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REVIEW ARTICLE

Probiotics, fibre and herbal medicinal products for functional and inflammatory bowel disorders

Correspondence Diego Currò, Institute of Pharmacology, School of Medicine, Catholic University of the Sacred Heart, L.go F. Vito, 1, I-00168 Rome, Italy. E-mail: diego.curro@unicatt.it

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Diego Currò[1], Gianluca Ianiro[2], Silvia Pecere[2], Stefano Bibbò[3] and Giovanni Cammarota[2]

[1]Institute of Pharmacology, School of Medicine, Catholic University of the Sacred Heart, L.go F. Vito 1 00168 Rome, Italy, [2]Department of Internal Medicine, School of Medicine, Catholic University of the Sacred Heart, L.go F. Vito 1 00168 Rome, Italy, and [3]Department of Clinical and Experimental Medicine, University of Sassari, V.le S. Pietro, 8 07100 Sassari, Italy

Functional bowel disorders (FBD), mainly irritable bowel syndrome (IBS) and functional constipation (FC, also called chronic idiopathic constipation), are very common worldwide. Inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease, although less common, has a strong impact on patients' quality of life, as well as being highly expensive for our healthcare. A definite cure for those disorders is still yet to come. Over the years, several therapeutic approaches complementary or alternative to traditional pharmacological treatments, including probiotics, prebiotics, synbiotics, fibre and herbal medicinal products, have been investigated for the management of both groups of diseases. However, most available studies are biased by several drawbacks, including small samples and poor methodological quality. Probiotics, in particular *Saccharomyces boulardii* and *Lactobacilli* (among which *Lactobacillus rhamnosus*), synbiotics, psyllium, and some herbal medicinal products, primarily peppermint oil, seem to be effective in ameliorating IBS symptoms. Synbiotics and fibre seem to be beneficial in FC patients. The probiotic combination VSL#3 may be effective in inducing remission in patients with mild-to-moderate ulcerative colitis, in whom *Escherichia coli* Nissle 1917 seems to be as effective as mesalamine in maintaining remission. No definite conclusions can be drawn as to the efficacy of fibre and herbal medicinal products in IBD patients due to the low number of studies and the lack of randomized controlled trials that replicate the results obtained in the individual studies conducted so far. Thus, further, well-designed studies are needed to address the real role of these therapeutic options in the management of both FBD and IBD.

LINKED ARTICLES

This article is part of a themed section on Principles of Pharmacological Research of Nutraceuticals. To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v174.11/issuetoc

Abbreviations

ACG, American College of Gastroenterology; CD, Crohn's disease; CDAI, Crohn's disease activity index; CFTR, cystic fibrosis transmembrane conductance regulator; CIC, chronic idiopathic constipation; DC, dendritic cell; DSS, dextran sulphate sodium; ECCO, European Crohn's and Colitis Organisation; ECN 1917, *Escherichia coli* Nissle 1917; FBD, functional bowel disorder; FC, functional constipation; FFA, free fatty acid; FOS, fructo-oligosaccharides; GBF, germinated barley foodstuff; GOS, galacto-oligosaccharides; HDAC, histone deacetylase; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with predominant constipation; IBS-D, irritable bowel syndrome with predominant diarrhoea; iNOS, inducible NOS; mPGES, microsomal prostaglandin E_2 synthase; MPO, myeloperoxidase; NNT, number needed to treat; OR, odds ratio; PHGG, partially hydrogenated guar gum; RCT, randomized controlled trial; RR, relative risk; SCFA, short-chain fatty acid; TNBS, 2,4,6-trinitrobenzenesulfonic acid; UC, ulcerative colitis; WHO, World Health Organization

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Tables of Links

TARGETS	
Other ion channels[a]	**Enzymes**[d]
Ca^{2+}-activated chloride channels	COX-2
CFTR	Histone deacetylases (HDACs)
GPCRs[b]	Inducible nitric oxide synthase (iNOS)
5-HT_4 receptor	Microsomal prostaglandin E synthase (mPGES)
Adenosine A_{2A} receptor	Myeloperoxidase (MPO)
Free fatty acid (FFA) receptors	Cathepsin G
M_3 receptor	**Catalytic receptors**[e]
Opioid receptors	Toll-like receptor (TLR) family
Voltage-gated ion channels[c]	**Nuclear hormone receptors**[f]
Transient receptor potential (TRP) channels	Peroxisome proliferator-activated receptor-γ

LIGANDS		
Acetate	IL-2	Propionate
Acetylcholine	IL-4	Serotonin
Apigenin	IL-8	TNF-α
Bradykinin	IL-10	
Butyrate	IL-12	
β-Catenin	IL-18	
Curcumin	LTB_4	
Histamine	Menthol	
IFN-γ	Mesalamine	
IL-1β	PGE_2	

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan *et al.*, 2016), and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 ([a,b,c,d,e,f]Alexander *et al.*, 2015a,b,c,d,e,f).

Introduction

The two most important functional bowel disorders (FBD), irritable bowel syndrome (IBS) and functional constipation (FC, also known as chronic idiopathic constipation [CIC]), have high worldwide prevalence in adults, between 5.8% and 17.5%, depending on the geographical areas (Sperber *et al.*, 2016), and approximately 14% (Suares and Ford, 2011) respectively. Their diagnosis is based on well-defined clinical criteria, established with the Rome III consensus, that have been very recently revised (Lacy *et al.*, 2016). The main inflammatory bowel diseases (IBD), ulcerative colitis (UC) and Crohn's disease (CD), have a prevalence in the Western countries much lower than that of IBS and FC (between 0.25% and 0.5%) (Ye *et al.*, 2015) and are diagnosed based on clinical, biochemical, endoscopic and histopathological criteria (Baumgart and Sandborn, 2012; Ordás *et al.*, 2012). However, although they are less common than FBD, they are similarly very important diseases, for their strong impact on patients' quality of life, as well as the high costs of patient treatments for our healthcare systems.

Different options of pharmacological treatment are available for FBD. FC is usually treated with laxatives, prosecretory agents and prokinetic drugs. All these therapeutic options are also used to treat IBS patients with predominant constipation (IBS-C). Anti-diarrheal drugs, bile salt sequestrants and antibiotics can be used to treat IBS patients with predominant diarrhoea (IBS-D). In all IBS patients, antispasmodic drugs and antidepressants can also be used, primarily to relieve abdominal pain (Lacy *et al.*, 2016). Aminosalicylates, corticosteroids, immunosuppressive drugs and monoclonal antibodies to TNF-α are well established pharmacological therapies for IBD. However, current treatment options suffer from some limitations. Several drugs used to treat IBS patients show low therapeutic gain with respect to placebo and some of them, in particular antispasmodic drugs and antidepressants, have poor profiles of tolerability (Barboza *et al.*, 2014). Systemic corticosteroids are still a first-line therapeutic option for IBD patients with severe disease or those not responding to aminosalicylates (or budesonide for ileocaecal CD), but they induce important short- and long-term adverse effects. Immunosuppressive drugs, that is thiopurines and methotrexate, and antibodies to TNF-α are currently the most important pharmacotherapies for IBD patients who do not maintain remission with aminosalicylates or those with severe disease not responding to corticosteroids. However, high percentages of patients do not achieve remission or discontinue treatment, at various times due to loss of response or adverse effects (Krishnareddy and Swaminath, 2014). That is why new therapeutic options are continuously sought and consideration has been also given to approaches alternative to traditional medicines.

In this review, we focus on probiotics, fibre and herbal medicinal products that provide other, not negligible, therapeutic options in the setting of FBD and IBD (Magge and Wolf, 2013; Holtmann and Talley, 2015). We have chosen to deal with such a wide range of disorders and these therapeutic options for several reasons. First of all, we wanted to compare the alternative therapies used in functional disorders with those used in organic diseases of the colon, to highlight differences and similarities. Probiotics and fibre could positively affect both categories of bowel disorders via the gut microbiota. In fact, the acknowledgment of the pathophysiological role of alterations in bowel microbiota

in IBS and IBD and the possibilities that probiotics, prebiotics and synbiotics offer to restore a functionally normal gut microbial environment is becoming increasingly important (Cammarota *et al.*, 2015, 2016; Spiller, 2016). On the other hand, some fibres are fermented by colonic bacteria, with the formation of short-chain fatty acids (SCFAs, mainly acetate, butyrate and propionate), which have anti-inflammatory effects (Cammarota *et al.*, 2015; Sivaprakasam *et al.*, 2016) and improve the propulsive colonic function (Soret *et al.*, 2010), mechanisms through which they could induce beneficial effects in inflammatory and FBD respectively. In addition, the therapeutic importance of fibre is attested by the advice generally given to IBS and FC patients to adopt lifestyle changes, including an adequate fluid intake (1.5–2 L per day), the increase in fibre intake with the diet (at least 25 g per day) and physical activity (Lee, 2014; Chey *et al.*, 2015). Constipation is a common clinical feature of both FC and IBC-C patients; consequently, fibre, acting as bulk-forming laxatives, can be effective in both types of constipated patients. Another reason is that the use of alternative medicines, mainly herbal products, is widespread among patients with IBS and IBD, as they are not completely satisfied with traditional drug therapies and consider them safe, even though pertinent data are generally not conclusive (Ng *et al.*, 2013; Grundmann and Yoon, 2014), and related adverse events have been sometimes observed (De Smet, 2004).

Irritable bowel syndrome

Probiotics, prebiotics and synbiotics

Probiotics. In 2001, the Food and Agriculture Organization of the United Nations and the World Health Organization (WHO) defined probiotics as live microorganisms which, if administered in an adequate amount, confer a health benefit to the host. Theoretically, probiotics might be able to exert beneficial influences on several pathogenetic pathways of IBS, including the restoration of altered gut microbiota, by increasing the number of beneficial bacteria (*Bifidobacteria* and *Lactobacilli* among others) and reducing the number of pathogens because of competition, and consequently the decrease of inflammation associated with the proliferation of pathogenic bacteria (Scully *et al.*, 2013), changes in the metabolism of biliary salts (Joyce *et al.*, 2014) and the restoration of a normal colonic fermentation (King *et al.*, 1998). In addition, probiotics were shown to decrease visceral hypersensitivity in several mouse models (Ait-Belgnaoui *et al.*, 2006; Kamiya *et al.*, 2006; Verdu *et al.*, 2006; Eutamene *et al.*, 2007). Furthermore, the finding of a low-grade inflammation or immune dis-reactivity in patients with IBS, with both an increase in inflammatory cells in the colonic mucosa and an increase of pro-inflammatory cytokines and Toll-like receptors (TLRs) (Talley and Butterfield, 1996; Scully *et al.*, 2010; Brint *et al.*, 2011), has been the pathophysiological support of the usefulness of probiotics, which are well known for their immunoregulatory effects (Cammarota *et al.*, 2015).

There is a relevant heterogeneity among different trials of probiotics in patients with IBS, in terms of subjects enrolled, design, outcomes and kind and dosage of probiotics used, which jeopardize the several systematic reviews and meta-analyses published on this topic. In particular, a series of meta-analyses pooled together studies evaluating different probiotic species/strains (Table 1). A meta-analysis by Hoveyda *et al.* (2009) found 14 randomized controlled trials (RCTs) of probiotics compared with placebo for IBS and showed a little amelioration of overall symptoms. One year later, Moayyedi *et al.* (2010) released a systematic review of 19 RCTs. Although the trials showed overall satisfactory quality, and the meta-analysis showed a significant benefit of probiotics in ameliorating IBS symptoms, the authors concluded that the real therapeutic importance of probiotics and the best probiotic strain/s are yet to be identified due to the heterogeneity of studies. A further meta-analysis, despite being released 4 years later, and including 35 RCTs, was affected by the same drawbacks, and reached, therefore, similar conclusions (Ford *et al.*, 2014b). Finally, Didari *et al.* (2015) pooled together 15 heterogeneous RCTs and they concluded that probiotics were better over placebo in reducing overall symptoms and abdominal pain after 8–10 weeks of therapy.

Nevertheless, pooling together the data on different probiotics has been claimed to be methodologically inappropriate, in that different strains may exert different actions on the human organism (Szajewska, 2014). The efficacy of specific probiotic strains in patients with IBS has also been evaluated through focused meta-analyses. One of them investigated the role of *Saccharomyces boulardii* (*S. boulardii*) for gastrointestinal diseases in adult patients; the authors found only one RCT, which evaluated patients with IBS, in which the probiotic group experienced, after 4 weeks of treatment, a significant relief in the daily number of bowel movements (McFarland, 2010). Another meta-analysis investigated the role of *Lactobacillus rhamnosus* (*L. rhamnosus*) GG in the relief of pain related to functional gastrointestinal disorders in children. In particular, among the retrieved studies, authors found three RCTs of patients with IBS, which showed, when pooled together, a significant reduction in the intensity and in the frequency of abdominal pain (Horvath *et al.*, 2011). Recently, a meta-analysis evaluated the effect of *Lactobacillus* species and strains in IBS. The authors found six RCTs, without heterogeneity among them; probiotic therapy with *Lactobacilli* achieved a significant relative risk (RR) of clinical improvement of 7.69 overall (Tiequn *et al.*, 2015).

Prebiotics. Prebiotics are defined as non-digestible, fermentable dietary components that exert beneficial effects on the host through the modulation of composition or activity of gut microbiota (Roberfroid *et al.*, 2010; see below the 'Fibre' section for more information). So far, only a few studies have investigated the efficacy of prebiotics in patients with IBS, with contrasting results. In a RCT with placebo, short-chain fructo-oligosaccharides (FOS) were shown to significantly improve digestive comfort and daily activities of patients with FBD according to Rome II criteria (Paineau *et al.*, 2008). In another RCT of patients with Rome II IBS, a *trans*-galacto-oligosaccharide prebiotic was significantly better than placebo in increasing the number of faecal *Bifidobacteria* and improving several symptoms, including stool consistency, flatulence, bloating, subjective global assessment and anxiety (Silk *et al.*, 2009).

Table 1

Probiotics, prebiotics, synbiotics, fibre and herbal medicinal products in irritable bowel syndrome

Reference	Study type	Disease	Intervention	Number of patients	Results
Probiotics, prebiotics and synbiotics					
Hoveyda *et al.*, 2009	Meta-analysis (14 RCTs)	IBS (no restriction for subtypes)	Probiotics	1225	Probiotics may have a role in alleviating some symptoms of IBS. OR was 1.6 for dichotomous data from seven trials; SMD was 0.23 for continuous data from six trials.
Moayyedi *et al.*, 2010	Meta-analysis (19 RCTs)	IBS (no restriction for subtypes)	Probiotics	1650	Probiotics were significantly better than placebo (RR of IBS not improving =0.71) with NNT = 4.
Ford *et al.*, 2014b	Meta-analysis (probiotics, 35 RCTs; synbiotics, two RCTs)	IBS (no restriction for subtypes)	Probiotics and synbiotics	3452 (probiotics) and 198 (synbiotics)	The significant RR of IBS symptoms persisting with probiotics versus placebo was 0.79. There were no significant effects of synbiotic in reducing symptoms.
Didari *et al.*, 2015	Meta-analysis (24 RCTs)	IBS (no restriction for subtypes)	Probiotics	1793	Probiotics improved abdominal pain (two trials, RR 1.96), global symptom score (two trials, RR 2.43), general symptoms (seven trials, RR 2.14), and an IBS severity score evaluating distension, bloating and flatulence (three trials, SMD 2.57).
Horvath *et al.*, 2011	Meta-analysis (three RCTs)	Children with abdominal pain-related functional gastrointestinal disorders	*L. rhamnosus GG*	290	*L. rhamnosus GG* supplementation was associated with a significantly higher rate of treatment responders (RR 1.31, NNT 7)
Tiequn *et al.*, 2015	Meta-analysis (six RCTs)	IBS (no restriction for subtypes)	*Lactobacillus* spp.	440 (273 adults and 167 children)	*Lactobacilli* induced therapeutic benefit with a significant RR of 7.69 (adults, 17.62; children, 3.71).
Fibre					
Ford *et al.*, 2008	Meta-analysis (12 RCTs)	IBS (no restriction for subtypes)	Fibre (bran or psyllium)	591	Fibre induced no clinical improvement with respect to placebo or a low fibre diet (RR 0.87). Bran had no significant effect (RR of persistent symptoms 1.02). Psyllium was significantly effective (RR of persistent or unimproved symptoms 0.78).
Ruepert *et al.*, 2011	Meta-analysis (12 RCTs)	IBS (no restriction for subtypes)	Fibre	621	No beneficial effect of fibre over placebo for improvement of abdominal pain (SMD 0.03), global assessment of symptoms (RR 1.10), or symptom score (SMD −0.00). Subgroup analyses for insoluble and soluble fibres also showed no significant benefit.
Moayyedi *et al.*, 2014	Meta-analysis (14 RCTs)	IBS (no restriction for subtypes)	Fibre (soluble and insoluble)	921	Significant clinical benefit of fibre (RR = 0.86), that was confirmed in RCTs on soluble fibre (RR = 0.83,

(Continues)

Table 1 (Continued)

Reference	Study type	Disease	Intervention	Number of patients	Results
					NNT = 7), but not in those on bran (RR = 0.90)
Everitt *et al.*, 2013	RCT	IBS (no restriction for subtypes)	Mebeverine versus methylcellulose versus placebo or self-management website for 6 weeks	135	No significant difference in IBS symptom severity scale or IBS-QOL scores between medication or website groups at 12 weeks, or in medication groups at 6 weeks, or IBS-QOL in website groups at 6 weeks
Toskes *et al.*, 1993	Crossover study	IBS (no restriction for subtypes)	Polycarbophil 6 g per day versus placebo for 6 months	23	15 patients chose polycarbophil over placebo for relief of the symptoms (71%)
Herbal medicinal products					
Liu *et al.*, 2006	Systematic review (75 trials)	IBS (no restriction for subtypes)	Herbal medicines were compared with placebo or conventional pharmacological therapy	7957	Improvement of symptoms with 6 and 22 herbal medicines compared with placebo or conventional therapy respectively; 29 herbal medicines were not significantly different from conventional therapy.
Madisch *et al.*, 2004	RCT	IBS (no restriction for subtypes)	STW 5 (iberogast), STW 5-II, bitter candytuft mono-extract or placebo for 4 weeks	208	STW 5 and STW 5-II were significantly better than placebo in reducing the total abdominal pain score and IBS symptom score.
Ford *et al.*, 2008	Meta-analysis (four RCTs)	IBS (no restriction for subtypes)	Peppermint oil	392	26% of patients randomized to peppermint oil had persistent symptoms compared with 65% of those receiving placebo (RR 0.43)
Khanna *et al.*, 2014	Meta-analysis (nine studies)	IBS (no restriction for subtypes)	Peppermint oil	726	Improvement of global symptoms (RR 2.23) and abdominal pain (RR 2.14) with peppermint oil with respect to placebo

IBS-QOL, IBS quality of life; SMD, standardized mean differences

Nevertheless, in two RCTs, neither oligofructose nor FOS induced any therapeutic benefit in ameliorating IBS symptoms, which were even worsened at the beginning of the treatment with FOS (Hunter *et al.*, 1999; Olesen and Gudmand-Hoyer, 2000). Additionally, a diet rich in fermentable carbohydrates increased breath hydrogen and worsened gastrointestinal symptoms in patients with IBS (Ong *et al.*, 2010). According to these results, prebiotic treatment may be considered a double-edged sword for patients with IBS, as high dosages of prebiotics can exacerbate symptoms rather than improve them, through their fermentation by microbiota and the consequent increase in the quantity of gas in the large bowel (Whelan, 2011). This evidence laid the groundwork for the development of a diet poor in fermentable oligo-, di-, monosaccharides and polyols (FODMAP), which was shown in several studies to achieve a higher control of symptoms with respect to standard dietary advice in patients with IBS (Rao *et al.*, 2015; Thomas and Quigley, 2015). However, an RCT of patients with IBS showed no therapeutic benefit of low-FODMAP diet over traditional dietary advice (Bohn *et al.*, 2015). Furthermore, a low-FODMAP diet decreased microbial abundance, particularly the number of *Bifidobacteria*, and diversity (Staudacher *et al.*, 2012; Halmos *et al.*, 2015), which are considered indices of the well-being of the gut microbiota. The low FODMAP diet has been considered effective in relieving symptoms in selected patients with IBS in the systematic review by Rao *et al.* (2015). Nevertheless, authors advocated the need for further, thorough studies, to assess the long-term efficacy and safety of low FODMAP diet, especially on gut microbiota homeostasis (Rao *et al.*, 2015).

Synbiotics. Synbiotics are dietary supplements which combine prebiotics and probiotics, to increase the levels and activity of beneficial microbes in the gut. Only few RCTs investigated the efficacy of synbiotics in patients with IBS, to date. *Bacillus coagulans* combined with FOS led to a

significantly higher improvement of abdominal pain and diarrhoea over placebo both in adult (Rogha *et al.*, 2014) and paediatric (Saneian *et al.*, 2015) patients with IBS. A synbiotic preparation, containing *Lactobacillus acidophilus*, *Lactobacillus helveticus* and *Bifidobacteria* in a medium enriched with phytoextracts, led to a significant amelioration of pain and bloating, in comparison with the heat-inactivated synbiotic, in patients with Rome II IBS (Tsuchiya *et al.*, 2004). Finally, a combination of cellulose, l-leucine and 29 probiotic species was more effective than placebo in improving some symptoms in a small trial of IBS patients (Bittner *et al.*, 2005). According to a recent meta-analysis, synbiotics appear to be significantly effective in improving IBS symptoms, but data are too few to draw any definitive conclusion (Ford *et al.*, 2014a, b).

Fibre

Generalities. The common meaning of the term 'fibre' is that of carbohydrates that are not digested or absorbed in the small intestine and thus reach the large intestine unchanged (Eswaran *et al.*, 2013). In an effort to standardize the various definitions of fibre which had been given by different national authorities, the Codex Alimentarius Commission has defined in 2010 dietary fibre as 'carbohydrate polymers with ten or more monomeric units, which are not hydrolysed by the endogenous enzymes in the small intestine of humans' (Jones, 2014). The definition has a footnote that leaves up to national authorities the decision on whether to include carbohydrates of 3 to 9 monomeric units. Since then, several national authorities have adopted the entire Codex definition, including short-chain carbohydrates. The Codex Commission categorizes dietary fibre as carbohydrate polymers that are: (i) edible, naturally occurring in the food as consumed; (ii) obtained from food raw material by physical, enzymatic or chemical means; or (iii) synthetic. The last two categories must have been shown to have physiological effects of benefit to health. Dietary fibre includes long-chain carbohydrates, such as cellulose, hemicelluloses, β-glucans, fructans, among which inulins, pectins, dextrins, gums and resistant starch, and short-chain carbohydrates, such as FOS and galacto-oligosaccharides (GOS). Fibres are usually classified on the basis of some characteristics, such as solubility, viscosity and fermentability by colonic microbiota. The latter feature leads to the production of SCFAs and gases (fermentable fibre). SCFAs are the preferred energy source for colonic mucosa cells, have anti-inflammatory and immunoregulatory activities (Cammarota *et al.*, 2015) and induce beneficial effects on myenteric neurons and colonic motility, improving peristalsis (Soret *et al.*, 2010). Viscous fibre can form a gel ('mucilage') in the intestinal tract. More or less widely commercially available dietary fibre are FOS, GOS, inulin, wheat dextrin, partially hydrogenated guar gum (PHGG) and resistant starch (soluble, highly fermentable fibre); oat bran (soluble, intermediate fermentable fibre); and wheat bran (insoluble, very little fermentable fibre) (Eswaran *et al.*, 2013). As discussed previously and subsequently in the sections on 'Prebiotics', various highly fermentable fibres, including FOS, GOS and inulin, have been studied as components of the category of prebiotics, in that they are an energy source for some gut bacteria and positively affect the composition and function of gut microbiota (Cammarota *et al.*, 2015). As already mentioned, it is thought that many beneficial effects of these prebiotic fibres are attributable to the SCFAs. acetate, propionate and butyrate, formed by their fermentation (Cammarota *et al.*, 2015). SCFAs have been shown to strengthen the intestinal barrier function (Corrêa-Oliveira *et al.*, 2016) and reduce neutrophil recruitment and inflammation in experimental models of colitis (Sivaprakasam *et al.*, 2016). SCFAs induce their effects by interacting with several molecular targets, among which important are the histone deacetylases (HDACs) and the metabotropic receptors free fatty acid 2 and 3 (FFA2 and 3; Bolognini *et al.*, 2016; Sivaprakasam *et al.*, 2016). Butyrate and propionate are inhibitors of the isoforms 1 and 3 of HDACs; this activity leads to the increase in histone acetylation, changes in the interaction between histones and DNA and modulation of the transcription of specific genes that affect cell processes such as apoptosis and cell cycle (Sivaprakasam *et al.*, 2016). In the gut, FFA2 and 3 receptors are expressed in enteroendocrine, immune and epithelial cells, and in enteroendocrine cells and enteric neurons, respectively (Sivaprakasam *et al.*, 2016). They are considered to be a link between dietary fibre and intestinal homeostasis through the gut microbiota (Sivaprakasam *et al.*, 2016). In particular, the activation of FFA2 receptors on dendritic cells (DCs) leads on one hand to the differentiation of naïve lymphocytes T into regulatory lymphocytes T and on the other hand, to the inhibition of the differentiation of naïve lymphocytes T into T helper 17 cells; in addition, the stimulation of FFA2 receptors expressed in dendritic and epithelial cells induces the production of the cytokines IL-10 and IL-18, respectively (Corrêa-Oliveira *et al.*, 2016; Sivaprakasam *et al.*, 2016). All these are well-known anti-inflammatory effects.

Fibres used for medical purposes, mainly for their laxative effects, can be separated into two broad classes, natural and synthetic (Gonzalez-Martinez *et al.*, 2014). The most commonly used natural fibres are psyllium and gum Karaya (sterculia; Eswaran *et al.*, 2013). Other less widely used natural fibres are kelp (Kim and Bhatnagar, 2011), agar gum (Kim and Bhatnagar, 2011), and tragacanth (Fu *et al.*, 2014). The most popular synthetic fibres are methylcellulose and calcium polycarbophil.

Natural fibre. The terms 'psyllium' or 'ispaghula' usually refer to the seed husk of the plant genus *Plantago*, mainly *Plantago ovata*. The husk is the mucilaginous portion of the seed coat; it contains soluble, viscous and intermediate fermentable fibre that is mainly able to retain water, swell and form a gelatinous mass which softens and increases the volume of stool, helping to stimulate the peristaltic movements (Eswaran *et al.*, 2013; Slavin, 2013). It is believed that additional actions contribute to the therapeutic effects of psyllium: the induction of beneficial microbiota changes, the increase in microbiota growth and faecal biomass and the production of SCFAs through fermentation. Wheat bran is the hard outer layers of wheat grain. It is composed for approximately 45–50% of fibre, mainly cellulose and hemicelluloses that is insoluble and minimally fermentable (Eswaran *et al.*, 2013; Slavin, 2013).

Differently from psyllium, bran has a low water holding capacity; it is thought that its laxative effects are primarily due to the increase in faecal mass and mechanical stimulation of the intestinal mucosa (Tomlin and Read, 1988).

Several RCTs investigated the effects of psyllium and wheat bran in patients with IBS; two meta-analyses, published by Ford *et al*. in 2008 and Ruepert *et al*. in 2011, selected the same number of eligible studies (12, 11 of which were the same studies), but came to different results. In fact, soluble fibre (psyllium) was found to be significantly more effective than placebo or no treatment in the first meta-analysis (Ford *et al*., 2008), whereas no statistically significant benefits were found for either soluble or insoluble fibre (wheat bran) in the second meta-analysis (Ruepert *et al*., 2011) (Table 1). In the discussion of the latter meta-analysis, the authors attributed the attainment of different conclusions to the choice of analysing different outcomes: they analysed separately improvement of abdominal pain, global assessment of symptoms and IBS symptom score, whereas Ford *et al*. (2008) pooled together these different outcomes; in addition, Ford *et al*. (2008) did not use an intention to treat analysis. An update of the meta-analysis of Ford *et al*. (2008) was published by Moayyedi *et al*. (2014); the authors added two RCTs to their previous meta-analysis and confirmed the superiority of psyllium over placebo for improving IBS symptoms or abdominal pain (Table 1).

Synthetic fibre. Methylcellulose is a derivative of cellulose in which some of the hydroxyl groups are substituted with methoxide groups and it should be considered more properly a semisynthetic fibre. It is soluble, viscous and non-fermentable fibre. Calcium polycarbophil is the Ca^{2+} salt of a highly branched, very hydrophilic fibre, formed by polyacrylic acid crosslinked with divinyl glycol. Once in the stomach, Ca^{2+} ions are replaced by H^{+} ions, giving rise to polycarbophilic acid, which is able to bind water molecules, markedly increasing its volume.

The therapeutic effects of methylcellulose were compared in an exploratory double-blind RCT with those of mebeverine and placebo. Patients with IBS fulfilling Rome III criteria were treated for 6 weeks and evaluated at 6 and 12 weeks; primary outcomes were the change in the IBS Symptom Severity Scale and Quality of Life questionnaire scores from baseline to 12 weeks. There were no significant differences among the three groups at 12 weeks, but the number of recruited patients was low (11, 14 and 15 for mebeverine, methylcellulose and placebo arms respectively) (Everitt *et al*., 2013). The effects of calcium polycarbophil, compared with those of placebo, were investigated in a double-blind, crossover RCT in 23 patients with IBS-C or IBS with mixed bowel habits. In this trial, calcium polycarbophil was rated better than placebo in monthly global response to therapy and for the relief of various symptoms, including pain (Toskes *et al*., 1993).

Herbal medicinal products

A Cochrane Library systematic review published by Liu *et al*. in 2006 found 75 RCTs comparing 71 different herbal medicines, including single herbal extracts or combination of plant extracts, to placebo or conventional pharmacological treatments in IBS patients. However, the methodological quality of 72 of these trials was assessed to be poor. A few herbal products showed efficacies significantly higher than placebo in improving global symptoms, including iberogast, Padma Lax (a Tibetan herbal medicine), the traditional Chinese preparation Tongxie Yaofang, a standard Chinese herbal formula, an individualized Chinese herbal medicine, and an Ayurvedic preparation (Liu *et al*., 2006). In addition, 72 herbal products, most of which were traditional Chinese medicine formulas, significantly improved symptoms of IBS when compared with standard drug treatments (Table 1). Very recently, berberine, a benzylisoquinoline alkaloid isolated from several plants, in particular from *Coptis chinensis*, a plant used for a very long time in China for medical purposes, has shown therapeutic efficacy in patients affected by IBS-D in a RCT with placebo (Chen *et al*., 2015b). On the basis of the findings of a study in a murine model of IBS-D, it has been proposed that berberine induces its beneficial effects through stimulation of μ and δ opioid receptors (Chen *et al*., 2015a). The herbal products most known in the Western countries for their beneficial effects in IBS patients are undoubtedly iberogast and peppermint oil. Strangely, the latter was not taken into account in the Cochrane systematic review on herbal medicines, but was included among the antispasmodic agents in another Cochrane systematic review evaluating the efficacies of bulking agents, antispasmodics and antidepressants for the treatment of IBS (Ruepert *et al*., 2011). We will focus our discussion on these two herbal medicinal products; the readers can refer to recent reviews for a general overview on this topic (Rahimi and Abdollahi, 2012) or the detailed discussion of traditional Chinese herbal medicines (Li *et al*., 2013; Xiao *et al*., 2015).

Iberogast. Iberogast, also termed STW 5, is a proprietary combination, in a liquid formulation, of hydroethanolic extracts of nine plants: bitter candytuft (*Iberis amara* L.) planta totalis, caraway (*Carum carvi* L.) fructus, chamomile (*Matricaria recutita* L.) flos, peppermint (*Mentha piperita* L.) folium, lemon balm (*Melissa officinalis*) folium, liquorice (*Glycyrrhiza glabra* L.) radix, angelica (*Angelica archangelica* L.) radix, greater celandine (*Chelidonium majus* L.) herba and milk thistle (*Silybum marianum* L.) fructus; a preparation without last three components (STW 5-II) is also available. Iberogast owes its name to its main constituent, the extract of *Iberis amara* L. STW 5 and STW 5-II were compared with placebo for their efficacy and safety in IBS patients in a double-blind, multicentre RCT. Both significantly decreased the IBS symptom score and the total abdominal pain score in an intention-to-treat analysis after 4 weeks of treatment (Madisch *et al*., 2004). Iberogast is well tolerated and the incidence of adverse effects, usually mild, has been estimated to be 0.04% and hypersensitivity reactions occur very rarely (Ottillinger *et al*., 2013).

Many mechanisms of action have been reported that could underlie the therapeutic efficacy of iberogast (Cremonini, 2014). STW 5 reduces the afferent nerve discharge activated by mechanical (pressure increases) or pharmacological (serotonin and bradykinin) stimulation from the rat small intestine *in vivo* (Liu *et al*., 2004), whereas STW 5-II decreases the afferent sensitivity to bradykinin only (Mueller *et al*., 2009). In addition, iberogast depolarizes the resting membrane potential of circular smooth muscle cells

in the small and large intestine, decreases amplitude and frequency of small intestinal slow waves and reduces fast and slow inhibitory junction potentials in the colon of the mouse (Storr *et al.*, 2004; Sibaev *et al.*, 2006). In the guinea pig ileum, it induces small longitudinal smooth muscle contractions and, on the other hand, importantly antagonizes the contractions produced by histamine or acetylcholine in a concentration-dependent manner (Ammon *et al.*, 2006; Heinle *et al.*, 2006). Iberogast also affects intestinal secretory function, as it dose-dependently increases Cl^- ion secretion from the mucosa of human small and large intestine by activating submucosal neurons and through mechanisms involving cystic fibrosis transmembrane conductance regulator and Ca^{2+}-activated chloride channels (Krueger *et al.*, 2009). It was later shown that iberogast-induced prosecretory effects are mainly attributable to the angelica extract, with minor contributions from peppermint and lemon balm extracts (Allam *et al.*, 2015). As regards the molecular drug targets that may underlie these actions, it has been shown that phytochemicals contained in iberogast bind with good affinity to acetylcholine M_3, 5-HT_4, opioid and adenosine A_{2A} receptors (Simmen *et al.*, 2006; Michael *et al.*, 2012). Iberogast contains over 350 substances, mainly belonging to the following five groups: coumarins, flavonoids, phenol carboxylic acids, terpenes and volatile oils (Wegener and Wagner, 2006). Sixty-two of these compounds have been shown to induce effects on gut contractility, mainly inhibitory (spasmolytic) (Wegener and Wagner, 2006). These compounds are the most probable active substances responsible for the predominant spasmolytic actions of iberogast, which are likely to contribute to its beneficial effects in IBS patients. As far as we know, no single component of iberogast has been evaluated for possible effects on intestinal afferent nerve firing or secretion.

Peppermint oil. The oil extracted from peppermint, an herb also contained in iberogast, is well known for its therapeutic efficacy in IBS patients. The first study investigating the effects of peppermint oil in IBS was a double-blind crossover RCT published by Rees *et al.* in 1979. Sixteen patients were treated with peppermint oil 0.2–0.4 mL tid or placebo for 3 weeks. The overall symptom score was significantly lower in patients taking peppermint oil than in those treated with placebo. A multicentre trial followed this first study 5 years later (Dew *et al.*, 1984), and then several other studies were published that confirmed the therapeutic efficacy of peppermint oil in both adult and paediatric IBS patients (Liu *et al.*, 1997; Kline *et al.*, 2001; Vejdani *et al.*, 2006; Cappello *et al.*, 2007; Merat *et al.*, 2010). In three recent meta-analyses, peppermint oil was found to be significantly more effective than placebo in improving global assessment of symptoms or IBS symptom score (Ruepert *et al.*, 2011), these two outcomes pooled together (Ford *et al.*, 2008; Khanna *et al.*, 2014) or abdominal pain (Khanna *et al.*, 2014) (Table 1). Overall, peppermint oil is a safe herbal preparation and no serious adverse effects were noted in RCTs (Ford *et al.*, 2008). The most frequently reported adverse effect is heartburn, very probably due to lower esophageal sphincter relaxation (Khanna *et al.*, 2014).

The main component of peppermint oil is menthol, a chemical compound belonging to the class of monoterpenes, which has long been known for its relaxant effects on gut smooth muscle (Hawthorn *et al.*, 1988). This substance binds to TRP ion channels and in particular, it activates the TRPM8 channels and blocks the TRPA1 channels. The latter play important roles in intestinal mechanosensation and pathophysiological mechanisms of visceral hypersensitivity (Brierley *et al.*, 2009; Brierley *et al.*, 2011). The activation of TRPM8 channels by menthol is responsible for the occurrence of the typical sensation of freshness when peppermint oil is inhaled or applied to the skin or oral mucosa. TRPM8 channels have been localized on colonic afferent neurons, where their activation inhibit chemo- and mechanosensory signalling due to TRPV1 and TRPA1 channel activation (Harrington *et al.*, 2011). Overall, these inhibitory actions of menthol on visceral chemo- and mechanosensation could contribute to its therapeutic efficacy in the setting of IBS.

Functional constipation

Therapeutic approaches other than those most frequently used, have been attempted to alleviate the symptoms of this condition, including probiotics, prebiotics, synbiotics, fibre and botanical medicines (Suares and Ford, 2011; Ford *et al.*, 2014a,b; Cirillo and Capasso, 2015; Rao *et al.*, 2015). Their role has been addressed by several RCTs, which have been pooled together through many systematic reviews and meta-analyses. Overall, these meta-analyses are biased by many drawbacks, such as either the paucity of included studies, or their poor quality and heterogeneity, according to several of them.

Probiotics, prebiotics and synbiotics

In a recent meta-analysis, Ford *et al.* (2014b) showed that probiotics are beneficial in FC, with a mean increase in weekly number of stools of 1.49; nevertheless, these findings came out from only two RCTs. Data on prebiotics, instead, were few, impeding any conclusions, whereas synbiotics overall exerted a beneficial effect, with a 22% decrease of the RR of failure to respond to treatments. Authors concluded that the efficacy of all three treatments in patients with FC is still uncertain (Ford *et al.*, 2014b) (Table 2). In another meta-analysis of 14 RCTs, probiotics significantly improved whole intestinal transit time, stool frequency and consistency. Nevertheless, at subgroup analysis, only *Bifidobacterium lactis* was confirmed to be significantly effective. Moreover, authors found high heterogeneity among studies, as well as high risk of attrition and reporting bias; therefore, such results should be considered with prudence (Dimidi *et al.*, 2014) (Table 2). Based on this evidence, the American College of Gastroenterology (ACG) recently stated that there is insufficient evidence to recommend probiotics for FC, as considered trials were few, heterogeneous, and with a risk of bias ranging from unclear to high. Nevertheless, some synbiotics may improve stool frequency in those patients (Ford *et al.*, 2014a).

Fibre

The increase in dietary fibre or the use of supplementary fibre is generally recommended to patients affected by FC.

Table 2

Probiotics, prebiotics, synbiotics, fibre and herbal medicinal products in FC

Reference	Study type	Intervention	Number of patients	Aim	Results
Probiotics, prebiotics and synbiotics					
Ford *et al.*, 2014b	Meta-analysis (probiotics, three RCTs; prebiotics, one RCT; and synbiotics, two RCTs)	Prebiotics, probiotics, and synbiotics	245 (probiotics), 198 (synbiotics), 60 (prebiotics)	To evaluate the global clinical response	Two trials on probiotics reported about dichotomous outcomes; both trials demonstrated a clinical benefit, but pooled data were not statistically significant (RR of failure to respond to therapy 0.29). Two trials on probiotics reported a significant increase in the mean number of bowel movements per week (1.49). Synbiotics appeared beneficial on FC symptoms (significant RR of failure to respond to therapy =0.78; NNT =5). The trial on prebiotic (inulin and PHGG) reported no difference in satisfaction in relief of constipation in prebiotic group versus placebo (32% vs 31%); also the mean number of bowel movements per week was not significantly different.
Dimidi *et al.*, 2014	Meta-analysis (14 RCTs)	Probiotics	1182	To investigate the effect of probiotics on gut transit time, stool output, and constipation symptoms	Probiotics significantly reduced the whole gut transit time by 12.4 h and increased stool frequency by 1.3 bowel movements per week; the latter was significant for *B. lactis* (WMD: 1.5 bowel movementsper week), but not for *L. casei Shirota* (WMD: −0.2 bowel movements per week). Probiotics improved stool consistency (SMD: +0.55), and this was significant for *B. lactis* (SMD: +0.46), but not for *L. casei Shirota* (SMD: +0.26)
Fibre					
Ford *et al.*, 2014a	Meta-analysis (six RCTs)	Soluble fibre	293	To investigate the mean increase in stool frequency	Formal meta-analysis was conducted with 3 RCTs, which concluded that soluble fibre has therapeutic superiority over placebo with NNT of 2
Christodoulides *et al.*, 2016	Meta-analysis (seven RCTs)	Fibre (including prebiotic)	287	To investigate the effects on global symptom response and stool output	Patients assigned to fibre responded to therapy (RR of success to respond 1.71). Fibre significantly increased stool frequency (SMD = 0.39), and softened stool consistency (SMD = 0.35). Flatulence was significantly higher with fibre (SMD = 0.56)
Herbal medicinal products					
Cheng *et al.*, 2011	RCT	Hemp seed pill versus placebo for 8 weeks	120	To assess the efficacy and safety of Hemp seed pill	Response rates for the Hemp seed pill and placebo groups were significantly different (43.3% and 8.3% respectively)
Jia *et al.*, 2010	RCT	Yun-chang capsule versus placebo tid for 2 weeks	140	To assess the changes in main symptom score and cumulative symptom score	Beneficial effects, assessed as significant reductions in main and cumulative symptom scores, with Yun-chang

B. lactis, *Bifidobacterium lactis*; *L. casei Shirota*, *Lactobacillus casei Shirota*; SMD, standardized mean differences; WMD, weighted mean differences

A recent monograph of the ACG on the treatment of IBS and CIC ranks this recommendation as 'strong', even though it classifies the quality of evidence as 'low' (Ford *et al.*, 2014a). The authors of this monograph found six parallel-group RCTs comparing the effects of fibre to those of placebo or no therapy in adult patients with FC diagnosed by any of the Rome criteria or clinical evaluation. They conducted a formal meta-analysis with three of these studies, all of which investigated the effects of soluble fibre (two of them used psyllium, the third a combination of inulin and a resistant maltodextrin), which concluded that soluble fibre has therapeutic superiority over placebo with the number needed to treat (NNT) of 2 (Table 2). A more recent meta-analysis found seven RCTs with parallel-group or crossover design, in which the effects of fibre were compared with those of placebo or control interventions in adult patients with FC diagnosed by clinical or Rome criteria, or self-report. A formal meta-analysis included the four studies that reported dichotomous data on the response to therapy evaluated as symptomatic improvement; the authors underlined the considerable variability of the studies as for fibre type (psyllium, wheat bran, inulin plus PHGG and inulin plus resistant maltodextrin respectively) and dose used, and duration of treatment (2 to 4 weeks) (Christodoulides *et al.*, 2016). Also, in this meta-analysis, it has been found that fibre determines symptomatic improvement in a proportion of patients significantly higher than that of placebo (77 vs 44% respectively; RR = 1.71, NNT = 3) (Table 2). However, it was recognized once again that the overall quality of the studies is low. A possible weakness of these two meta-analyses is that they have grouped together studies with soluble bulk-forming fibre (psyllium) and studies with highly fermentable fibre (inulin plus resistant maltodextrin or PHGG, all of which are considered prebiotics) and/or insoluble fibre (wheat bran). Subgroup analyses performed in the second meta-analysis indicate that there is evidence for therapeutic efficacy for psyllium but not for prebiotics (Christodoulides *et al.*, 2016).

Herbal medicinal products

Stimulant laxatives of plant origin have been commonly used for a long time for the treatment of constipation. The most popular of them are senna, cascara, frangula, aloe and rhubarb, obtained from the dried leaves and pods of some *Cassia* species, the dried barks of *Rhamnus purshiana* or *Rhamnus frangula*, the latex contained in the leaves of some *Aloe* species and the dried rhizome of some *Rheum* species respectively (Cirillo and Capasso, 2015). Senna and cascara are the most used; they contain some anthraquinone drugs, known as sennosides and cascarosides, which are glycoside derivatives of hydroxyanthracene. These glycosides arrive intact to the colon, where the glycosidases produced by the microbiota break the glycoside bond and release the active substances, mainly rhein and rhein-anthrone. The latter stimulate the colonic peristalsis through activation of the secretory and motor functions, mediated by the increase in the synthesis and release of PGs and other autacoids (Cirillo and Capasso, 2015). Despite being widely used and effective laxatives, no RCT has been, however, carried out with them in patients affected by FC.

Two herbal medicinal products, the proprietary medicines Hemp seed pill and Yun-chang, both Chinese, have been investigated and found to be effective in RCTs of patients with FC. Significantly more patients treated for 8 weeks with the Hemp seed pill, a mixture of six herbs (*Cannabis* fructus [hemp seed], *Rheum* rhizoma, *Paeonia alba* radix, *Prunus armeniaca* semen, *Citrus aurantium* fructus immaturus and *Magnolia officinalis* cortex) attained the primary outcome (a mean increase of complete spontaneous bowel movement ≥1 per week compared with their baselines) than those treated with placebo (43.3 vs 8.3%) (Cheng *et al.*, 2011). A statistically significant difference in rates of the primary outcome was also observed during the 8-week follow-up period. In addition, the hemp seed pill improved the global assessment of symptoms and the sensation of straining, with respect to baseline levels, significantly more than placebo. Yun-chang, a herbal mixture containing seven herbs, only five of which were disclosed (*Aloe*, *Panax ginseng*, *Polygoni multiflori* radix, *Citrus aurantium* fructus immaturus and *Asini corii* colla) showed beneficial effects, assessed as significant reductions in main and cumulative symptom scores, in a 2-week RCT (Jia *et al.*, 2010).

Inflammatory bowel disease

Probiotics, prebiotics and synbiotics

One of the pathogenetic pathways of IBD is represented by an imbalanced immune response to microbes, together with an impairment of gut microbiota, in individuals with genetic susceptibility (Ewaschuk and Dieleman, 2006). Probiotics, prebiotics and synbiotics may restore the intestinal microbial balance, thus enhancing gut barrier function and improving local immune response (Cammarota *et al.*, 2015; Wasilewski *et al.*, 2015).

Probiotics. In recent years, several studies have investigated the effects of probiotics in IBD, suggesting that certain microbial strains could be useful in the management of the disease. The therapeutic effects of probiotics have been related to several cytoprotective mechanisms, different for each probiotic strain. Oral administration of VSL#3, a probiotic combination composed of three *Bifidobacterium* species, four *Lactobacillus* species and *Streptococcus thermophilus*, was shown to modulate intestinal DCs, that mediate the recognition of microbes and induce the response of T lymphocytes. Oral VSL#3 decreased TLR-2 expression, increased IL-10 production, and down-regulated IL-12p40 levels in DC of UC patients (Ng *et al.*, 2010). Moreover, Petrof *et al.* (2004) showed that VSL#3 produces soluble factors that decrease the chymotrypsin-like activity of proteasome in enterocytes, inhibits NF-κB, and stimulates the enterocyte production of cytoprotective heat shock proteins, pointing out the anti-inflammatory and cytoprotective pathways as novel mechanisms of microbial-epithelial interaction. *Lactobacilli* are known to act mainly on the cascade of pro-inflammatory cytokines. When administered to IL-10 knockout mice, *L. reuteri* and *L. casei* attenuated the severity of *Helicobacter hepaticus*-induced

colitis, decreasing colonic levels of TNF-α and IL-12 (Pena *et al.*, 2005). Moreover, Braat *et al.* (2004) demonstrated that a different *Lactobacillus* species, *L. rhamnosus*, influenced DC maturation, leading to a decrease in T lymphocyte proliferation and cytokine release (mainly IL-2, IL-4 and IL-10). In addition, they reported that peripheral CD4+ T cells obtained from healthy volunteers after a 2 wk oral supplementation with *L. rhamnosus* produced less IL-4 than lymphocytes isolated before the treatment, whereas peripheral CD4+ T cells isolated from CD patients after the same treatment produced less IFN-γ and IL-2. These findings indicate that probiotics induce their beneficial effects through anti-inflammatory mechanisms, by direct or indirect, via antigen presenting cells, actions on both Th1 and Th2 lymphocytes, and suggest that peripheral T-cell hypo-responsiveness might be an important mechanism of the beneficial effects of probiotic treatment *in vivo*. Probiotics may also induce their beneficial effects by counteracting the activity of pathogenic bacteria, through the inhibition of their growth and proliferation, via the reduction of bowel luminal pH and the synthesis of defensins, and mechanisms that inhibit their adherence to and translocation across the epithelium (Wasilewski *et al.*, 2015; Durchschein *et al.*, 2016). In addition, probiotics have been shown to strengthen the gut barrier function by modulating the secretion of mucus and chloride and the expression of the proteins that make the tight junctions, and reducing apoptosis of the epithelial cells (Wasilewski *et al.*, 2015; Durchschein *et al.*, 2016).

When translated into clinical practice, those interesting results were not always confirmed, although a large body of evidence is available both for single probiotic strains and for probiotic combinations. Among single strains, *E. coli* Nissle 1917 (ECN 1917), a nonpathogenic *E. coli*, is the most extensively investigated. In three RCTs, oral ECN 1917 showed efficacy and safety comparable to those of mesalamine in maintaining remission in patients with quiescent UC (Kruis *et al.*, 1997; Rembacken *et al.*, 1999; Kruis *et al.*, 2004). Additionally, rectal administration of ECN 1917 was more effective than placebo in inducing remission of patients with distal mild-to-moderate active UC (Matthes *et al.*, 2010). *L. rhamnosus* GG showed a significantly longer relapse-free time with respect to mesalamine in patients with quiescent UC (Zocco *et al.*, 2006). Moreover, an 8-week-rectal administration of *L. reuteri* ATCC 5573 obtained significantly higher rates of clinical remission than placebo in children with active UC (Oliva *et al.*, 2012). Among probiotic combinations, VSL#3 provides the most relevant evidence. In several RCTs, it was effective in the induction of remission in patients with mild-to-moderate UC, together with conventional treatment (Tursi *et al.*, 2004, 2010), or alone (Sood *et al.*, 2009). In a recent meta-analysis of RCTs of patients with active UC, VSL#3 probiotics, given as adjuvant therapy to mesalamine or immunomodulators, was significantly more effective than conventional therapy alone in inducing both remission [odds ratio (OR) = 2.4] and response (OR = 3.03; NNT: 3–4) (Mardini and Grigorian, 2014) (Table 2). Other probiotic combinations, based mainly on *Bifidobacteria* and *Lactobacilli*, did not replicate the reliable results of VSL#3 (Ishikawa *et al.*, 2003; Kato *et al.*, 2004; Wildt *et al.*, 2011).

Many systematic reviews and meta-analyses evaluated the effect of probiotics in patients with UC, with discordant results. In a systematic review from a Cochrane group, probiotics were not more effective than placebo or active comparators in inducing remission of patients with active UC (Mallon *et al.*, 2007). Further reports confirmed such findings (Zigra *et al.*, 2007; Sang *et al.*, 2010; Jonkers *et al.*, 2012). Nonetheless, in a recent meta-analysis of RCTs, probiotics showed a significant advantage over placebo in inducing remission in patients with active UC (RR 1.80) (Shen *et al.*, 2014), although this finding was confirmed only for VSL#3 at subgroup analysis (RR 1.74) (Table 3). In another systematic review from the Cochrane Library, probiotics were not effective in maintaining remission in patients with quiescent UC (Naidoo *et al.*, 2011). On the contrary, probiotics were shown to be able to prevent pouchitis in a meta-analysis of RCTs (Elahi *et al.*, 2008). As for IBS, the heterogeneity of studies, as well as the inclusion of different strains, dosages and therapy lengths, jeopardizes the findings of available meta-analyses. Based on this consideration, guidelines for the treatment of IBD kept a very limited role for probiotics. The latest European Crohn's and Colitis Organisation (ECCO) guidelines do not support the use of probiotics in the achievement of remission, although recognizing a certain role for VSL#3. Moreover, ECN 1917 was suggested as a comparable treatment to mesalamine to maintain remission of patients with quiescent UC (Dignass *et al.*, 2012). In ECCO-ESPGHAN paediatric guidelines, VSL#3 and ECN 1917 are prudently suggested as single treatment in children with mildly active UC who do not tolerate mesalamine, or as adjuvant treatment in children who do not achieve complete remission with standard therapy (Turner *et al.*, 2012).

While available data on the efficacy of probiotics in UC are discordant, the majority of studies performed on CD patients reported no significant advantages for probiotics with respect to placebo, both in adults and in children (Prantera *et al.*, 2002; Schultz *et al.*, 2004; Bousvaros *et al.*, 2005). No benefit with probiotic therapy was shown either for the prophylaxix of CD recurrences after surgical resection, as reported by Prantera *et al.* (2002), who investigated the effects of 1 year administration of LGG, and recent studies that evaluated the effects of *L. johnsonii* (Marteau *et al.*, 2006; Van Gossum *et al.*, 2007). The only study that reported positive effects of probiotics on clinical outcomes in CD patients is the one published by Guslandi *et al.* in 2000. In this study, 32 patients with CD in remission were randomized to receive for 6 months either mesalamine 1 g tid or mesalamine 1 g bid plus *S. boulardii*. In the group treated with the combination mesalamine plus *S. boulardii*, significantly fewer patients relapsed compared with the mesalamine alone group (6.25 vs. 37.5%, $p < 0.05$). These results were not, however, confirmed in a larger study, in which *S. boulardii* did not significantly reduce the rate of CD relapse at 52 weeks compared with placebo in patients not receiving any other prophylactic therapy (Bourreille *et al.*, 2013). Finally, probiotics did not show any advantage over placebo, either for the induction or for the maintenance of remission in CD, according two systematic reviews from the Cochrane Library (Rolfe *et al.*, 2006; Butterworth *et al.*, 2008). Therefore, the latest ECCO guidelines do not support the use of probiotics for

Table 3

Probiotics, prebiotics, synbiotics, fibre and herbal medicinal products in inflammatory bowel disease

Reference	Study type	Disease	Intervention	N. of patients	Aim	Results
Probiotics, prebiotics and synbiotics						
Mardini and Grigorian, 2014	Meta-analysis with three RCTs	Mild-to-moderate active UC	VSL#3 versus placebo in patients concomitantly receiving mesalamine and/or immunomodulators	319	Induction of remission	The response rate was 53.4% in VSL#3-treated patients versus 29.3% in patients given placebo ($P < 0001$; OR, 3.03; NNT = 3–4). The remission rate was 43.8% in VSL#3-treatedpatients versus 24.8% in patients given placebo ($P = 0007$; OR, 2.4; NNT = 4–5).
Shen *et al.*, 2014	Meta-analysis with 23 RCTs	Active UC, CD, and pouchitis	Probiotics versus placebo	1763	Induction and maintenance of remission	The remission rates were significantly higher in patients with active UC treated with probiotics than in those treated with placebo (RR = 1.80). VSL#3 (RR = 0.18) significantly reduced the clinical relapse rates for maintaining remission in patients with pouchitis.
Rahimi *et al.*, 2008	Meta-analysis with seven RCTs	CD	Probiotics (*L. johnsonii*, *L. rhamnosus*, ECN 1917, *S. boulardii*) versus placebo	320	Maintenance of remission	Pooling of data for the outcome of clinical relapse yielded an OR of 0.92 (95% confidence interval of 0.52–1.62). The OR with three studies for the outcome of endoscopic relapse was 0.97 (95% confidence interval of 0.54–1.78).
Benjamin *et al.*, 2011	RCT with placebo	Active CD	15 g per day FOS versus placebo	103	Clinical response: fall in CDAI of ≥70 points	There were no significant differences in the number of patients achieving a clinical response between the FOS and placebo groups
Steed *et al.*, 2010	RCT with placebo	Active CD	Synbiotic including *B. longum* and Synergy 1	24	Clinical remission assessed by CDAI to <150 or a drop in CDAI of >75 from baseline; reduction in mucosal TNF-α	In the synbiotic group there were significant reductions in CDAI, histological score, and TNF-α expression at 3 months
Fujimori *et al.*, 2009	RCT	Quiescent or mild active UC	Synbiotic formulation of one daily capsule of *B. longum* 2 x 10^9 CFU + 8.0 g daily of psyllium versus prebiotic alone versus probiotic alone	120	Improvement of IBDQs scores	Individual scores significantly improved as follows: probiotics, emotional function; prebiotics, bowel function, and synbiotics, systemic and social functions
Ishikawa *et al.*, 2011	RCT with placebo	Mild-to-moderate UC	*B. breve* and GOS	41	Improvement of endoscopic score (Matts classification)	The mean endoscopic score of patients receiving synbiotics was significantly

(Continues)

Table 3 (Continued)

Reference	Study type	Disease	Intervention	N. of patients	Aim	Results
						decreased compared with that before treatment
Fibre						
Hallert *et al.*, 1991	RCT with placebo	Quiescent UC	Psyllium	29	Relieve of gastrointestinal symptoms	Grading of symptoms judged psyllium to be significantly superior to placebo
Fernandez-Banares *et al.*, 1999	RCT	Quiescent UC	Psyllium (10 g bid.) versus mesalamine (500 mg tid), versus psyllium + mesalamine	105	Maintenance of remission	Psyllium might be as effective as mesalamine to maintain remission
Herbal medicinal products						
Holtmeier *et al.*, 2011	RCT with placebo	Quiescent CD	*Boswellia serrata* (3 × 2 capsules per day; 400 mg each)	108	Maintenance of remission	The mean time to diagnosis of relapse was 171 days for the active group and 185 days for the placebo group ($P = 0.69$). The treatment group showed no advantage in maintaining remission compared with placebo
Hanai *et al.*, 2006	RCT with placebo	Quiescent UC	Curcumin 2 g per day	19	Decrease of UCDAI and endoscopic index	Curcumin significantly improved both UCDAI and the endoscopic index
Gerhardt *et al.*, 2001	RCT	Active CD	*Boswellia serrata* extract H 15 versus mesalamine	83	Change of CDAI	The therapy with H15 was not significantly inferior to mesalamine
Langmead *et al.*, 2004a	RCT with placebo	Mild-to-moderate UC	*Aloe vera*	44	Induction of remission	Significantly higher rates of clinical remission, improvement and response occurred in the treatment group compared with placebo
Hanai *et al.*, 2006	RCT	Quiescent UC	Curcumin 2 g per day plus sulfasalazine or mesalamine versus placebo plus sulfasalazine or mesalamine	89	Prevention of relapse	Relapse rates: 4.65% in the treatment group versus 20.51% in the placebo group ($P = 0.040$)
Omer *et al.*, 2007	RCT with placebo	Active CD	*Artemisia absinthium*	40	Steroid-sparing effect	Clinical remission was observed in 65% of patients treated with *Artemisia* and none of the patients receiving placebo. 10% of patients had to re-start steroids in the treatment group versus 80% of patients receiving placebo
Sandborn *et al.*, 2013	RCT	Active UC	*Andrographis paniculata* extract (HMPL-004) 1200 versus 1800 mg per day versus placebo	224	Clinical response	45% and 60% of patients receiving *Andrographis paniculata* 1200 and 1800 mg daily, respectively, were in clinical remission at week 8, compared

(Continues)

Table 3 (Continued)

Reference	Study type	Disease	Intervention	N. of patients	Aim	Results
						with 40% of those receiving placebo ($P = 0.5924$ for 1200 mg and $P = 0.0183$ for 1800 mg)
Tang *et al.*, 2011	RCT	Mild-to-moderate UC	1200 mg per day *Andrographis paniculata* extract (HMPL-004) versus 4500 mg per day slow release mesalamine	120	Clinical remission and response	There were no significant differences between the two treatment groups
Langhorst *et al.*, 2013	RCT	Inactive UC	Herbal preparation of myrrh, chamomile and coffee charcoal versus mesalamine	96	Maintenance of remission	No significant differences between the two treatment groups
Naftali *et al.*, 2013	RCT with placebo	Active CD	115 mg of Δ^9-tetrahydrocannabinol (THC)	21	Clinical response	A clinical response (decrease in CDAI score of >100) was observed in 10 of 11 subjects in the cannabis group and 4 of 10 in the placebo group, $P = 0.028$

B. breve, *Bifidobacterium breve*; CI, confidence intervals; IBDQs, Inflammatory Bowel Disease Questionnaires; *L. johnsonii*, *Lactobacillus johnsonii*; UCDAI, ulcerative colitis disease activity index

the maintenance of remission in patients with CD (Dignass *et al.*, 2010).

Prebiotics and synbiotics. The use of prebiotics and synbiotics in IBD has been little investigated. A systematic review of RCTs found only two studies investigating prebiotics and other two studies investigating synbiotics in patients with CD (Ghouri *et al.*, 2014). Neither FOS nor lactulose showed any efficacy in patients with CD (Hafer *et al.*, 2007; Benjamin *et al.*, 2011). Lactulose did not improve clinical activity index, endoscopic score or immunohistochemical parameters in patients with UC, in whom, however, it improved the quality of life (Hafer *et al.*, 2007). A synbiotic consisting of *B. longum* and Synergy 1, an inulin/oligofructose mixture, was compared with placebo in a small randomized trial of patients with active CD, showing a significant improvement in Crohn's Disease Activity Index (CDAI) score over placebo (Steed *et al.*, 2010) (Table 3). Moreover, Synbiotic 2000, a combination of several probiotics and four prebiotics, showed no advantage over placebo in improving CDAI score, endoscopic and biochemical parameters (Chermesh *et al.*, 2007).

In another RCT of patients with active UC, the combination of *B. longum* and the prebiotic Synergy 1 provided a statistically significant decrease of the inflammatory markers, together with a non-significant improvement of endoscopy features, with respect to placebo (Furrie *et al.*, 2005). In an RCT, Fujimori *et al.* (2009) compared psyllium, *B. longum* and their synbiotic combination for the effects on quality of life and C-reactive protein levels in patients with quiescent or mildly active UC; the patients in the synbiotic group obtained a significant advantage over those in the other two groups for the improvement of quality-of-life scores and achieved a statistically significant reduction in C-reactive protein levels, but the study had many drawbacks, including high drop-out percentages, short duration of treatment and absence of endoscopic or histological assessments. Finally, another synbiotic, constisting of *B. breve* strain Yakult and GOS, showed significant efficacy over placebo in improving the clinical status of patients with mildly-to-moderately active UC (Ishikawa *et al.*, 2011).

Fibre

Dietary fibres showed, both in pre-clinical studies in mice and in clinical studies with humans, beneficial effect on IBD. In a mouse model of experimental colitis provoked by 2,4,6-trinitrobenzenesulfonic acid (TNBS), psyllium decreased, respectively, intestinal inflammation, and levels of TNF-α and inducible NOS (Rodriguez-Cabezas *et al.*, 2002). In two RCTs of patients with quiescent UC, psyllium was shown both to relieve symptoms better than placebo (Hallert *et al.*, 1991), and to maintain the remission at rates similar to those of mesalamine (Fernandez-Banares *et al.*, 1999) (Table 3).

In a mouse model of dextran sulphate sodium (DSS) colitis, germinated barley foodstuff (GBF), a preparation rich in protein and fibre made by milling and sieving brewer's spent grain (Kanauchi and Agata, 1997), was able to prevent the damage of the mucosa (Kanauchi *et al.*, 1998). Furthermore, in a pilot study, GBF supplementation improved clinical activity and endoscopic scores in patients with mild-

to-moderately active UC (Mitsuyama *et al.*, 1998). Finally, GBF supplementation was able to taper corticosteroids and to lengthen remission in subjects with UC (Hanai *et al.*, 2004).

Nevertheless, according to a recent questionnaire-based survey, subjects with IBD usually avoid high-fibre diets, irrespective of the activity of the disease (Zallot *et al.*, 2013). Practical recommendations include the consumption of a regular diet in the case of mild or moderate activity of both UC and CD, and that fibres should be avoided only in specific cases, including acute relapse of the disease, small intestinal bacterial overgrowth, gastrointestinal stenosis and selected surgical interventions (Brown *et al.*, 2011).

Herbal medicinal products

Herbal products may be of help for IBD through different pathways, for example by modulating the immune system, inhibiting LTB_4 synthesis, NF-κB or platelets (Gilardi *et al.*, 2014; Somani *et al.*, 2015). Several herbal products have been shown to be effective in IBD patients (Holtmann and Talley, 2015; Langhorst *et al.*, 2015; Table 3).

In experimental models of intestinal inflammation, an extract of *Boswellia serrata* reduced the interplay between endothelium and white blood cells and attenuated the inflammatory process (Krieglstein *et al.*, 2001; Hartmann *et al.*, 2014). It has been suggested that the anti-inflammatory effects of this plant extract are due to the inhibition of microsomal prostaglandin E_2 synthase (mPGES) and the serine protease cathepsin G by β-boswellic acid (Abdel-Tawab *et al.*, 2011). In a double-blind RCT, an extract of *Boswellia serrata* resin induced remission of disease in a percentage of patients with active CD similar to that of mesalamine (Gerhardt *et al.*, 2001). Nevertheless, in a RCT of 108 outpatients with quiescent CD, an extract of this plant resin did not show any advantage over placebo in maintaining remission (Holtmeier *et al.*, 2011).

Several therapeutic pathways of curcumin, the major constituent of *Curcuma longa*, have been found in mouse models of IBD. First, it decreases levels of pro-inflammatory cytokines (e.g. IFN-γ, TNF-α, IL-1β and IL-12) (Sugimoto *et al.*, 2002; Jian *et al.*, 2004, 2005; Jiang *et al.*, 2006; Zhang *et al.*, 2006a, b; Camacho-Barquero *et al.*, 2007), then regulates several transcription factors and signal pathway molecules, such as β-catenin, NF-κB, signal transducer and activator of transcription, activator protein 1, PPAR-γ (Jian *et al.*, 2005) and finally, it down-regulates the activity of COX-2 (Camacho-Barquero *et al.*, 2007), and decreases both iNOS and myeloperoxidase (MPO) activity (Ukil *et al.*, 2003; Zhang *et al.*, 2006a; Camacho-Barquero *et al.*, 2007; Deguchi *et al.*, 2007). Few clinical studies have investigated the potential of curcumin in IBD. Curcumin, administered by enema to patients with mild-to-moderate distal UC taking mesalamine, was more effective than placebo in inducing endoscopic improvement and remission of the disease (Singla *et al.*, 2014). In a RCT of 89 patients with quiescent UC treated with sulfasalazine or mesalamine, curcumin showed higher efficacy than placebo in maintaining remission (Hanai *et al.*, 2006).

Wheat grass, a preparation obtained from the cotyledons of *Triticum aestivum*, the common wheat plant, has shown significantly higher efficacy than placebo in reducing, after 4 weeks, an overall disease activity index in patients with active distal UC (Ben-Arye *et al.*, 2002). The beneficial clinical activity of wheat grass probably relates to its antioxidant properties, due to the high content of phenolic and flavonoid substances, the down-regulation of mPGES, COX-2 and iNOS, and the inhibition of the synthesis of pro-inflammatory cytokines by its main component, apigenin (Marquez-Flores *et al.*, 2016).

The central pulp of *Aloe vera* leaves has been known for centuries for its medicinal effects, above all for the treatment of skin disorders. The gel extracted from this pulp has been shown to ameliorate the colitis produced by DSS in rats, by down-regulating the expression of pro-inflammatory mediators, including TNF-α and IL-1β, and the activity of MPO (Park *et al.*, 2011), and to reduce the synthesis of PGE_2 and IL-8 and the production of ROS in human colorectal mucosa *in vitro* (Langmead *et al.*, 2004b). The main active substances contained in this gel, aloesin, aloin and aloe-emodin, mimicked the gel-induced effects in the inflamed rat colon (Park *et al.*, 2011). The *Aloe vera* gel has been investigated for its therapeutic effects in a double-blind RCT of 44 patients with mild-to-moderate active UC. It induced significantly higher rates of disease remission, improvement and response with respect to placebo after a 4-week treatment (Langmead *et al.*, 2004a).

An RCT of CD patients treated with a stable daily dose of corticosteroids suggested that the herb *Artemisia absinthium*, commonly known as wormwood, has corticosteroid sparing effects. In this trial, 40 patients were randomized to receive the herbal extract or a placebo for 10 weeks during which the corticosteroid daily doses were tapered until discontinuation. Remission of the disease was observed in 65% of patients treated with *Artemisia* and none of the patients receiving placebo. The remission was maintained in the 10 weeks following the end of treatment, and only two patients in the *Artemisia* arm had to re-start the therapy with corticosteroids, which, on the contrary, were re-started in 80% of patients receiving placebo (Omer *et al.*, 2007). The anti-inflammatory effects of *Artemisia* are very probably due to its flavonoid components; in fact, 5,6,3′,5′-tetramethoxy 7,4′-hydroxyflavone, a flavonoid isolated from *Artemisia*, has been shown to inhibit the activation of NF-κB and reduce the expression of COX-2 and iNOS in a macrophage cell line stimulated with LPS (Lee *et al.*, 2004). Another substance isolated from *Artemisia*, cardamonin, also reduces the expression of iNOS in macrophage cell lines incubated with LPS by inhibiting NF-κB DNA-binding (Hatziieremia *et al.*, 2006).

HMPL-004, a proprietary extract of *Andrographis paniculata*, induced a clinical response at week 8 in a percentage of patients with mild-to-moderate UC significantly higher than that of patients treated with placebo, in a double-blind RCT in which approximately 60% of patients were taking concomitantly mesalamine (Sandborn *et al.*, 2013). This trial followed a double-blind RCT published by Tang *et al.* in 2011, in which HMPL-004 had shown an efficacy not significantly different from that of mesalamine, at week 8, in patients with mild-to-moderate UC (Tang *et al.*, 2011). In a T-cell-driven model of murine intestinal inflammation, HMPL-004 was able to prevent the development of colitis by inhibiting the proliferation of CD4+ T lymphocytes and their differentiation into Th1/Th17 cells (Michelsen *et al.*, 2013). These anti-inflammatory effects of *Andrographis paniculata*

were mimicked by its main component, andrographolide, in mice with TNBS-induced colitis (Liu *et al.*, 2014).

A double-blind, double-dummy RCT of patients with quiescent UC investigated the efficacy of a proprietary combination of myrrh, chamomile extract and coffee charcoal for the maintenance of the remission; the non-inferiority of the herbal mixture with respect to mesalamine was evaluated by the mean Clinical Colitis Activity Index (Langhorst *et al.*, 2013). After 12 months of treatment, the relapse rate in the herbal product arm (53%) was not significantly different from that in the mesalamine arm (45%), indicating its use as a possible alternative to mesalamine for the maintenance of remission.

Finally, conflicting results come from studies of *Cannabis sativa* (the marijuana plant) in patients with CD. Twenty-one patients with active CD not responding to steroids, immunosuppressants and/or biological agents, were randomized to cannabis or placebo, as cigarettes, for 8 weeks. Although the difference in clinical remission rates was not significant between the two groups, the clinical response rate (defined as a reduction in CDAI score of more than 100 points) was significantly higher in the cannabis group (Naftali *et al.*, 2013). In a following survey of 313 patients with CD, nearly 18% of them used cannabis to improve symptoms (mainly diarrhoea, abdominal pain and joint pain). Nevertheless, a chronic (>6 months) use of cannabis predicted the further need for surgery (OR = 5.03) (Storr *et al.*, 2014).

Safety of probiotics, fibre and herbal medicinal products

Probiotics are generally available without the need of a medical prescription, as they are mostly considered as food supplements. Moreover, both the U.S. FDA and the WHOclassed probiotics to be generally safe (Mattia and Merker, 2008). However, defining a safety profile for probiotics has become a paramount need for the medical community (Shanahan, 2012). Some systematic reviews of the literature have tried to address it and they agreed that probiotics can be considered partially, but not totally, safe (Whelan and Myers, 2010; Didari *et al.*, 2014). The most relevant safety concerns on probiotics include the infectious adverse events (mainly sepsis), imbalance of the immune system and transmission of antibiotic resistance genes to pathogenic bacteria (Boyle *et al.*, 2006). Therefore, probiotics should be avoided, or used with great care, in critically ill patients, in subjects with immunodeficiency, immune dysregulation, or taking immunosuppressant and/or antineoplastic drugs, patients with central venous catheters, those with cardiac valve diseases, replacement or history of endocarditis, premature infants, and in subjects with altered gastrointestinal barrier (e.g. graft-versus-host disease, or radiation enteritis, or severe acute pancreatitis), at high risk of bacterial translocation (Boyle *et al.*, 2006; Williams, 2010; Doron and Snydman, 2015). In particular, probiotics were associated with increased mortality rates in patients with severe acute pancreatitis (Besselink *et al.*, 2008); moreover, *S. boulardii* was responsible for more than a half of total events of fungal sepsis in France (Enache-Angoulvant and Hennequin, 2005). Therefore, the FDA has recently stated that probiotics should be considered as food supplements only when used in healthy subjects, whereas they should be considered as drugs when used in ill subjects (Venugopalan *et al.*, 2010).

Fibres do not generally pose important safety problems (Eswaran *et al.*, 2013; Moayyedi *et al.*, 2014). The herbal products deserve, instead, a more thorough discussion. The widespread use of plants as medicines or dietary supplements is mainly attributable to the fact that everything is natural is generally considered safe. Actually, this assumption does not exactly match the reality. Many pharmacologically active substances are contained in plants and they can induce adverse events as can traditional drugs. A recent multicentre retrospective study based on data from selected poisons centres as part of the PlantLIBRA project funded by the European Community aimed to investigate the incidence of adverse events related to the intake of plants as food or food supplements in the years 2006–2010 (Lüde *et al.*, 2016). Overall, 75 cases from 10 centres met the inclusion criteria of the study and the observed adverse events affected more frequently the nervous and gastrointestinal systems and only five were severe. Thus, the toxicity of plants ingested for health reasons seems to be infrequent and generally not severe. A recent systematic review on the adverse events caused by 66 plants ingested as food supplements or botanical preparations has come to similar conclusions (Di Lorenzo *et al.*, 2014). This work showed that reports of adverse events related to the ingestion of botanicals are many in the literature, but those with an adequate evidence of causal link, according to the WHO Causality Assessment Criteria, are much less (Di Lorenzo *et al.*, 2014). The plants causally associated with adverse events were 39 out of the 66 considered, and a minimum number of papers regarded as significant by the authors (at least 10), was found only for 14 of them, which were responsible for 86.6% of all adverse events. Four plants, namely, in decreasing order of importance, *Glycine max* (soybean), *Glycyrrhiza glabra* (liquorice), *Camellia sinensis* (green tea) and *Ginkgo biloba* (ginkgo) caused approximately 50% of all adverse events (Di Lorenzo *et al.*, 2014). A recent overview of systematic reviews on the adverse events associated with the use of herbal medicines also concluded that these latter are reasonably safe and the adverse events they may cause are usually mild, even though some of them can induce severe health problems (Posadzki *et al.*, 2013). Therefore, on the basis of these possible serious adverse events reported in the literature and the increasing use of herbal products, it has been suggested that constant attention is required to herbal products both in terms of the regulation and in terms of the healthcare consequences (Izzo *et al.*, 2016; Lüde *et al.*, 2016).

Discussion

Over the years, several therapeutic approaches complementary or alternative to traditional pharmacological treatments, including probiotics, prebiotics, synbiotics, fibre and herbal medicinal products, have been investigated for the management of FBD and IBD. Due to increasing consumer spending on nutritious and healthy dietary supplements globally, their market has shown consistent growth during the past few years. On the basis of the present medical evidence, a few conclusions can be summarized. Probiotics, in particular

S.boulardii and *Lactobacilli* (among which *L. rhamnosus*), synbiotics, psyllium, and some herbal medicinal products, primarily peppermint oil, seem to be effective in ameliorating IBS symptoms. Synbiotics and fibre seem to be beneficial in FC patients. The probiotic combination VSL#3 may be effective in inducing remission in patients with mild-to-moderate UC, in whom ECN 1917 seems to be as effective as mesalamine in maintaining remission. As for the efficacy of fibre and herbal medicinal products in IBD patients, although several RCTs showed beneficial effects with different preparations, no definite conclusions can be drawn due to the low number of studies and the lack of RCTs that replicate the results obtained in the individual studies conducted so far.

Few considerations can be made from these conclusions. Interventions aimed to affect the gut microbiota seem to induce therapeutic effects in both functional and organic bowel diseases, giving support to the hypothesis that perturbations of a healthy microbiota may have a pathogenic role in both categories of colonic disorders. We do not know exactly yet what happens to the gut microbiota when we administer probiotics. A recent meta-analysis based on seven studies suggests that probiotics do not modify the composition of gut microbiota in healthy subjects (Kristensen *et al.*, 2016). However, these findings do not exclude the possibility that probiotics affect the function or the homeostasis, that is the ability to resist to or recover from the perturbations induced by different stressors, of gut microbiota (Sanders, 2016). In addition, it is possible that some probiotics exert beneficial effects on composition and/or function and/or homeostasis of the gut microbiota in subjects with gut dysbiosis, such as IBS and IBD patients, with amelioration of gastrointestinal symptoms (McFarland, 2014). Fibres seem to be effective in the treatment of both IBS and FC patients. Most evidence is available for psyllium, a soluble, viscous and intermediate fermentable fibre. It is probable that its efficacy in ameliorating symptoms in patients with IBS-C and FC is mainly attributable to the bulk-forming property, that is the ability to form a mucilage that increases the faecal mass and stimulate the colonic propulsive activity, thus relieving constipation. However, it cannot be ruled out that psyllium fermentation by the microbiota, and the consequent beneficial effects of fermentation products on the microbiota itself, epithelium and immune cells, can importantly contribute to its therapeutic effects, particularly in IBS patients. The efficacy of psyllium in relieving symptoms and maintaining remission in UC patients shown in two RCTs and the results of some studies showing the therapeutic efficacy of prebiotics in IBS patients may support this possibility. Very few RCTs investigating the effects of prebiotics in patients affected by functional or inflammatory bowel disorders have been done so far; thus, it would be desirable that other RCTs are conducted, in particular with intermediate fermentable fibre or low doses of highly fermentable prebiotics, to avoid the production of high levels of gases that could worsen the symptoms. The real contrast between functional and inflammatory colonic disorders concerns the herbal medicinal products that have been shown to be effective in RCTs. It seems now proven that iberogast and peppermint oil are therapeutic in IBS patients. Their therapeutic efficacy is very probably due to their ability to reduce the afferent nerve discharge activated by various stimuli, and thus, the visceral hypersensitivity and the smooth muscle spasms that have been hypothesized to be among the most important pathophysiological mechanisms underlying the abdominal pain in IBS patients. In contrast, in line with expectations, all herbal medicinal products that produce clinical improvement in IBD patients have been shown to act on molecular mechanisms involved in the inflammatory process. Unfortunately, confirmatory RCTs are missing for all of them.

In summary, probiotics, prebiotics, synbiotics, fibre and herbal medicinal products are, for some aspects, at the same time both current and promising therapeutic approaches for the management of FBD and IBD. Nevertheless, available studies on probiotics and synbiotics are biased by several drawbacks. Most meta-analyses included trials differing each other in strains, dosages and duration of probiotic or synbiotic treatment; moreover, most trials included subjects from different populations, differing for gender, age, BMI and other features. This 'one-size-fits-all' approach risks to flatten different findings on probiotics or synbiotics. Additionally, the good fortune of most probiotic and synbiotic trials has been hampered by their small sample size, and by the enormous number of species/strains investigated, either alone or in combination. Finally, as suggested in the very recent Rome IV Foundation report, future trials on probiotics should include microbiota analysis to check their presence in the gut microbiota of a representative subset of exposed patients, and should undergo the same rigorous methodology applied to clinical trials of traditional drugs (Irvine *et al.*, 2016). Prebiotics seem to be promising therapeutic options in both functional and inflammatory bowel disorders, but more studies are necessary, in particular with low doses and larger numbers of enrolled patients. Finally, confirmatory studies for the therapeutic efficacy of herbal medicinal products in IBD patients are awaited.

Conflict of interest

The authors declare no conflicts of interest.

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