The role of dietary supplements in inflammatory bowel disease: a systematic review

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Inflammatory bowel diseases (IBD) are chronic immune disorders of unclear aetiology. Dietary deficiencies may be a potential pathogenic factor in their development. Patients often take food supplements without knowledge of any evidence base. We have therefore assessed the evidence for food supplementation in the management of IBD. A PubMed search was performed for the terms Inflammatory bowel disease; nutritional deficiencies; dietary supplements; curcumin; green tea; vitamin D/other vitamins; folic acid; iron; zinc; probiotics; andrographis paniculata; and boswellia serrate. PubMed was used to search for all relevant articles published between January 1975 and September 2015. Curcumin supplementation has been reported to be effective in reducing the symptoms and the inflammatory indices in IBD patients. Similar results have been observed for green tea; however, pertinent studies are limited. Vitamin D supplementation may help to increase bone mineral density in IBD patients and to reduce disease activity. IBD patients with ileal resections higher than 20 cm may develop vitamin B_{12} deficiency that requires parenteral supplementation. There is no current evidence to support fat-soluble vitamin supplementation in IBD patients. Zinc and iron should be supplemented in selected cases. Probiotics (VSL#3) may reduce disease activity in IBD patients with pouchitis. Complementary and alternative medicines are used by IBD patients and some studies have shown promising results. In summary, attention to dietary factors such as curcumin, green tea and vitamins, including vitamins D and B_{12}, appears to be beneficial and, if necessary, supplementation may be appropriate. Eur J Gastroenterol Hepatol 28:1357–1364
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Introduction

Inflammatory bowel disease (IBD) is a heterogeneous group of chronic immune disorders of unclear aetiology, which mainly includes Crohn's disease (CD) and ulcerative colitis (UC), the former involving any part of the gastrointestinal tract and the latter involving only the large intestine. The pathogenesis of IBD is complex and involves genetic and environmental factors. A number of environmental risk factors have been explored, including smoking, appendectomy, oral contraceptives, diet, breastfeeding, infections/vaccinations, antibiotics and childhood hygiene; however, most of these factors have shown inconsistent findings so far. Notably, diet has been implicated as a potential pathogenic factor. The 'Western diet' (i.e. processed and highly refined sugars and fats) has been considered to be partially responsible for the increasing incidence of IBD [1–3]. In patients with IBD, both deficiencies of macronutrients and, more often, deficits of specific micronutrients have been described.

The main symptoms during flare-ups of IBD are diarrhoea, abdominal pain and possibly weight loss. Such flares are generally managed by anti-inflammatory drugs, for example, the 5-aminosalicylic (5-ASA) class, immunosuppressants (such as steroids, azathioprine, cyclosporine and methotrexate) and antitumour necrosis factor (TNF) agents. Recently, probiotics have been used particularly for the subset of patients with pouchitis. The high cost and the rate of adverse effects associated with drugs and frequent relapse have promoted the use of alternative options and many patients will take supplements of their own accord without any evidence base.

On the basis of the above considerations, the present review was aimed at elucidating the possible role of food supplements in the management of IBD, focusing both on supplementation of patients who show nutritional deficiencies and on the administration of pharmacological doses of food supplements with potential therapeutic effects.

Methods

A bibliographical search was performed in PubMed for the Mesh terms inflammatory bowel disease; nutritional deficiencies; diet; dietary supplements; curcumin; green tea; vitamin D; folic acid; iron; zinc; probiotics; andrographis paniculata; and boswellia serrate and free text searches (alternative and complementary medicine). PubMed was used to search for all relevant articles published from January 1975 to September 2015. Reference lists from studies selected by the electronic search were searched manually to identify further relevant reports. Reference lists from all available review articles, primary studies and
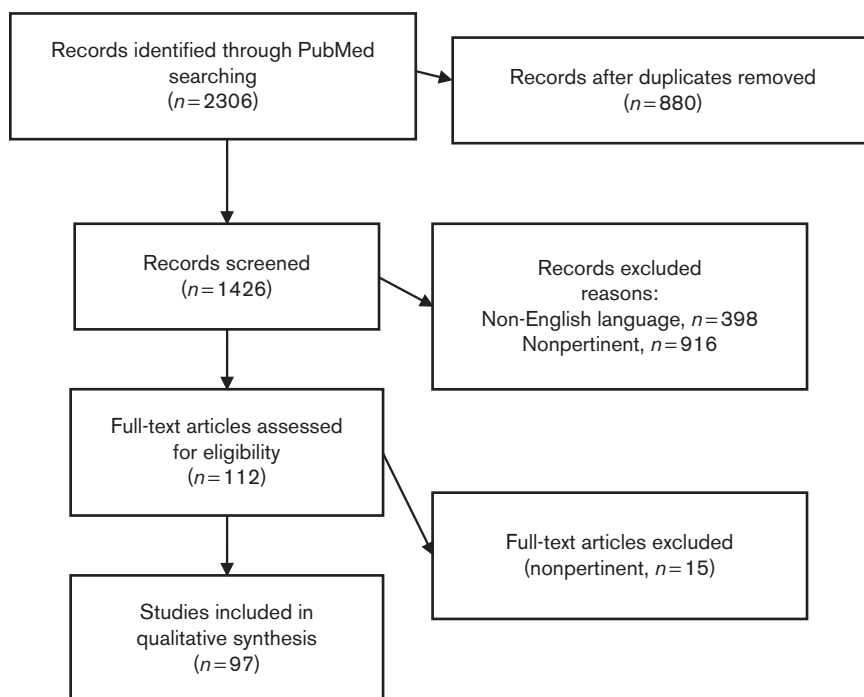
Fig. 1. Flow diagram of the studies included.

proceedings of major meetings were also considered. Articles published as abstracts were included, whereas non-English language papers were excluded. The quality and strength level of the results were considered. For each nutrient, botanical extract or probiotic bacteria, we excluded most in-vitro and animal studies unless specifically relevant to the human conditions and we focused the review on meta-analyses and systematic reviews, large epidemiological studies and, where available, randomized-controlled trials. Information on clinical trials was sourced from the URL: *http://clinicaltrials.gov/*. A total of 2306 records were reviewed and 97 were defined as fulfilling the criteria for final consideration. Fig. 1 presents the flow chart showing the process of study selection.

Results

Curcumin

Curcumin, a bright yellow polyphenol extract from the Indian spice turmeric, has been used in various gastrointestinal disorders and studied for its anti-inflammatory effects [4]. Curcumin has been reported to attenuate inflammatory responses by inhibiting cyclooxygenase-2, lipoxygenase, nuclear factor (NF)-κB, inducible nitric oxide interferon-γ-activated or TNF-α-activated macrophages and natural killer cells [5–7]; as a result, it has been considered alone or in combination with standard medications in the management of IBD. Recently, curcumin has been reported to reduce inappropriate epithelial cell transport and increase anti-inflammatory cytokines, thus reducing inflammation associated with IBD [8].

In a recent series including a pilot study of 10 IBD patients, five UC patients receiving curcumin 1000–1600 mg daily showed a significant reduction in both the symptoms and the inflammatory indices. Of five

CD patients consuming 360 mg three or four times per day, four patients showed a reduction in both the CD activity index (CDAI) and symptomatic parameters [9]. Again, benefit has been reported in UC associated with enteropathic arthropathy [10]. In a randomized-controlled trial on 89 UC patients, the addition of 2 g/day of curcumin to standard therapy significantly reduced risk relapse (4.65 vs. 20.51%) and improved clinical activity and endoscopic indices after 6 months. In detail, 45 patients received curcumin, 1 g after breakfast and 1 g after the evening meal, plus sulphasalazine or mesalamine, and 44 patients received placebo plus sulphasalazine or mesalamine for 6 months [11]. In a recent series aimed at assessing the effect of curcumin on the levels of enzymes and signalling proteins that stimulate immune responses in the gut of children and adults with IBD, a suppression of unwanted immune response and enhancement in beneficial immune response were reported [12]. Moreover, the most recent placebo-controlled, double-blind randomized study in UC showed that the addition of 3 g curcumin to mesalamine therapy was superior to the combination of placebo and mesalamine in inducing clinical and endoscopic remission in patients with mild-to-moderate active UC after 1 month, with no apparent adverse effects [13]. Conversely, a recent randomized, double-blind, single-centre pilot trial was conducted in patients with distal UC (< 25 cm involvement) and mild-to-moderate disease activity. Forty-five patients were randomized to either NCB-02 (standardized curcumin preparation) enema plus oral 5-ASA or placebo enema plus oral 5-ASA. Although the outcome difference was not statistically significant on intention-to-treat analysis, there was a trend towards better outcomes in the NCB-02 group, which highlights the need for further investigations on this novel promising therapy for IBD patients [14].

Summary: Curcumin supplementation shows effectiveness in reducing both the symptoms and the inflammatory indices in IBD patients, with no apparent side effects, although further studies are needed to draw more definitive conclusions.

Green tea

Green tea is a popular drink containing polyphenolic compounds, constituted mainly from (–)-epigallocatechin gallate (EGCG), which is the most potent antioxidant compound, as well as other polyphenolic catechins including (–)-epicatechin (EC), (–)-epigallocatechin and (–)-epicatechin-3-gallate [15].

In-vitro studies have reported that EGCG could downregulate the inflammatory response in inflamed intestinal epithelial cells (by a pathway largely implicating a posttranscriptional regulatory mechanism) and could lead to a decrease in the interleukin (IL)-6 and IL-8 oversecretion by 50 and 60%, respectively [16]. EGCG's immunosuppressive properties can block STAT1-dependent events in gut epithelia and monocytes and prevent interferon-γ-induced increased epithelial permeability [17].

In animal models, polyphenols from green tea have been reported to inhibit inflammatory responses by downregulating cyclooxygenase and Bcl-2 activity, and inhibiting κβ kinase activity in the intestinal epithelial cell line IEC-6 [15,18–21].

A recent randomized double-blinded, placebo-controlled pilot trial in patients with mild-to-moderate UC showed a significant decrease in the activity index (67% green tea vs. 0% decrease in placebo) as well as clinical index (53% green tea vs. 0% placebo) by taking 400 or 800 mg of total EGCG daily for 56 days [22]. However, this trial was small (19 patients – 15 active treatment, four placebo), with a placebo arm of three patients and another who withdrew. This may explain the unusual low response rate in the placebo group. Furthermore, in the same study, half of the patients in the active treatment arm were taking azathioprine for at least 8 weeks, whereas none of the patients included in the placebo group was taking azathioprine, which may have also influenced the results.

Summary: Green tea extract could be promising in inducing remission in IBD patients, although further studies are needed.

Vitamin D

Although sunlight is commonly considered the most important source of this essential nutrient, whose deficiency is common, dietary and supplementary intake is now receiving more attention.

Epidemiological evidence shows higher incidence and prevalence of IBD in temperate climates and lower risk in individuals living near the equator [23–29]. Other environmental, behavioural or genetic factors associated with geographical location may contribute towards the association between sun exposure and IBD [24]. Higher 25-OH vitamin D plasma levels in the Nurses' Health Study were also shown to be associated with a lower incidence of CD and UC [30]. Optimizing vitamin D levels is important [26,27,29], especially as low vitamin D levels have also been associated with longer disease duration [26,28]. Disease severity may also impact on vitamin D status as suggested by one series in which intestinal resection, a stricturing disease phenotype, the need for oral corticosteroids within 3 months from diagnosis and a diagnosis of pancolitis in UC were more prevalent in severely vitamin D-deficient patients (< 25 nmol/l) compared with those with higher values (> 50 nmol/l) [12]. In addition, the prevalence of at least one intestinal resection was significantly higher in those with vitamin D deficiency than those with adequate levels ($P < 0.05$) [29].

The role of ethnicity as a risk factor for vitamin D deficiency in IBD has also been examined, vitamin D levels often being lower in non-Caucasians [27,29,31]. Other risk factors for lower vitamin D levels may include decreased nutritional intake because of anorexia associated with CD [27,32], fear of gastrointestinal discomfort from dairy because of lactose intolerance and active disease responsible for decreased physical activity resulting in reduced sun exposure [27]. Genetic variations in the vitamin D receptors and binding protein have been shown to be associated with an increased risk of IBD [33,34].

In addition to more active disease as vitamin D levels decrease [32,34–36], patients with vitamin D deficiency appeared to have a more aggressive disease course, with 14% of deficient patients requiring surgical management [37]. However, an association between low vitamin D levels and increased disease activity in IBD patients has been challenged by other series [38].

In animal models, supplementation of vitamin D_3 improves colitis by upregulation of anti-inflammatory IL-10 production [39]. Preclinical models also showed that vitamin D and its receptors play an important role in maintaining gut integrity and protecting the intestine from pathogenic enteric bacterial infection, with vitamin D suppressing bacterial-induced NF-κβ activity. Intestinal vitamin D receptors have also been reported to protect against bacterial infection by abrogating proinflammatory IL-6 and IL-17 pathways [40,41].

In a randomized double-blind placebo-controlled multicentre study, the benefits of vitamin D_3 treatment were assessed in patients with inactive CD. During a 1-year follow-up, serum $25(OH)D_3$ levels increased significantly, but only marginally from 27 to 38 ng/ml in those supplemented without concomitant change in free serum calcium, and there was no effect on relapse rate [42].

Notably, some authors reported that when higher doses of vitamin D were used (up to a maximum of 5000 IU), achieving a serum concentration of 40 ng/ml of $25(OH)D_3$, a significant reduction in CDAI and an improvement in the IBD questionnaire score were observed [40].

Optimizing vitamin D is relevant not only for therapeutic response but also in reducing relapse as reported by Zator *et al.* [43], who noted a significant association between earlier failure of anti-TNF therapy in IBD patients with insufficient vitamin D levels before initiation of anti-TNF therapy. Such findings support the relevance of both correcting and maintaining adequate vitamin D levels in IBD patients, specifically above 30 ng/ml (75 nmol/l), to reduce the risk of flares and to maintain response to IBD-targeted medical regimens [43,44]. Pertinent data were derived from a randomized placebo-controlled study in which oral vitamin D supplementation of 1200 IU in adult patients with CD in remission was shown to both increase

the serum 25-OH vitamin D levels and reduce the risk of relapse from 29 to 13% at 1 year ($P = 0.06$) [45]. Moreover, the active form of vitamin D (1,25-OH vitamin D) treatment resulted in a significant decrease in CDAI scores and C-reactive protein (CRP) levels, as well as improvement in quality-of-life scores, compared with the 25-OH vitamin form [46]. In another study, patients received an initial dose of 1000 IU/day of vitamin D_3 and the dose increased every 2 weeks by 1000 IU until serum $25(OH)D_3$ levels were above 40 ng/ml (100 nmol/l). At 24 weeks, 78% of patients achieved clinical response defined by a decreased CDAI score of 70 points or more and 67% of patients were in remission, with a significant improvement in disease-specific quality of life [47].

Summary: Vitamin D_3 is important for its associated effects in the reduction of IBD but also therapeutic levels are associated with response to therapy and reduced relapse.

Other vitamin and nutritional deficiency

IBD may predispose the patient to vitamin B_{12} deficiency through several mechanisms including ileal disease or resection, fistula formation, small bowel bacterial overgrowth, reduced alimentary intake, increased physiologic requirements, protein-losing enteropathy and hepatic dysfunction [48]. CD patients are at a higher risk of developing vitamin B_{12} deficiency as one-third to half of the patients have isolated ileal disease and 30–55% have ileocolonic disease [48]. Despite the above considerations, a recent systematic review showed that CD, irrespective of ileal involvement, is not associated with vitamin B_{12} deficiency as only ileal resections greater than 20 cm in CD predispose to deficiency and warrant treatment, which is usually life-long and administered parenterally. Further studies are needed to confirm these findings [49].

Folate deficiency should also be taken into account as it affects 20–60% of IBD patients. Risk factors for deficiency include active disease and sulphasalazine or methotrexate treatment [50,51]. European Crohn's and Colitis Organisation guidelines recommend measuring folate level at least annually or if macrocytosis is present in the absence of thiopurine use and its supplementation is generally recommended [52].

CD patients with terminal ileum disease or ileal resection may also experience fat-soluble vitamin (i.e. A, D, E, and K) deficiencies as a consequence of bile acid and fat malabsorption. However, supplementation with fat-soluble vitamins has not been recommended routinely for IBD patients often because of lack of awareness or lack of testing for vitamin concentrations. One also has to consider that supplementation, if not checked, can be associated with toxicity, for example, vitamin A supplementation may be associated with bone and liver toxicity [53]. It is important to note that supplementation can result in different concentrations of vitamin and potential for toxicity depending on whether it has been administered for example as a combination of tocopherols or as single vitamin E or in the form of carotenoids as a natural β-carotene or a single vitamin A supplement.

Among IBD patients, a deficit of antioxidant agents including ascorbic acid, β-carotene and vitamin E has been observed, even if the actual clinical implications of these deficiencies and the benefits of supplementation are not fully understood. In addition, supplementation of vitamin E has been reported to be potentially responsible for an increase in the all-cause mortality rate, which therefore discourages the indiscriminate use of supplements with high antioxidant content [54].

Zinc deficiency has been described in about 15% of patients with IBD [55]. Recently, zinc deficiency was shown to be correlated with inflammation in IBD. Moreover, zinc was previously found to be related to the inflammatory process by improving the transmucosal leak in CD and by decreasing the numbers of proinflammatory cells [55].

It has been suggested that for patients with significant diarrhoea (>300 g of stool/day), zinc gluconate of 20–40 mg/day should be considered [56]. There is additional benefit for wound healing where zinc supplementation of 40 mg of elemental zinc for 10 days has been suggested [56]. Zinc sulphate 220 mg twice daily has been used as a standard adult oral replacement dose. Unless patients have severe ongoing diarrhoea, such doses should not be administered for longer than 2–3 weeks as excess zinc can interfere with iron and copper absorption and can lead to deficiency of these important minerals [57].

Between 36 and 90% of adults with IBD develop iron deficiency, which is the main cause of anaemia in IBD patients [58]. Even if low ferritin is usually considered the best indicator of iron deficiency it can be normal or increased in response to inflammation. Thus, it has been suggested that the threshold for defining a low serum ferritin level should be increased to 100 mg/l in the presence of inflammation [58]. New diagnostic tools have been developed, including hepcidin and soluble transferrin receptors. Hepcidin is a protein acting as a central regulator of iron absorption and of its release from stores in the reticuloendothelial system. At high hepcidin levels, the duodenal absorption of iron is depressed, resulting in retention of iron in macrophages [55]. Soluble transferrin receptor is elevated in iron-deficient states, but is significantly less affected by inflammation than other iron indexes. However, these assays are not generally available for routine use [55].

In terms of symptoms, a recent population-based cohort study reported that iron deficiency in the absence of anemia does not correlate with clinically relevant fatigue in IBD patients [59]. Therefore, in this specific setting, the decision to supplement iron in patients without anaemia is controversial and individualized [52]. Some studies suggested an advantage of parenteral treatment over oral supplementation [60]. The common side effects of oral iron (i.e. nausea, abdominal pain or diarrhoea) are mainly related to the relatively high dosing of elemental iron (>120 mg/day), whereas lower doses of iron (i.e. 60 mg elemental iron per day) appear as efficacious as higher doses, with fewer side effects [61]. European Crohn's and Colitis Organisation guidelines recommend intravenous iron to be considered the first line of treatment in patients with clinically active IBD, previous intolerance to oral iron, haemoglobin below 10 g/dl or the need for erythropoiesis-stimulating agents [52].

Summary: Vitamin B_{12} and folic acid should be supplemented in CD patients with ileal resection greater than 20 cm, whereas there is no current evidence to support fat-

soluble vitamin supplementation in IBD patients. Zinc should be supplemented in selected cases (i.e. patients with severe diarrhoea). Iron should be supplemented in the cases of iron-deficiency anaemia and the route of administration should be tailored to each individual patient.

Probiotics

Given that an imbalance or the pathological response to intra-luminal bacteria may be involved in the pathogenesis of IBD, including pouchitis, probiotic therapy aiming at modifying the bacterial flora is an attractive option [62].

Three studies using *Lactobacillus rhamnosus GG* failed to show any effect of probiotics in CD [63–65]. In line with these findings, a meta-analysis of eight clinical trials looking at different probiotic strains also confirmed this lack of benefit [66]. There is limited evidence that *Saccharomyces boulardii* probiotic administered in association with mesalazine can prolong remission time [67]. The British Dietetic Association 2013 guidelines conclude that there is no evidence of a benefit for probiotic use in CD patients [68].

Conversely, the use of probiotics in UC can induce remission [69]. Studies using preparations containing mainly *Bifidobacteria* and commercial mixtures, including VSL#3, which is a mixture of *Bifidobacteria* spp. (*Streptococcus thermophilus* DSM 24731, *Bifidobacterium longum* DSM 24736, *Bifidobacterium breve* DSM 24732, *Bifidobacterium infantis* DSM 24737) and *Lactobacilli* spp. (*Lactobacilli acidophilus* DSM 24735, *Lactobacilli plantarum* DSM 24730, *Lactobacilli paracasei* DSM 24733, *Lactobacilli delbrueckii* subsp. *bulgaricus* DSM 24734), [70–76] showed effectiveness in the maintenance therapy of UC patients. In a meta-analysis of 23 randomized controlled trials (RCTs), only VSL#3 significantly increased the remission rates compared with controls in patients with active UC [77] and the most recent meta-analysis reports that the same formulation is also safe and more effective than conventional therapy alone in achieving higher response and remission rates in mild to moderately active UC [78].

Up to 60% of patients following proctocolectomy and ileal-anal pouch formation develop an inflammatory condition often associated with bowel urgency and frequency, termed pouchitis [69]. There appears to be a derangement in the pouch microbiome; hence, benefit has been shown for both antibiotics and probiotics.

Studies have tended to be small and of variable length. One study used the probiotic *L. rhamnosus GG* [79]; the other studies used combinations of probiotics [80–84] including VSL#3. The comparison was made with placebo-treated control groups receiving maize starch or microcrystalline cellulose. The clinical effectiveness of the probiotic intervention was evaluated on the basis of clinical, histological, endoscopic and microbiological criteria including the pouchitis disease activity index. The five studies using a high-dose probiotic mixture showed clinical efficacy in pouchitis [80–84], whereas the study using *L. rhamnosus* GG alone reported modifications in intestinal microbiota, but no effects on clinical parameters [79]. In the most recent meta-analysis of 23 RCTs, only VSL#3 significantly reduced the clinical relapse rates in patients with pouchitis [78]. Primary prevention of pouchitis and

reduction of the likelihood of relapse after successful antibiotic treatment have led to the highest possible rating, an 'A' recommendation [85].

Summary: Evidence supporting probiotic supplementation in IBD patients is still controversial; however, supplementation with VSL#3 can be recommended as a therapeutic trial in patients with pouchitis.

Other therapies

A randomized, double-blind, placebo-controlled trial of oral aloe vera gel for active UC showed benefit for both clinical and histological parameters [86]. Other herbs, including *Andrographis paniculata*, appear to inhibit TNF-α, IL-1s and NF-κβ in an in-vitro setting [87]. Chamomile dry extract of chamomile flowers, because of its anti-inflammatory effects and antibacterial, spasmolytic and ulcer-protective potential, has shown initial promising evidence in maintenance therapy of UC [88]. In addition, cannabinoids were found to improve inflammation in an animal model of colitis [89] by reducing inflammatory cytokine release [90,91].

Boswellia spp. (*Boswellia serrata*), which belongs to the family of trees producing resin, has been shown to exert therapeutic effects in the IBD setting. In a single randomized study, 30 patients with UC were randomized to receive either *B. serrata* resin (900 mg/day in three doses, $n = 20$) or sulphasalazine (3 g/day in three doses, $n = 10$) for 6 weeks. Remission of the disease was achieved in 14 of 20 patients who received *Boswellia* gum resin compared with four of 10 who received sulphasalazine [92]. In a randomized double-blind study, 102 patients with active CD were randomized to receive *B. serrata* extract (H15) or mesalazine. The mean reduction in the CDAI was 90 for H15 and 53 for mesalazine [93].

A. paniculata (and its extract HMPL-004) is a member of the plant family Acanthaceae. It has been used widely in Asian countries as well as in Sweden and Chile to treat a variety of inflammatory and infectious diseases, including a phase I study in China in UC [94]. Diterpene lactones, composed of Andrographolide and its derivatives, correspond to the main known components of *A. paniculata*.

A recent randomized, double-blind, placebo-controlled study compared the aqueous ethanol extract of *A. paniculata* (HMPL-004) with placebo in 224 adult patients with mild to moderately active UC. Treatment with HMPL-004 at a dose of 1800 mg/day resulted in a statistically significantly better clinical response compared with placebo (60 vs. 40%; $P = 0.018$), although the proportion of remission after 8 weeks did not differ in the two groups [87]. Another randomized, double-blind, multi-centre study showed that HMPL-004 had similar effectiveness with mesalazine (response 76 vs. 82%; remission 21 vs. 16%) in patients with mild to moderate UC, even if no difference was found in the proportion of endoscopic remission in the two groups after 8 weeks (28 vs. 24%) [95].

A recent systematic review including 26 RCTs and three controlled trials for herbal medicine showed that complementary alternative medicine might be effective for the treatment of IBD; however, further studies are needed to confirm these results [96].

Table 1. Summary of current evidence on the association between food/vitamin supplements and inflammatory bowel diseases

Key points
Nutritional deficiencies are common in IBD patients. Optimizing diet is important and food/vitamin supplements may be appropriate.
Curcumin supplementation appears to be effective in reducing both the symptoms and the inflammatory indices in IBD patients, with no apparent side effects, although further studies are needed.
Green tea extract may be effective in inducing remission in IBD patients; however, studies are limited.
Vitamin D_3 is important for its associated effects in the reduction of IBD but also therapeutic levels are associated with response to therapy and reduced relapse.
Vitamin B_{12} should be supplemented in Crohn's disease patients with ileal resections greater than 20 cm.
Zinc should be supplemented in selected cases, that is, patients with severe diarrhoea.
Iron should be supplemented in the cases of iron-deficiency anaemia and the route of administration should be tailored to each individual patient.
Supplementation with the probiotic VSL#3 can be considered in patients with pouchitis.
A complete nutritional assessment is an important aspect of the treatment of IBD patients; however, more randomized-controlled trials are needed to enable definitive conclusions

IBD, inflammatory bowel disease.

Summary: A number of herbal therapies including *A. paniculata* and *B. serrata* show promise in IBD and further clinical trials are warranted.

Conclusion

Nutritional deficiencies are common in IBD patients and food supplements may be considered complementary therapies. Curcumin, green tea, vitamin D and probiotic supplements are all attractive options. Curcumin supplementation has been reported to be effective in reducing both the symptoms and the inflammatory indices in IBD patients, although further studies are needed. Green tea also seems to be a promising supplement, even if, at present, few data are available. Vitamin D deficiency is common in IBD patients and several authors supported the role of its supplementation to both increase bone mineral density and to reduce disease activity. CD patients with ileal resection greater than 20 cm may develop vitamin B_{12} deficiency that requires parenteral supplementation; conversely, there is no current evidence to support fat-soluble vitamin supplementation in IBD patients. Zinc should be supplemented in selected cases. Iron should be supplemented in the cases of iron-deficiency anaemia and the mode of administration should be tailored for each single patient. Probiotics, particularly VSL#3, have been reported to reduce disease activity in IBD patients with pouchitis. Although the benefits of supplementation have been highlighted, the evidence on toxicity is limited because of the lack of randomized trials. Table 1 summarizes current evidence on the association between food supplements and IBD.

In conclusion, food supplements may be useful in IBD patients. A complete nutritional assessment is therefore an important aspect of the treatment of IBD patients, which highlights both the relevance of multidisciplinary management of individual patients and the need for a more individualized treatment approach. More randomized-controlled trials are needed to better define the role of food and vitamin supplementation in IBD.

Acknowledgements

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