j.1600-0447.1983.tb09716.x)
- Boudreau MD, Beland FA. An evaluation of the biological and toxicological properties of Aloe barbadensis (miller), Aloe vera. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* 2006; 24: 103-154. doi: [10.1080/10590500600614303](https://doi.org/10.1080/10590500600614303)
- Tornblom H, Van Oudenhove L, Sadik R, Abrahamsson H, Tack J, Simren M. Colonic transit time and IBS symptoms: what's the link? *Am J Gastroenterol* 2012; 107: 754-760. doi: [10.1038/ajg.2012.5](https://doi.org/10.1038/ajg.2012.5)
- Langmead L, Makins RJ, Rampton DS. Anti-inflammatory effects of aloe vera gel in human colorectal mucosa in vitro. *Aliment Pharmacol Ther* 2004; 19: 521-527. doi: [10.1111/j.1365-2036.2004.01874.x](https://doi.org/10.1111/j.1365-2036.2004.01874.x)
- Drossman DA. The functional gastrointestinal disorders and the Rome III process. *Gastroenterology* 2006; 130: 1377-1390. doi: [10.1053/j.gastro.2006.03.008](https://doi.org/10.1053/j.gastro.2006.03.008)
- Ohman L, Simren M. Pathogenesis of IBS: role of inflammation, immunity and neuroimmune interactions. *Nat Rev Gastroenterol Hepatol* 2010; 7: 163-173. doi: [10.1038/nrgastro.2010.4](https://doi.org/10.1038/nrgastro.2010.4)
- Van Oudenhove L, Vandenberghe J, Vos R, Holvoet L, Tack J. Factors associated with co-morbid irritable bowel syndrome and chronic fatigue-like symptoms in functional dyspepsia. *Neurogastroenterol Motil*. 2011; 23: 524-e202. doi: [10.1111/j.1365-2982.2010.01667.x](https://doi.org/10.1111/j.1365-2982.2010.01667.x)
- Friedman G. Diet and the irritable bowel syndrome. *Gastroenterol Clin North Am* 1991; 20: 313-324.
- Camilleri M, Northcutt AR, Kong S, Dukes GE, McSorley D, Mangel AW. Efficacy and safety of alosetron in women with irritable bowel syndrome: a randomised, placebo-controlled trial. *Lancet* 2000; 355: 1035-1040. doi: [10.1016/s0140-6736\(00\)02033-x](https://doi.org/10.1016/s0140-6736(00)02033-x)
- Tack J, Muller-Lissner S, Bytzer P, Corinaldesi R, Chang L, Viegas A, et al. A randomised controlled trial assessing the efficacy and safety of repeated tegaserod therapy in women with irritable bowel syndrome with constipation. *Gut* 2005; 54: 1707-1713. doi: [10.1136/gut.2005.070789](https://doi.org/10.1136/gut.2005.070789)
- Kanat O, Ozet A, Ataergin S. Aloe vera-induced acute toxic hepatitis in a healthy young man. *Eur J Intern Med* 2006; 17: 589. doi: [10.1016/j.ejim.2006.04.017](https://doi.org/10.1016/j.ejim.2006.04.017)
- Rabe C, Musch A, Schirmacher P, Kruis W, Hoffmann R. Acute hepatitis induced by an Aloe vera preparation: a case report. *World J Gastroenterol* 2005;11:303-304. doi: [10.3748/wjg.v11.i2.303](https://doi.org/10.3748/wjg.v11.i2.303)
- Bottenberg MM, Wall GC, Harvey RL, Habib S. Oral aloe vera-induced hepatitis. *Ann Pharmacother* 2007; 41: 1740-1743. doi: [10.1345/aph.1k132](https://doi.org/10.1345/aph.1k132)