PHYTOTHERAPY RESEARCH
Phytother. Res. **15**, 58–61 (2001)

Artichoke Leaf Extract Reduces Symptoms of Irritable Bowel Syndrome in a Post-marketing Surveillance Study

Ann F. Walker,[1]* Richard W. Middleton[2] and Otto Petrowicz[3]

[1]The Hugh Sinclair Unit of Human Nutrition, School of Food BioSciences, The University of Reading, PO Box 226, Whiteknights, Reading RG6 6AP, UK
[2]Lichtwer Pharma UK Ltd, Regency House, Mere Park, Dedmere Road, Marlow, Buckinghamshire SL7 1FJ, UK
[3]Institut für experimentelle Onklogie und Therapieforschung der Technischen, Universität München, Germany

Irritable bowel syndrome (IBS) is a problem reported to affect 22% of the general population. It is characterized by abdominal pain and altered bowel habit, but has so far defied elucidation of its pathogenesis and proved difficult to treat. There is a growing body of evidence which indicates therapeutic properties for artichoke leaf extract (ALE). Dyspepsia is the condition for which the herb is specifically indicated, but the symptom overlap between dyspeptic syndrome and IBS has given rise to the notion that ALE may have potential for treating IBS as well. A sub-group of patients with IBS symptoms was therefore identified from a sample of individuals with dyspeptic syndrome who were being monitored in a post-marketing surveillance study of ALE for 6 weeks. Analysis of the data from the IBS sub-group revealed significant reductions in the severity of symptoms and favourable evaluations of overall effectiveness by both physicians and patients. Furthermore, 96% of patients rated ALE as better than or at least equal to previous therapies administered for their symptoms, and the tolerability of ALE was very good. These results provide support for the notion that ALE has potential value in relieving IBS symptoms and suggest that a controlled trial is justified. Copyright © 2001 John Wiley & Sons, Ltd.

Keywords: irritable bowel syndrome; dyspepsia; artichoke leaf extract; cynara scolymus; post-marketing surveillance.

INTRODUCTION

Irritable bowel syndrome (IBS) is characterized clinically by abdominal pain and altered bowel habits (Maxwell *et al.*, 1997) and may include symptoms such as dyspepsia, flatulence, nausea, cramping, constipation and/or diarrhoea (Kirsner, 1981). Although there is considerable symptom overlap with organic abdominal disease and other functional gastrointestinal disorders (Talley, 1998), reliable diagnostic criteria for IBS are available (Manning *et al.*, 1978; Thompson *et al.*, 1992). Between 30% and 60% of patients with either functional dyspepsia or irritable bowel syndrome also meet the criteria for the other diagnosis (Whitehead *et al.*, 1998). Prevalence figures of 22% have been reported for IBS in the United Kingdom (Jones and Lydeard, 1992), with similar results from China, Japan, India and South America (Thompson *et al.*, 1992) as well as other Western European countries, New Zealand and the United States (Maxwell *et al.*, 1997). A community survey (Heaton *et al.*, 1992) revealed three or more typical IBS symptoms in 13% of women and 5% of men, with women more likely to consult a doctor about their symptoms. IBS is the most common gastrointestinal condition encountered by general practitioners (Farthing, 1998) and accounts for up to 50% of the work of gastroenterologists in secondary care (Farthing, 1995), even though between 60% and 75% of people with symptoms of IBS do not consult a doctor (Farthing, 1998).

No specific cause of IBS has been identified. Lines of investigation have focused on possible hyperactivity or hypersensitivity of the intestine, abnormalities in smooth muscle response or disrupted interaction with the central nervous system (Farthing, 1995). Besides altered motility and sensitivity of the intestine, psychosocial 'stress' factors are considered as another major mechanism of IBS (Camilleri and Choi, 1997). Other potential aetiological factors include infection or inflammation, food sensitivities, insufficient dietary fibre and antibiotics (Maxwell *et al.*, 1997). The failure to define satisfactorily the pathophysiology of IBS, makes the treatment of IBS a difficult task and there is no universally accepted effective therapeutic agent. Clinical trails have produced conflicting results and have suffered from methodological flaws as well as the problem of a high placebo

Table 1. Demographic information for patients with IBS symptoms (n = 279)

	Mean (SE)	Median (SD)
Age (years)	56.83 (0.86)	59 (14.28)
Height (cm)	169.46 (0.63)	169 (10.36)
Weight (kg)	74.84 (0.75)	74 (12.32)
Length of illness (weeks)	156.72 (15.45)	48 (258.06)
Dose (capsules per day)	4.87 (0.092)	6 (1.52)

* Correspondence to: Dr A. F. Walker, The Hugh Sinclair Unit of Human Nutrition, Department of Food Science and Technology, The University of Reading, PO Box 226, Whiteknights, Reading RG6 6AP, UK.
E-mail: food@afnovell.reading.ac.uk

Received 22 March 2000
Accepted 7 June 2000

Table 2. Mean (SE) ratings of symptom severity and percentage change over 6 weeks

	N	Baseline	3 weeks	6 weeks	Total change
Abdominal pain	265	1.76 (0.042)	0.96 (0.039)	0.43[a] (0.034)	−75.6%
Right sided abdominal cramps	168	1.80 (0.053)	0.89 (0.052)	0.40[a] (0.043)	−77.6%
Bloating	276	2.11 (0.044)	1.26 (0.044)	0.73[a] (0.039)	−65.5%
Flatulence	247	1.88 (0.047)	1.13 (0.045)	0.63[a] (0.038)	−66.4%
Constipation	279	1.79 (0.046)	0.99 (0.048)	0.53[a] (0.042)	−70.6%

[a] Significant reduction from baseline ($p \leq 0.05$) using Wilcoxon signed rank test.

response. Dietary and drug therapies for IBS generally fall into one of two categories: end-organ treatment which targets the gut and addresses dominant symptoms or central therapy where the focus is on the central nervous system with the intension of relieving associated affective disorders and modifying pain pathways. Common prescriptions include antidiarrhoeal, antimuscarinics and antispasmodic agents, laxatives and tricyclic antidepressants. Other drugs considered to have potential value in alleviating symptoms of IBS include opioid and serotonin antagonists, somatostatin, selective serotonin reuptake inhibitors (SSRIs) anxiolytics and more speculatively, cholecystokinin antagonists and the gonadotrophin-releasing hormone analogue, leuprorelin (Farthing, 1998). Reliable evidence from clinical trials has yet to be provided for some of these drugs.

Since Roman times, artichoke leaf has been documented in Europe as a traditional medicine with choleretic and diuretic properties (Bianchini and Corbetta, 1977). A growing body of scientific evidence on the therapeutic properties of artichoke leaf extract (ALE) has vindicated the traditional use of the herb. ALE has been shown to exert effects on lipid metabolism as well as liver and gastrointestinal tract function (Gebhardt, 1997, 1998; Kraft, 1997). A marked choleretic action has been demonstrated, which for the most part has been attributed to the presence of cynarin (1,5 dicaffeoyl quinic acid) (Kirchhoff *et al.*, 1994). Furthermore, antiemetic, spasmolytic and carminative effects have been described (Kraft, 1997) and probably contribute to the success of ALE in treating dyspepsia, for which it is indicated in Germany, Switzerland and Finland. There is considerable overlap between the symptoms of dyspepsia and IBS and approximately one third of individuals with functional dyspepsia concurrently suffer from IBS (Talley, 1998). ALE may therefore have potential use for alleviating symptoms in patients with IBS, although this has yet to be investigated in a controlled trial.

This paper describes the results of a sub-group analysis of data from a post-marketing surveillance study of ALE in patients with dyspeptic syndrome (Fintelmann and Menssen, 1996). The aim of the sub-group analysis was to examine the data in those dyspeptic patients who fulfilled at least three IBS symptom criteria. Based on the existing clinical data and established pharmacological effects of ALE, an improvement of IBS symptoms was anticipated.

MATERIALS AND METHODS

Patients. The patients were a sub-group (n = 279) taken from a sample of 553 patients in Germany with non-specific gastrointestinal complaints or dyspeptic syndrome, fulfilling at least three of five IBS symptom criteria (abdominal pain, right-sided abdominal cramps, bloating, flatulence or constipation).

Design. This sub-group analysis was generated from data collected prospectively from a 6-week intervention, post-marketing surveillance study (Fintelmann and Menssen, 1996), conducted under routine therapeutic conditions in 52 outpatients centres.

Treatment. Patients were treated with Hepar-SL® forte (Serturner Arzneimittel GmbH, Stadtring Nordhorn 113, D-33332 Gutersloh, Germany), a high-dose standardized

Table 3. Distribution of scores and results of CMH-test (χ^2)

Parameter	Comparison	None	Minor	Marked	Severe	χ^{2a}
Abdominal pain	Baseline	0	99	129	37	284
	6 weeks	169	96	9	0	
Right sided abdominal cramps	Baseline	0	60	81	27	185
	6 weeks	106	56	6	0	
Bloating	Baseline	0	61	124	91	275
	6 weeks	103	147	24	2	
Flatulence	Baseline	0	84	108	55	229
	6 weeks	104	131	11	1	
Constipation	Baseline	0	117	103	59	139
	6 weeks	162	90	24	3	

[a] Levels of significance for 1 degree of freedom are: $p \leq 0.05$, $\chi^2 \leq 3.84$; $p \leq 0.01$, $\chi^2 \leq 6.63$.

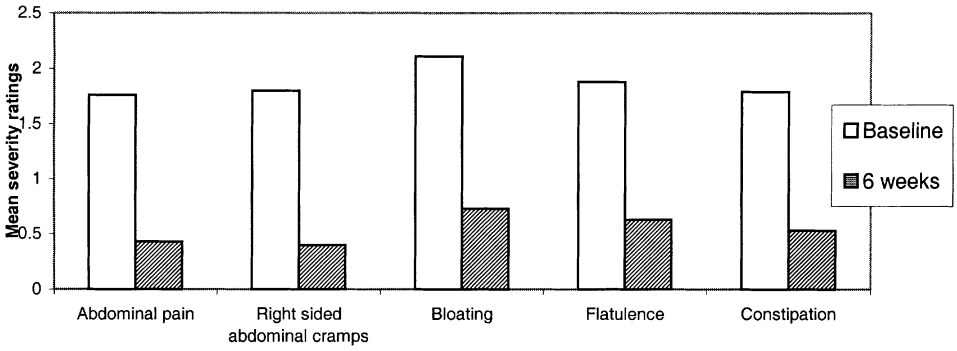

Figure 1. Mean ratings of symptom severity at baseline and 6 weeks.

aqueous-alcohol extract of artichoke leaf (Cynara scolymus L.). One 400 mg capsule contained 320 mg ALE. The average ratio of raw material: native extract was 4.5: 1. Other constituents were lactose, talcum, magnesium, stearate and silicon dioxide. The recommended dosage was two capsules three times daily, swallowed whole with liquid, at mealtimes.

Outcome measures. A case report form (CRF) was used to record results at three measurement points: pre-treatment (baseline), at 3 weeks (intermediate visit and at 6 weeks (end of study). Individual symptoms were rated by the physician on a 4-point scale (0 = none, 1 = minor, 2 = marked, 3 = severe). Overall effectiveness was rated by both the physician and the patient on a 5-point scale (1 = excellent, 2 = good, 3 = moderate, 4 = minimal, 5 = insufficient). Patients evaluated the effectiveness of ALE compared with other treatments tried in the past, using a 5-point scale (substantially better, a little better, no difference, a little worse, substantially worse). Adverse events were also recorded and attempts were made to determine their cause.

Data analysis. All results were analysed using descriptive statistical methods. The effect of treatment on, clinical symptoms was assessed by comparing pre- and post-treatment scores. Comparisons of means were performed by the Wilcoxon signed rank test combined with the Cochron–Mantel–Haenszel Test (CMH-Test) with a significance level of $p \leq 0.05$.

RESULTS

Demographic Information. The inclusion criteria were met by 279 patients. Demographic variables are shown in Table 1. The male:female ratio was 103 : 170 (gender was unknown in 6 patients). The mean age was 56.8 years (range 20–87 years). The median duration of dyspeptic symptoms was 48 weeks with 45% of patients having suffered for over 12 months. The median number of ALE capsules taken per day during the study was 6 (range 2–9).

IBS symptom changes. Over the 6 week treatment period, statistically significant reductions in mean scores on the rating scale were demonstrated for all symptoms. These improvements are recorded in Table 2 and illustrated in Fig 1. In addition, Table 3 shows the distribution of scores (baseline vs 6 weeks) with the corresponding X^2 results of the CMH-test: the results show a clear shift towards health improvement. The overall reduction in IBS symptoms was 71%. According to patient reports, the mean number of days before which improvements were noticeable was 10.4, with 34% detecting an effect within 7 days.

Overall effectiveness

Using the scale from 1 (excellent) to 5 (insufficient), the mean score for overall effectiveness as evaluated by the physicians was 1.95 (SEM 0.043), with approximately 84% rating ALE as either good or excellent (Fig. 2). This was consistent with patient evaluations which produced a mean score of 1.99 (SEM 0.044). Again, ALE was rated as good or excellent by 84% of the patients (Fig. 3). Compared with previous treatments, 86% of patients rated ALE as substantially or slightly better (Fig. 4).

Adverse events

Seven reports of adverse events were documented during the study. Only in three cases (hunger, $n = 1$ and transient

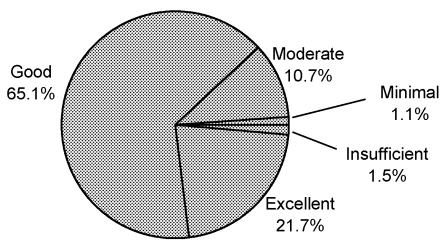

Figure 2. Physician-rated overall mean effectiveness.

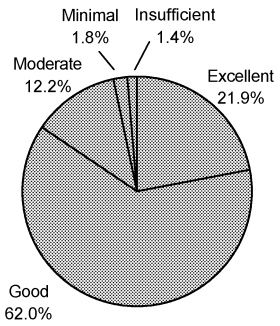

Figure 3. Patient-rated overall mean effectiveness.

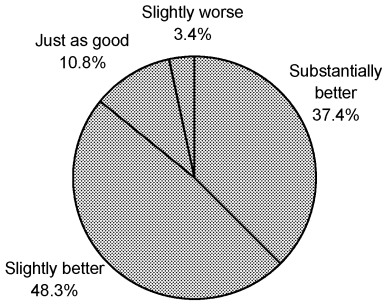

Figure 4. Comparison with previous treatments.

increases in flatulence, $n = 2$) was the adverse event judged to be associated with ALE. In the four other cases who all complained of flatulence, the patients had already suffered from this condition before the study began. For all these patients, there was an improvement during the course of the study, although only after the dose of ALE was reduced.

DISCUSSION

The results of this analysis are encouraging with regard to the effectiveness of ALE in treating patients with IBS. The reduction in IBS symptoms observed in patients with dyspeptic syndrome over a 6-week treatment period suggests that ALE may have potential as a therapeutic agent for IBS.

It is not possible to know how many patients in this study could have been diagnosed as suffering from IBS, since the original CRF for patients with dyspeptic syndrome did not include all the diagnostic criteria for IBS (Thompson *et al.*, 1992. However, since several of the key IBS symptoms were present, and patients were required to fulfill at least three of these, it is likely that the patients sample was representative of those with IBS.

Clearly, it is not possible to estimate how much of the symptom reduction observed in this study was due to spontaneous improvement, since there was no control group with which to compare results. Similarly, the effects of patient expectation are impossible to quantify. However, positive data from post-marketing surveillance studies, such as those found in this study, are valuable for providing a basis for undertaking a randomized, controlled trail. ALE has not yet been tested as a treatment for IBS, although the antidyspeptic effects of ALE have been documented in the scientific literature (Kraft, 1997). Furthermore, the evidence showing that ALE has antiemetic, spasmolytic and carminative properties (Kraft, 1997) provides further support for the notion that ALE may be of benefit in IBS.

The principal strength of surveillance studies of this nature is in providing data about the tolerability of a product as it is used in normal practice. The small number and mild nature of adverse events reported in this study suggests that ALE is a well-tolerated treatment. This confirms the findings of another short-term observational study on ALE (Held, 1991, 1992) and a longer, 6 month study (Fintelmann and Petrowicz, 1998).

Given the lack of universally accepted approaches for treating IBS (Farthing, 1998), there is justification for investigating the efficacy of ALE as a therapeutic option. In our sub-group, over 96% of patients claimed that ALE was as good as or better than any previous treatment they had tried for their symptoms. Significant improvements were observed during the 6 weeks of the study and both patient and physician evaluations of overall effectiveness were very favourable. These results provide preliminary evidence for the potential value of ALE in treating IBS and form the basis upon which to conduct a controlled investigation.

REFERENCES

Bianchini F, Corbetta F. 1977. *Health Plants of the World—Atlas of Medicinal Plants*. Newsweek Books: New York.

Camilleri M, Choi MG. 1997. Irritable bowel syndrome. *Aliment Pharmacol Ther* **11**: 3–15.

Farthing, MJG. 1995. Irritable bowel, irritable body or irritable brain? *Br Med J* **310**: 171–175.

Farthing MJG. 1998. New drugs in the management of the irritable bowel syndrome. *Drugs* **56**: 11–21.

Fintelmann V, Menssen HG. 1996. Artichoke leaf extract: current knowledge concerning its efficacy as a lipid-reducer and antidyspeptic agent. *Dtsch Apoth Ztg* **136**: 1405–1414.

Fintelmann V, Petrowicz O. 1998. Dyspepsia: long-term administration of an artichoke extract for dyspepsia symptoms, results of an observational study. *Natura Med* **13**: 17–26.

Gebhardt R. 1997. Antioxidative and protective properties of extracts from leaves of the artichoke (*Cynara scolymus* L.) against hydroperoxide-induced oxidative stress in cultured rat hepatocytes. *Toxicol Appl Pharmacol* **144**: 279–286.

Gebhardt R. 1998. Inhibition of cholesterol biosynthesis in primary cultured rat hepatocytes by artichoke (*Cynara scolymus* L.) extracts. *J Pharmacol Exp Ther* **286**: 1122–1128.

Heaton KW, O'Donnell LJD, Braddon FEM, Mountford RA, Hughes AO, Cripps PJ. 1992. Symptoms of irritable bowel syndrome in a British urban community: consulters and nonconsulters. *Gastroenterology* **102**: 1962–1967.

Held C. 1991. *Artischocke bei Gallenwegsdyskinesien*. Workshop 'Neue Aspekte zur Therapie mit Choleretika', Kluvensiek 2.9.

Held C. 1992. Von der 1. deutsch-ungarischen Phytopharmaka-Konferenz, Budapest, 20. November 1991. *Z Klin Med* **47**: 92.

Jones R, Lydeard S. 1992. Irritable bowel syndrome in the general population. *Br Med J* **304**: 87–90.

Kirchhoff R, Beckers C, Kirchoff GM, Trinczek-Gärtner H, Petrowicz O, Reimann HJ. 1994. Increase in choleresis by means of artichoke extract. *Phytomedicine* **1**: 107–115.

Kirsner JB. 1981. The irritable bowel syndrome. A clinical review and ethical considerations. *Arch Intern Med* **141**: 635–639.

Kraft K. 1997. Artichoke leaf extract—recent findings reflecting effects on lipid metabolism, liver and gastrointestinal tracts. *Phytomedicine* **4**: 369–378.

Manning AP, Thompson WG, Heaton KW, Morris AF. 1978. Towards positive diagnosis of the irritable bowel. *Br Med J* **2**: 653–654.

Maxwell PR, Mendall MA, Kumar D. 1997. Irritable bowel syndrome. *Lancet* **350**: 1691–1695.

Talley NJ. 1998. Scope of the problem of functional digestive disorders. *Eur J Surg* **582**: 35–41.

Thompson WG, Creed F, Drossman DA, Heaton KW, Mazzacca G. 1992. Functional bowel disease and functional abdominal pain. *Gastroenterology Int* **5**: 75–91.

Whitehead WE, Gibbs NA, Li Z, Drossman DA. 1998. Is functional dyspepsia just a subset of irritable bowel syndrome? *Baillieres Clin Gastroenterol* **12**: 443–461.

