

Review article: complementary and alternative therapies for inflammatory bowel disease

L. LANGMEAD* & D. S. RAMPTON†

*Department of Gastroenterology,
University College London Hospitals,
NHS Foundation Trust, London;
†Barts and the London School of
Medicine and Dentistry, Queen Mary,
University of London, London, UK

Correspondence to:
Dr L. Langmead, Department of
Gastroenterology, UCLH, 2nd Floor
Maple House, Ground Floor
Rosenheim Wing, 25 Grafton Way,
London WC1E 6DB, UK.
E-mail: louise.langmead@uclh.nhs.uk

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SUMMARY

Complementary and alternative medicine includes a wide range of practices and therapies outside the realms of conventional western medicine. Despite a lack of scientific data in the form of controlled trials for either efficacy or safety of complementary and alternative medicine, use by patients with inflammatory bowel disease, particularly of herbal therapies, is widespread and increasing.

There is limited controlled evidence indicating efficacy of traditional Chinese medicines, aloe vera gel, wheat grass juice, *Boswellia serrata* and bovine colostrum enemas in ulcerative colitis. Encouraging results have also been reported in small studies of acupuncture for Crohn's disease and ulcerative colitis. Contrary to popular belief, natural therapies are not necessarily safe: fatal hepatic and irreversible renal failure have occurred with some preparations and interactions with conventional drugs are potentially dangerous.

There is a need for further controlled clinical trials of the potential efficacy of complementary and alternative approaches in inflammatory bowel disease, together with enhanced legislation to maximize their quality and safety.

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INTRODUCTION

The terms complementary and alternative medicine (CAM) denote theories and practices of medicine which deviate from the conventional. The combined term, CAM, encompasses a vast and heterogeneous range of diagnostic and therapeutic procedures as well as systematic and comprehensive concepts of health and disease, which include traditional practices such as acupuncture, traditional Chinese medicine, Ayurvedic medicine, homeopathy and herbal medicine, as well as more modern complementary practices including aromatherapy and reflexology (Table 1).

The denominator common to all types of CAM is their exclusion from the realms of conventional scientific medicine, and consequently their under-representation in research and teaching at universities. Alternative medicine practices are often based on ideas or beliefs, which ignore modern pathophysiological and pharmacological mechanisms, relying more on ancient practices and on 'natural' remedies, which are perceived as being less toxic than conventional drugs. CAM differs further from much conventional medicine by taking a holistic approach to patient care, calling on self-healing by the body and being applied in an

individualized way. Indeed, although increasing numbers of controlled trials and meta-analyses are being reported,¹ much information relating to the possible effectiveness of CAM remains anecdotal or historical.

USE OF CAM

Over 30% of the western population now uses some form of CAM. The single most commonly used modality in most surveys is herbal therapy.²⁻⁴ Indeed, annual spending on herbal products by the general population is said to exceed £40 million/year in the UK⁴ and \$5 billion/year in the US.² These are extraordinary figures given the dearth of scientific evidence about the efficacy or safety of herbal therapies in almost all the contexts in which they are used.

Surveys of use of CAM by patients with gastrointestinal complaints have reported rates of usage ranging from 9%⁵ to over 50%.^{6, 7} CAM for all digestive indications appears to be more popular in North America than Europe, although the growth of the industry in Europe is now probably faster. As in other contexts, the single most used type of CAM for gastrointestinal disorders is herbal therapy.^{8, 9}

Alternative medical systems

Homeopathy Naturopathy Traditional Chinese medicine (including acupuncture) Ayurveda	Complete systems of theory and practice
Mind-body interventions Meditation Hypnotherapy Creative therapies, e.g. art, music, dance	Techniques to enhance the mind's capacity to affect bodily function
Biologically based therapies Herbalism Dietary manipulation and supplements Vitamins	Use of naturally occurring substances
Manipulative and body-based Chiropractic Osteopathy Reflexology Massage	Based on movement or manipulation of one or more parts of body
Energy therapies Biofield, e.g. Reiki Bioelectromagnetic field therapy	Unconventional use of magnetic and electromagnetic fields

Table 1. Types of complementary and alternative therapy potentially relevant to inflammatory bowel disease (IBD; derived from <http://www.nccam.nih.gov/health/whatiscam>)

Usage appears to be most common in patients with inflammatory bowel disease (IBD)^{6, 8, 9} and with irritable bowel syndrome.¹⁰ This may be related to the chronic and refractory nature of these disorders^{9, 11} as well as to psychological factors.¹¹ Indeed recent surveys in the UK and Hong Kong have shown that use of CAM by patients with IBD is most common in those with poor quality of life,^{12, 13} a finding analogous to that occurring in patients with breast cancer.¹⁴ In a national survey from Germany, 51% of IBD patients had experience with CAM, with homeopathy and herbal therapy the most popular. Patients' total systemic steroid intake, suggesting poorly controlled disease, was a strong predictor of the use of CAM.⁷

Given its widespread usage, doctors in general, and gastroenterologists in particular, can no longer ignore the potential benefits and dangers of CAM.

EVALUATING THE EFFICACY OF CAM IN IBD

The difficulties associated with designing, executing and interpreting trials of new conventional therapies in IBD are numerous;¹⁵ they include the heterogeneity of ulcerative colitis (UC) and particularly Crohn's disease, the definition of indications for treatment and the selection of appropriate therapeutic end points. Such problems are compounded in relation to trials involving alternative therapies. Indeed, some authors believe that attempts to resolve questions of effectiveness of CAM using randomized-controlled trials (RCTs) are misguided in view of their exclusion from the realms of scientific hypotheses.^{16, 17}

Trial design

The huge variety of herbal products available and the lack of standardization of their manufacture, content and directions for use, reduces the likelihood of different trials of the same remedy giving reproducible results. Similar comments apply to physical treatments, where standard protocols are often lacking. The widely used CAM practice of individualized therapy is also difficult to incorporate into conventional clinical trial design, although meaningful results can be obtained by using, for example, a crossover design and multiple groups.¹⁸ Devising appropriate control arms, for example sham acupuncture points, for physically or psychologically based therapies often raises arguments about blinding and the placebo response.

Trial execution

Initiation of therapeutic trials of conventional medicines, in the UK at least, has recently become more complicated. All clinical trials of investigational medicinal products, which fall under the Medicines for Human Use (Clinical Trials) Regulations 2004, must be registered on the EudraCT database. This has been established to provide an overview of all clinical trials in the European Community (EC) and to improve communications between competent authorities, such as the Medicines and Healthcare Products Regulatory Agency (MHRA), in member states. When registered, each trial is issued with a unique EudraCT number, which identifies the protocol and trial throughout its lifespan (<http://eudract.emea.eu.int/>). Most forms of intervention in CAM do not meet the stringent requirements of licensing nor, often, do they have a sponsoring manufacturing or pharmaceutical company, or, as yet, recognized regulatory body (see below). Because of this, the process of exact specification of the intervention or product can be difficult, and the consequent registration of the trial even more complex than with conventional medications.

Funding issues tend also to exceed those relating to trials involving standard agents. For example, analytical dossiers are difficult to generate for complementary and particularly herbal medicines. The costs of analysis are high and place a significant financial burden on researchers or companies wishing to carry out clinical trials. Given the expense, it is unlikely that commercial companies will fund clinical trials for existing remedies which already have a successful market, particularly when it is expected that most will be covered by the Traditional Use Directive (see below).¹⁹

Lastly, most grant giving bodies remain wary, at best, of research involving CAM, so that funding from such sources for trials (or laboratory research) is even harder than usual to obtain.

Trial interpretation

A number of studies of CAM for the treatment of IBD have been described in the literature (Table 2), some claiming at least equivalence to conventional therapies. In many instances trial design has been insufficiently rigorous to permit reliable conclusions to be drawn. In particular, many studies have been unrandomized, uncontrolled and unblinded; many have

Table 2. Trials of complementary and alternative therapy in active IBD

CAM	Disease	n	Trial design	Comparator	Duration of treatment	Remission on CAM (%)	Remission on comparator (%)	Reference
Jian Pi Ling tablets, RSF-FS enemas	UC	153	Randomized, controlled	Oral sulfasalazine, dexamethasone enemas	90 days	53	28	Chen <i>et al.</i> ²⁰ (article in Chinese)
Kui jie qing enemas	UC	106	Controlled	Oral sulfasalazine, oral prednisolone, prednisolone enema	20 days	72	9	Wang <i>et al.</i> ²¹
Yukui tang tablets, herbal decoction enemas	UC	118	Controlled	Oral prednisolone, neomycin and vitamin B	40 days	33	17	Chen and Zhang ²²
Aloe vera gel	UC	44	Randomized, double-blind, placebo-controlled	Placebo	4 weeks	30	7	Langmead <i>et al.</i> ²³
Wheat grass juice	UC	23	Randomized, double-blind, placebo-controlled	Placebo	4 weeks	Not stated, but wheat grass improved symptoms and bleeding more than placebo	Not stated	Ben-Arye <i>et al.</i> ²⁴
Germinated barley	UC	21	Open	-	24 weeks	Not stated, but bleeding and nocturnal diarrhoea improved	-	Kanauchi <i>et al.</i> ²⁶
<i>Boswellia serrata</i> gum resin	UC	30 ²⁹	Controlled	Sulfasalazine	6 weeks	82 ²⁶ ; 70 ²⁹	75 ²⁶ ; 40 ²⁹	Gupta <i>et al.</i> ^{28, 29}
<i>Boswellia serrata</i> extract H15	CD	102	Controlled, non-inferiority	Mesalazine	8 weeks	36	31	Gerhardt <i>et al.</i> ³⁰ (article in German)
Curcumin	UC and CD	10	Open	-	12 weeks	Not stated, but 9/10 patients improved	-	Holt <i>et al.</i> ³²
Acupuncture with moxibustion	CD	51	Randomized, single-blind, controlled	Sham acupuncture	10 sessions over 4 weeks	41	33	Joos <i>et al.</i> ³³
Acupuncture with moxibustion	UC	62	Comparative	Sulfasalazine	Not stated	62	33	Yang and Yan ³⁴
Bovine colostrum enemas	UC	14	Randomized, double-blind, placebo-controlled	Placebo	4 weeks	Not stated, but colostrum improved symptoms and histology more than placebo	Not stated	Khan <i>et al.</i> ³⁵

CD, Crohn's disease; CDAL, Crohn's Disease Activity Index; RSF-FS, 'Radix sophorae flavescens' and 'Flos sophorae'; UC, ulcerative colitis; IBD, inflammatory bowel disease; CAM, complementary and alternative medicine.

contained small numbers of patients and are underpowered. There is also likely to have been bias introduced by failure to publish negative trials. Finally, trials published in languages other than English are not always easy to obtain or interpret.

REVIEW OF THE LITERATURE OF EFFICACY OF CAM IN IBD

The literature review below was compiled using a systematic search of Medline database 1966–2005. Reports published either in English or with English abstracts available were used. Search headings and key words used were combinations of complementary, alternative, herbal, acupuncture, hypnosis, hypnotherapy, reflexology, aromatherapy, remedies, homeopathy, osteopathy, chiropractic, naturopathy, traditional Chinese medicine, prayer, and IBD, colitis, Crohn's, UC or proctitis. The review is restricted to human studies.

HERBAL THERAPIES

Traditional Chinese medicine

Although there are numerous reports in the Chinese literature about the treatment of UC with herbal remedies, often only the abstracts are available in English.

In a RCT, 153 patients with UC were given either Jian Pi Ling tablets and 'Radix sophorae flavescens' and 'Flos sophorae' (RSF-FS) decoction enemas, conventional treatment with oral 5-aminosalicylic acid (5-ASA) and prednisolone enemas, or oral placebo and RSF-FS enemas.²⁰ Remission rates in the first group were reported to be significantly higher (53%) than in the other two (28% and 19% respectively), but the very low success rate of conventional therapy makes this study hard to interpret.

In another study, the traditional Chinese remedy, Kui jie qing (KJQ) was given as a four times daily enema to 95 patients with active UC.²¹ Eleven patients given sulfasalazine (sulphasalazine) 1.5 g three times daily, oral prednisolone 30 mg daily and prednisolone enemas 20 mg four times daily for 20 days were used as controls. Effective 'cure' was reported in 72% of KJQ-treated patients but in only 9% of controls ($P < 0.001$). A further 23% of patients using KJQ enemas improved compared with 53% of the controls, leading the authors to conclude a 95% effectiveness rate for KJQ, as against 62% for conventional western treatment. This study does not provide definitions for

'cure' or 'improvement' but the conventionally treated patients had less good response rate than would usually be expected.

In a similar trial, 118 patients with active UC were treated with Yukui tang ('decoction for ulcer healing') orally and herbal decoction enemas, plus oral prednisolone 15 mg daily, neomycin and vitamin B for 40 days.²² The overall effectiveness rate was 84% for the herbal therapy group (33% 'cured', 51% improved) and 60% for 86 control patients (17% 'cured', 43% improved; $P < 0.01$) who were given a low dose of prednisolone (15 mg), neomycin and vitamin B only.

Interpretation of the results of these comparative studies is compromised by a lack of randomization and blinding, and the rather unusual combinations of the 'conventional' therapies used in the comparator groups.

Other herbal therapies

A randomized, double-blind, controlled study showed that aloe vera gel, given for 4 weeks to patients with moderately active UC, produced a clinical response in significantly more patients than did placebo. Clinical remission, improvement and response occurred in nine (30%), 11 (37%) and 14 (47%), respectively, of 30 patients given *Aloe vera*, compared with one (7%), one (7%) two (14%; $P < 0.05$), respectively, of 14 patients taking placebo (using a 2:1 *A. vera*:placebo randomization schedule). The Simple Clinical Colitis Activity Index and histological scores decreased significantly during treatment with *A. vera* but not with placebo.²³

In a randomized, double-blind, controlled trial, 23 patients with active distal UC were given oral wheat grass juice or placebo for 4 weeks.²⁴ Treatment with wheat grass juice was associated with greater reductions in a composite clinical disease activity index, in the severity of rectal bleeding and in the doctor's global assessment than occurred in the placebo group. No side-effects were reported.

Two open-label Japanese trials suggested efficacy in UC for a germinated barley foodstuff (GBF), which consists mainly of dietary fibre and glutamine-rich protein, and which the authors believe to act primarily as a prebiotic.^{25, 26} In the first report, 11 patients given GBF for 4 weeks as adjunctive treatment showed a greater fall in clinical disease activity than nine patients given conventional therapy alone. In a follow-up study, 24 weeks of treatment of 21 patients with GBF together with continuing 5-ASA and steroid

therapy reduced rectal bleeding and nocturnal diarrhoea. Adjunctive GBF also produced a lower relapse rate over 12 months when given to 22 patients with UC in remission than did conventional therapy in 37 such patients.²⁷ GBF was well tolerated and appeared to be safe in all three reports.

Boswellia serrata ('frankincense') is a traditional Ayurvedic remedy and a component of incense. In India, the effect of the gum resin from *B. serrata* in moderately active UC was compared with sulfasalazine: remission rate in the *Boswellia* group (82%) resembled that occurring in patients given conventional therapy (75%).²⁸ The same authors reported a similar study in 2001 resulting in a 70% remission rate in 20 patients taking *Boswellia* for 6 weeks compared with 40% in 10 on sulfasalazine.²⁹ In a randomized, double-blind, controlled 8 week trial, the *B. serrata* extract, H15, was compared with mesalazine for active Crohn's disease.³⁰ The study included 102 patients and was powered to show non-inferiority. The mean Crohn's Disease Activity Index (CDAI) fell in both groups and H15 was well tolerated. This result was interpreted by the authors as evidence for efficacy of H15 in treatment of active Crohn's disease but the clinical remission rates on both therapies, as in previous trials with 5-ASA preparations,³¹ were only moderate.³⁰

Curcumin is the yellow pigment of turmeric (*Curcuma longa*), a major ingredient of curry: in animal and *in vitro* studies it has a range of anti-inflammatory effects. In a recent pilot study, curcumin, when given orally, was reported to benefit five patients with proctitis and five with Crohn's disease.³²

OTHER CAM MODALITIES

Acupuncture and moxibustion

In a single-blind controlled trial of 51 patients with mild to moderately active Crohn's disease, acupuncture and moxibustion (in which heat is added by burning herbs over the acupuncture site) reduced CDAI and α -1 acid glycoprotein, and improved general well being. CDAI fell to a significantly greater degree (87 points) than occurred in the control group in whom needles were inserted into non-acupuncture points (39 points; $P = 0.003$), but there was no difference in the remission rates achieved in the two groups.³³ Furthermore, a comparative study from China suggested that acupuncture with moxibustion was as effective as conventional western therapy in 62 patients with UC.³⁴

Bovine colostrum

Bovine colostrum has a range of potentially beneficial constituents which include immunoglobulins and growth factors. Fourteen patients with mild to moderately severe distal colitis, received colostrum enemas (100 mL of 10% solution) or placebo (albumin solution) twice daily for 4 weeks. Both groups also received mesalazine (1.6 g/day) or, if already taking it, had a dose increment of 1.6 g/day. After 4 weeks, the colostrum group showed a mean reduction in symptom score of -2.9 [95% confidence interval (CI): -5.4 to -0.3], whereas the placebo group showed a mean response of $+0.5$ (95% CI: -2.4 to $+3.4$). The histological score improved in five of the eight patients in the colostrum group.³⁵

POSSIBLE MODES OF ACTION OF CAM

One barrier to the acceptance of CAM by conventional doctors has been the apparent lack of any scientific explanation for their possible efficacy. Indeed, types of CAM such as acupuncture have been based on historical and cultural constructs entirely unfamiliar to the majority of western clinicians. Recently, however, mechanisms by which some of these modalities may work have become apparent.

Herbal therapies

Unpurified herbal preparations contain a huge range of biologically active compounds,³⁶ some of which may have beneficial and others adverse effects. Extensive work of varying quality, clinical relevance and accessibility has suggested that, *in vitro* at least, individual chemicals derived from a variety of plants may have antibacterial, antioxidant, anticytokine, antispasmodic and neuromodulatory actions.³⁶ *In vivo*, the polysaccharide content of plant preparations means that they may also act as prebiotics.³⁷ It is clearly difficult, however, to extrapolate from a knowledge of the chemical composition and activities *in vitro* of an extract from a given plant to its possible efficacy (or safety) *in vivo*. This will depend on a number of factors including the amounts of individual constituents in the extract (which may vary with the plant's geographical origin and the method of preparation of the extract), interactions between individual constituents, and their pharmacokinetics, of which little is known in most instances.

Physical therapies

It is now clear from the emerging field of psychoneuroimmunology that neuronal connections between the brain and the enteric nervous system, and in turn with immune and inflammatory cells in the lamina propria, could mediate any anti-inflammatory gastrointestinal effects of modalities such as acupuncture and hypnotherapy.³⁸ Indeed in the latter context, recent work has shown that a 45-min period of gut-directed hypnotherapy (unlike a rest period of the same duration) reduces serum interleukin (IL)-6 concentration and rectal mucosal production of substance P and IL-13 (J. E. Mawdsley, M. Macey, L. Langmead, 2005, unpublished data).

Placebo response

It has been suggested that the clinical response to CAM relates largely to its placebo effect³⁹ and that placebo responses to alternative remedies will be high in individuals strongly committed to the concept that such therapy will work.⁴⁰ Discussion of the mechanism of the placebo effect and the extent to which it related to the quality of the therapist⁴¹ is beyond the scope of this review.

SIDE-EFFECTS OF CAM

Direct toxicity

Contrary to the widely held popular view that because it is 'natural' it is safe, herbal therapy is likely to carry more risks and produce more serious side-effects than any other forms of alternative therapy.^{4, 42} Indeed toxicity from herbal therapies has included fatal liver and renal failure.^{36, 43} Unfortunately, there are limited formal data on the incidence even of acute severe side-effects such as these, and knowledge of possible longer term sequelae such as mutagenicity and carcinogenicity is still more scanty.

Toxic effects have also been associated with the deliberate inclusion of prescription medicines in some herbal preparations: these have included corticosteroids, fenfluramine and glibenclamide.⁴⁴ Other toxic products found in some preparations have included mercury, arsenic, lead, human placenta (with a risk of transmitting hepatitis C or HIV) and bat excreta.

Reports of injuries during manipulative therapies such as osteopathy are infrequent. Injuries from acu-

puncture needles such as pneumothorax are also seldom reported, but hepatitis B and C have occurred,⁴⁵ and in one notorious incident in 1998, contaminated blood led to a major outbreak of hepatitis B in patients treated in north London by a variant of acupuncture known as autohaemotherapy.⁴⁶

Drug interactions

The interaction of herbal therapies with conventional drugs needs further clarification. In the context of UC; however, St John's Wort reduces blood levels of ciclosporin by enhancing the activity of cytochrome P450 enzymes.³⁶ Indeed, in a systematic review, 17 studies reported a decrease in systemic bioavailability of conventional drugs when used in conjunction with St John's Wort.⁴⁷

Indirect adverse effects

Perhaps more importantly than direct toxicity or drug interactions, use of CAM may be complicated by indirect adverse effects. For example, patients with IBD initially consulting alternative practitioners may be wrongly diagnosed, for example, with irritable bowel syndrome. Others may delay or forego appropriate conventional options in favour of ineffective unconventional ones; this may lead to late presentation to a gastroenterologist with severe or complicated IBD.

REGULATION

At present, the frequency with which adverse responses to CAM are reported to the World Health Organization's monitoring centre is small compared with that of conventional drugs.^{48, 49} A mandatory national systematic reporting scheme for the collection of adverse responses to herbs has been considered desirable for some years.^{4, 50}

In response to a report from a House of Lords Select Committee⁵¹ and a Department of Health (DoH) Consultation Document published in 2003, a number of new measures to regulate complementary medicine have been developed in the UK. The DoH will provide funding over the next 3 years to the Prince of Wales's Foundation for Integrated Health to develop robust systems for the regulation of the main complementary healthcare professionals.

A new Herbal Medicines Advisory Committee is proposed to advise ministers directly on the safety and

quality of herbal medicines.⁵² The regulatory framework will require descriptions of Good Agricultural Practice, Good Laboratory Practice, Good Manufacturing Practice and Good Clinical Practice. Analytical techniques which provide reproducible fingerprinting used to verify the chemical components of products should help prevent adulteration of products, either by similar but toxic plant species such as *Aristolochia*, or by chemicals such as heavy metals or steroids.

With regard to efficacy, the recommendations are less stringent. The EU Traditional Use Directive¹⁹ suggests that evidence of 30 years' use, of which 15 years must be in the Community, provides confirmation of efficacy. For many, it is difficult to accept the logic of this approach, which of course contrasts strongly with that taken for conventional drugs: it appears that decisions about efficacy of many herbal remedies will be based on tradition and even folklore⁵² rather than rigorous clinical trials.

CONCLUSIONS

Up to 50% of patients with IBD have tried some form of CAM. Although there is a wide range of therapies available, there is a lack of reliable data about the efficacy and safety of most remedies. This is in part a consequence of the problems associated with designing and funding clinical trials involving CAM modalities. As patients with IBD are increasingly resorting to alternative and complementary therapies, it is imperative that efforts are accelerated to assess their therapeutic efficacy and safety, and to regulate more closely their quality and marketing. Lastly, further education of doctors and other healthcare workers about the potential benefits and dangers of CAM is essential if we are to give well-informed advice to patients who are considering or already using CAM for their IBD.

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