

THE ROLE OF COMPLEMENTARY AND ALTERNATIVE MEDICINES

in managing chronic bowel conditions

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Inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) are considered to be chronic bowel conditions. IBS is the most common gastrointestinal (GI) condition, affecting approximately 11 per cent of the global population. IBD, which affects an estimated five million people globally, occurs in two forms – ulcerative colitis (UC) and Crohn’s disease (CD) – that are characterised by relapsing and remitting inflammation of the GI tract. In contrast, IBS is described as a functional GI disorder that lacks structural and biochemical abnormalities. The symptoms of IBD are variable and may include diarrhoea, vomiting, pain, weight loss and malnutrition; while IBS patients suffer from the persistent symptoms of bloating, pain and chronic diarrhoea or constipation.

The quality of life of individuals with IBD and IBS is severely impaired. Recent surveys have found that IBS patients would be willing to give up 25 per cent of their remaining life (approximately 15 years) to live symptom free, and 14 per cent of respondents say they would risk a one in 1000 chance of death to live symptom free. While the personal impact is unmistakable, there is also a significant effect on the wider community through loss of productivity and reduced performance at work. The cost of IBS to society in terms of direct medical costs and work absenteeism is in excess of \$21 billion annually. For IBD, the total annual financial burden in the United States alone was estimated to be \$15–\$32 billion in 2014.

Understanding chronic bowel conditions

The causative factors of IBD and IBS are still not fully understood, but genetic predisposition and environmental risk factors appear central to the development of these chronic bowel conditions. When exploring the pathophysiological mechanisms of IBD and IBS, three common factors emerge:

1. **Increased intestinal permeability:** In a healthy individual, the intestinal epithelium is a dynamic

cellular layer that serves as a barrier between the contents of the GI tract and the underlying immune system, while simultaneously supporting water, nutrient and ion transport. A wide variety of factors, such as microbial dysbiosis, alcohol consumption, strenuous exercise, systemic inflammation, nutrient deficiencies and medications like antibiotics can irritate the gut, resulting in a loss of the integrity of the gut lining, often referred to as ‘leaky gut’. Individuals with leaky gut can have increased circulating levels of proinflammatory proteins and endotoxins, which have been directly linked to IBS and IBD.

2. **Inflammation:** IBD is recognised as a chronic inflammatory condition, but until recently, IBS was thought to be a non-inflammatory disorder. Current evidence shows that low levels of inflammation are present in IBS, with exacerbated inflammation in a subset of patients with IBS-D (irritable bowel syndrome – diarrhoea dominant), highlighting that inflammation may also play a role in the pathogenesis of IBS.
3. **Dysbiosis of the microbiome:** The intestinal tract is home to the gut microbiota, which comprises tens of trillions of microorganisms. Intestinal microbiota play a critical role in numerous physiological functions, such as the maturation and continued education of the host immune response, protection against pathogen overgrowth, regulation of intestinal endocrine functions and as a source of energy biogenesis. Current hypotheses propose that, in genetically susceptible individuals, various factors trigger an increase in gut permeability or mucosal inflammation, which acts on the gut microbiota, favouring the expansion of opportunistic pro-inflammatory microbes. Microbial gene products from the dysbiotic gut communities promote local or systemic morphologic and functional changes that result in disease. Although it can adapt to change, an appropriate host-microbiota balance

must be maintained to guarantee the protective, structural and metabolic effects of the microbiota, both systemically and within the gut. Extensive research has identified a direct correlation between a dysbiotic gut and the development of both IBD and IBS.

The role of complementary and alternative medicines in the treatment of IBD and IBS

Current treatment options for IBS and IBD are limited due to the complex pathophysiology of these conditions. IBD pharmaceutical treatments are targeted at reducing chronic inflammation, and IBS therapies are targeted towards the management of

the symptoms of pain or altered bowel habits. Short-circuiting the shared underlying causes of IBD and IBS would ultimately require a therapeutic approach that addresses the key disease components of microbial dysbiosis, leaky gut and inflammation.

Current pharmaceutical treatments have high failure rates and severe side effects, leading to more than 50 per cent of IBS and IBD patients trying complementary and alternative medicines (CAMs) in the hope of effectively managing their chronic bowel condition. If a non-conventional practice is used in combination with a pharmaceutical, it is classified as a complementary medicine, but if a non-conventional practice is used in

Therapy	Bowel condition	Target pathophysiology		
		Microbiome Repair	Inflammation	Reduces intestinal permeability
Pharmaceutical treatments				
5-Aminosalicylic acid	IBD			
Corticosteroids	IBD			
Immunomodulators	IBD			
Anti-TNF antibody	IBD			
Antibiotics	IBS & IBD			
PEG, secretagogue, 5-HT4 receptor agonists	IBS-C			
Loperamide, 5-HT3 antagonist, bile acid sequestrant, mixed opioid agonist/antagonist	IBS-D			
Antispasmodic, antidepressant (tricyclic antidepressant, SSRI)	IBS			
	IBD			
Complementary Medicines*				
Cannabis	CD			
Curcumin	UC			
Herbal: Powder of daikenchuto, Zingiberis	CD			
Herbal: Artemisia absinthium	CD			
Herbal: Andrographis paniculate Extract	CD			
Herbal: Holarrhena antidysenterica	CD			
Alternative Medicines				
Exercise	IBS			
	IBD			
Diet-increased fiber	CD			
Diet: semi-vegetarian	CD			
Diet: IBD-AID	CD			
Psychological therapy	IBS			
	IBD			
Moxibustion and acupuncture	IBD			
Fecal microbiota transplantation	IBD			
Prebiotics: Low dose	IBS			
Cannabis	CD			
Curcumin	UC			
Punica granatum peel extract	CD			
Wheat grass juice	CD			
Vitamin D3	CD & IBS			
Vitamins B12, E, C	CD			
Herbal extract: Iberogast	IBS			
Probiotics: VSL#3	UC & IBS			

No effect or unknown Strong effect

Figure 1. The effectiveness of pharmaceutical, complementary and alternative medicines in treating the common pathophysiologies of IBD and IBS. The strengths of each therapy are presented in the heat-map as colour intensity (ranging from light yellow, which demonstrated no efficacy or has not been determined [0 per cent], to dark green for more than 70 per cent efficacy). * Non-conventional practice used in combination with a pharmaceutical treatment

place of the conventional medicine it is considered an alternative medicine. As many patients perceive the risk/benefit of CAMs to be favourable, they are willing to spend significant amounts of money on CAMs. In 2018, expenditure on gastrointestinal supplements and over-the-counter digestive remedies was US\$8 billion in the United States alone, with the use of over-the-counter digestive remedies having increased by 12 per cent over the previous five years. Between 2012 and 2018, there were 4104 digestive health products launched globally, with the United States and India presenting as the top markets.

Pre-marketing regulatory requirements for CAMs are low and the primary focus is placed on safety instead of efficacy. Therefore, very few products have conclusive scientific or clinical proof of efficacy. To fully understand the therapeutic potential of currently available products to concomitantly treat the common IBD and IBS pathophysiologies, an extensive review of clinical studies was conducted, with the findings summarised in Figure 1.

The data presented in Figure 1 is a summary of more than 300 peer-reviewed publications, where the inclusion criteria was demonstrating a statistically significant benefit in randomised, controlled clinical trials.

This analysis clearly demonstrates that there is a severe, unmet clinical need for products that can treat inflammation, increased intestinal permeability and microbial dysbiosis. Antibiotics were able to provide significant benefit; however, antibiotic side effects and bacterial resistance precludes their long-term use. While Iberogast and VSL probiotic have demonstrated some efficacy in IBS and UC, there remains a need for a product that addresses the underlying causes of these chronic bowel conditions.

GI-reprogramming CAM shows promise

Having recognised the unmet medical need in chronic bowel conditions, Anantara Lifesciences has been developing a proprietary regenerative, multi-component dietary supplement that is specifically designed to address the three common pathophysiologies of IBD and IBS. This product is known as the Gastrointestinal ReProgramming (GaRP) product, and, unlike other CAMs commonly marketed, GaRP selectively targets specific formulation components to the small intestine and colon where they can exert their greatest therapeutic effect.

Human *in-vitro* gut proof-of-concept studies demonstrated that Anantara's GaRP dietary supplement was highly efficacious and, with further development, may be a breakthrough complementary medicine. The GaRP CAM addressed the dysbiosis of the microbiome by inhibiting the attachment and invasion of pro-inflammatory bacteria (obtained from IBD and IBS patients) into healthy gut cells by more than 95 per cent. The level of inflammation commonly observed in IBD and IBS-D patients was reduced by 85 per cent by significantly reducing the production of pro-inflammatory proteins. By addressing both the microbiome imbalance and the inflammation, specifically selected GaRP components were able to accelerate the regeneration of the mucosal layer, which restored gut integrity (see Figure 2). The therapeutic effect of GaRP is currently being confirmed in a mouse model of moderate IBD and severe IBS, Anantara has the objective of taking this CAM into a human clinical trial to demonstrate its ability to induce and maintain remission in patients suffering from chronic bowel disorders. 🌱

* Non-conventional practice used in combination with a pharmaceutical treatment

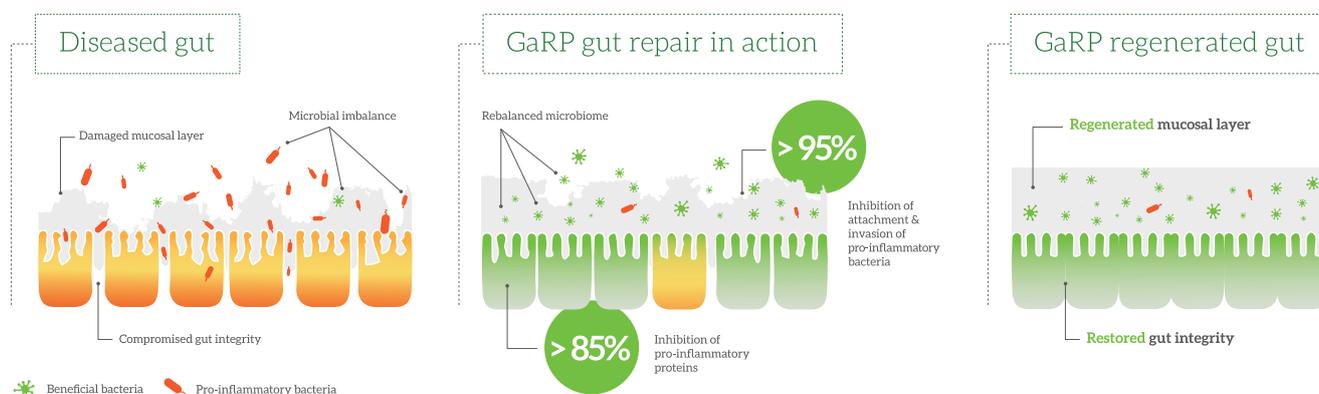


Figure 2: Diagrammatic representation of the mechanism of action of Anantara's GaRP CAM and its ability to collectively overcome the common underlying causes of chronic bowel conditions