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Probiotics and constipation: mechanisms of action, evidence for effectiveness and utilisation by patients and healthcare professionals

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The aim of this narrative review is to assess and present evidence on the mechanisms of action of probiotics in constipation, their effectiveness and their utilisation by patients and healthcare professionals. Chronic constipation is a common bothersome disorder that has a considerable impact on patients' quality of life. Probiotics have been increasingly investigated for their effectiveness in various disorders, including chronic constipation. Probiotics may affect gut motility and constipation through their impact on the gut microbiota and fermentation, the central and enteric nervous system and the immune system. However, evidence for the effectiveness of probiotics in the management of constipation remains varied, with some strains demonstrating improvements, while others show no effect. Despite the uncertainty in evidence and the fact that the majority of healthcare professionals do not recommend probiotics for constipation, an increased prevalence of probiotic use by people with constipation has been shown. Therefore, there is a need for public health strategies to inform the public about where strong evidence of probiotic effectiveness exist, and where evidence is still weak. Education of healthcare professionals on the increased utilisation of probiotics for constipation by the public and on current evidence for the effectiveness of specific strains is also required.

Constipation: Probiotics: Mechanisms

Chronic constipation is a functional gastrointestinal disorder characterised by persistently difficult, infrequent or incomplete defaecation that affects approximately 14 % of the general population[1,2]. It may be diagnosed using symptom-based diagnostic criteria, such as the Rome IV criteria, according to which a diagnosis is made when two or more of the following symptoms are present for at least a quarter of bowel movements: hard or lumpy stools, straining, a sense of incomplete evacuation, use of manual manoeuvres to pass stool and a sense of anorectal obstruction[1]. Nevertheless, both the general population and some doctors consider various other symptoms important for a diagnosis of constipation, including spending a long time on the toilet without achieving a bowel movement[3,4]. Furthermore, a large cross-sectional survey in over 3000 members of the general population and doctors revealed differences in the symptoms considered important for a diagnosis of constipation between the general population, general practitioners (GP) and gastroenterology specialists, and that there was imperfect agreement with the Rome IV criteria, highlighting the difficulties and variability in the diagnosis of chronic constipation[3,4].

However chronic constipation is diagnosed, it impacts on people's lives, with straining, bloating, abdominal discomfort, abdominal pain and spending a long time on

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Abbreviations: GP, general practitioner; GTT, gut transit time; QoL, quality of life; RCT, randomised controlled trial; SMD, standard mean difference.
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the toilet without a bowel movement being the symptoms most commonly described as being burdensome[3,5,6]. A multinational survey has shown a negative correlation between the total number of symptoms of constipation experienced and quality of life (QoL), and lower health-related QoL has been reported by women, as well as by those under psychological stress, such as unemployment[5]. Chronic constipation also impacts on work productivity[6].

The high prevalence of constipation, its chronicity and its impact on QoL contribute to the utilisation of significant healthcare resources. The direct annual cost associated with the management of constipation has been shown to range from $1912 to $7522 annually per patient in the USA[7], whilst in the UK, there are more than 1 million GP consultations and 69 054 hospital admissions annually where constipation is a diagnosis[8,9]. Treatment failure for constipation is also associated with a total incremental cost of $2978, with 60 % being spent on medical service costs[10], highlighting the importance of early successful management.

A variety of different management options exist for constipation, ranging from dietary interventions (e.g. dietary fibre[11]) and over-the-counter products (e.g. laxatives) to prescription drugs (e.g. serotonin receptor agonists), behavioural interventions (e.g. biofeedback) and different surgical options[12]. However, patient satisfaction is variable; for example, 49 % of patients initiating over-the-counter therapies and 58 % of patients initiating prescription therapies experience failure of that treatment[10]. Another study reported that almost half of respondents were not completely satisfied with their current constipation treatment[13]. The reasons for patient dissatisfaction were mainly related to efficacy and safety, as well as cost issues and inconsistent results. These findings are supported by another recent web survey demonstrating that 17 % of patients with constipation were dissatisfied with laxative use[14]. Taken together, these results show that there is still a substantial unmet need for new effective therapeutic strategies that would be appealing and satisfactory for people with constipation.

Over the past decade there has been an increase in research investigating the effect of probiotics on chronic constipation as a potential alternative management strategy. This review aims to assess and present evidence on the mechanisms of action of probiotics in constipation, their utilisation by patients and healthcare professionals and evidence for their effectiveness from clinical trials.

Potential mechanisms of action of probiotics in constipation

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host[15]. There are several mechanisms of action of probiotics relevant to constipation, including modulation of the gut microbiota and fermentation, nervous system and immune system, as shown in Fig. 1[16].

Several studies have demonstrated differences in the gut microbiota composition between people with and without constipation[16], with a decreased concentration of bifidobacteria and lactobacilli, as well as increased numbers of *Bacteroidetes*, identified in people with constipation[16–18]. Faecal microbiota composition has been shown to correlate with colonic transit time, while the colonic mucosal microbiota composition correlates with constipation status[18]. Although the impact of probiotics on the microbiota in constipation is not well understood, a small number of trials have demonstrated significant changes in gut microbiota composition following probiotic supplementation[16]. For example, supplementation of *Bifidobacterium lactis* GCL2505 or *Lactobacillus casei* Shirota increased the concentration of bifidobacteria, however *B. lactis* NCC2818 and VSL#3, a multi-strain probiotic, had no impact on gut microbiota composition[19–22]. These results suggest that administration of probiotics may impact on certain microbiota components, but it is yet to be determined what impact this change has on constipation, and whether effects are mediated through microbiota modification or other mechanisms.

It is likely that it is the physiologically active substances produced by the gut microbiota that have an impact on motility, rather than the microbiota *per se*. Metabolic byproducts of the microbiota that might contribute to a change in gut function in response to probiotic supplementation include SCFA, which are primary end-products of fermentation of non-digestible food components including carbohydrates (Fig. 1)[23]. *In vitro* and *ex vivo* experiments have shown that SCFA may affect gut motility by stimulating mucosal receptors connecting to enteric or vagal nerves[24], acting directly on colonic smooth muscle[25,26] or via increasing intraluminal serotonin concentration, an excitatory neurotransmitter[27]. When investigating the impact of probiotics on SCFA concentrations in people with constipation, several human studies show significant changes[21,28–30], however others show little impact[31,32]. These results may be attributed to the different strains used in the studies and because stool, rather than luminal SCFA concentrations are measured, which is not predictive of SCFA production in the proximal colon[33].

The colonic mucus may also play a role in regulating gut motility as it acts as a lubricant and facilitates stool passage[34], while bile acids may affect motility through luminal electrolyte and water transport regulation as demonstrated by *in vitro* and animal studies[35,36]. However, there is currently much less evidence that probiotics affect bile acid metabolism or mucin excretion in human subjects[37–39].

Modulation of microbiota–gut–brain interactions with probiotics has been demonstrated in healthy people[40], while *L. reuteri* has been shown to increase the excitability of myenteric neurons in rats and interact with the gut–brain axis via alterations in afferent sensory nerves that affect gut motility, indicating that that probiotics do impact on the enteric nervous system[41,42]. Hence, probiotic-mediated modulation of microbiota–gut–brain interactions has been proposed as a potential novel therapeutic tool for the treatment of gut motility disorders, including constipation; however, there are no human studies in constipation.
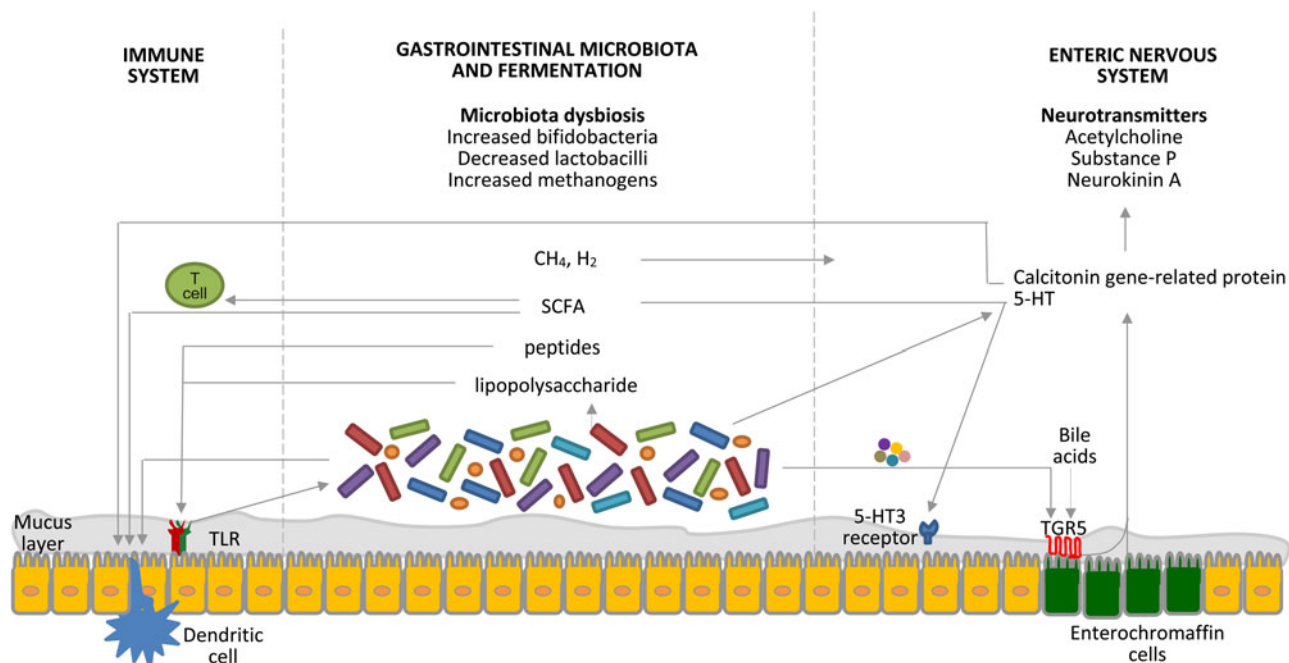
Fig. 1. (Colour online) Interrelated factors involved in the pathophysiology of constipation as potential targets for the therapeutic role of probiotics. Probiotics affect the gastrointestinal microbiota composition, the byproducts of which interact with pattern-recognition receptors, such as toll-like receptors (TLR), as well as with dendritic cells. SCFA increase intestinal regulatory T cells, which limit intestinal inflammation, by reducing histone deacetylase 9 gene expression[71]. The gastrointestinal microbiota regulates 5-hydroxytryptamine (5-HT) production by elevating its synthesis by host enterochromaffin cells via the release of metabolites, such as deoxycholate, which activates TGR5, a G protein-coupled receptor, expressed by enterochromaffin cells[72]. 5-HT is also released from enterochromaffin cells in response to SCFA produced by the gastrointestinal microbiota and stimulates 5-hydroxytryptamine type 3 (5-HT3) receptors located on the vagal afferent fibres, resulting in muscle contractions[27]. Gases produced by the gastrointestinal microbiota seem to affect gut motility via the enteric nervous system, rather than the brain–gut axis; however, the exact mechanisms are still unknown[73]. Moreover, the gastrointestinal microbiota is key to the development of the enteric nervous system, which is the primary regulator of gut motility, and certain bacteria are known to produce 5-HT. Calcitonin gene-related protein, a sensory neuropeptide, modulates dendritic cell function and may signal the presence of gastrointestinal microbiota to the brain[74]. Components of the gastrointestinal microbiota also act via intestinal dendritic cells to influence the inflammatory process[75]. TLR signalling controls the enteric nervous system structure and neuromuscular function and hence motility[76]. Bile acids activate TGR5 expressed by enterochromaffin cells and myenteric neurons and release 5-HT and calcitonin gene-related peptide. Furthermore, probiotics appear to interact with the gut–brain axis via the modulation of afferent sensory nerves that influence gut motility. CH$_4$, methane; H$_2$, hydrogen. Taken with permission from Dimidi et al.[16].

Lastly, there is emerging evidence of an inflammatory response in some people with constipation[43], which may alter enteric sensory and motor function[44]. A potential impact of the probiotics on inflammatory response may, therefore, potentially affect gut motility regulation and, hence, constipation. Indeed, certain probiotics modulate the mucosal immune barrier or systemic immune barrier, and normalise dysmotility[45,46]. For example, *L. paracasei* has been shown to produce antagonistic metabolites and antioxidants, such as glutathionine, to stimulate the immune system *in vitro*[47], while people who consumed *B. lactis* for 6 weeks had significantly higher interferon-α, and polymorphonuclear cell phagocytic capacity compared to placebo[48]. Hence, probiotics may have beneficial effects with regards to some components of the immune system that could potentially influence gut motility, but the effect on their immune regulation in constipation has yet to be extensively investigated.

Therefore, there is evidence that certain probiotics may confer beneficial effects on constipation via their impact on the gut microbiota and fermentation, the enteric and central nervous system, and the immune system. However, the vast majority of evidence originates from *in vitro* and animal studies and thus the mechanisms of action of probiotics in human subjects remain unclear and warrants further research.

Effectiveness of probiotics in constipation

The impact of probiotics on gut transit time (GTT) and the management of constipation have been investigated by many randomised controlled trials (RCT), as well as in systematic reviews and meta-analyses, and these have been performed mainly for the probiotics bifidobacteria and lactobacilli.

In terms of bifidobacteria, one study that investigated the effect of *B. lactis* DN-173010 revealed significant improvement in stool consistency, as well as an increase in stool frequency by +1·5 bowel movements per week,

compared to placebo in 135 women with chronic constipation[49]. Another triple-blind, three arm, placebo-controlled RCT that compared consumption of two different doses of *B. lactis* HN019 and placebo for 2 weeks in eighty-eight people with constipation showed that the probiotic significantly decreased whole GTT in a dose-dependent manner; the high dose probiotic group experienced a reduction of −28 h in whole GTT compared to −19 h decrease and +1 h increase in the low dose and placebo group respectively ($P < 0.001$)[50]. Interestingly, a subsequent double-blind RCT that investigated the effect of the same *B. lactis* HN019 strain on 228 people with chronic constipation showed no significant differences in whole GTT, gut symptoms, constipation-related QoL, stool frequency or stool consistency between the probiotic and placebo groups[51]. Similarly, a double-blind placebo-controlled RCT investigating the effect of *B. lactis* NCC2818 on seventy-five people with chronic constipation showed no significant differences in whole and regional GTT, stool frequency, stool consistency, gut symptoms, QoL and stool microbiota composition[22]. Therefore, differing results have been demonstrated even for different *B. lactis* strains, highlighting the effects of probiotics may be strain-specific.

In terms of lactobacilli, an RCT in twenty people with chronic constipation also showed a significant increase in stool frequency compared to controls following *L. reuteri* DSM 17938 administration, but no improvement in stool consistency[52]. *L. casei* Shirota has been shown to decrease the occurrence of hard stool compared to placebo in chronic constipation, while flatulence and bloating were unaffected[53]. It is worth noting that both the probiotic and placebo groups experienced an increase in stool frequency by +3 and +2 bowel movements per week compared to baseline, respectively, even though this difference between the two groups was significant[53]. Interestingly, an increase in stool frequency was also observed at baseline in both groups compared to the initial assessment which had taken place 2 weeks prior to baseline, indicating a possible placebo effect[53]. Another RCT in ninety people with chronic constipation showed that 4 weeks of *L. casei* Shirota administration did not improve stool consistency and quantity compared to placebo; however, a significant within-group improvement was seen following the probiotic[54]. A double-blind, three-arm RCT in 300 people with hard stools (but not specifically with a diagnosis of constipation) reported a significant improvement in stool frequency and consistency, ease of expulsion, sense of complete evacuation and bloating following the administration of *L. plantarum* LMG P-21021 and *B. breve* DSM 16604, or *B. lactis* LMG P-21384, compared to placebo[55].

Six systematic reviews have investigated the effect of probiotics on outcomes relevant to chronic constipation, as summarised in Table 1. Of these systematic reviews, one did not synthesise data into a meta-analysis due to studies not being sufficiently similar and of sufficient quality[56], and another[57] is similar to a subsequent systematic review published a year later by the same

group[58] and therefore both are summarised in the table but not discussed here. The findings of the remaining four systematic reviews are summarised below.

First, a systematic review and meta-analysis of eleven RCT (n 464) that assessed the effect of probiotics (including *B. lactis*, *B. longum*, *L. casei* and *L. rhamnosus* with doses ranging from $0.48 × 10^9$ to $97.5 × 10^9$ CFU/d and treatment duration from 10 to 28 d) on GTT in both healthy and constipated people was published in 2013 and revealed a significant decrease in GTT (standard mean difference (SMD): 0.40, $P < 0.001$) following probiotic (median period of consumption: 18 d), with the presence of constipation being predictive of greater GTT reductions[59]; greater reductions in GTT were seen in people with constipation compared to those without constipation in a further sub-group analysis of seven studies (SMD: 0.59, $P = 0.01$)[59].

Secondly, in 2014, a systematic review and meta-analysis of two RCT (n 110) that administered $6.5 × 10^9$ CFU/d *L. casei* Shirota for 3 weeks or $1.25 × 10^9$ CFU/d *B. lactis* for 2 weeks showed a significant increase in stool frequency (mean difference: +1.5 bowel movements per week (95 % CI 1.0, 2.0) bowel movements per week), but there was no significant difference in the dichotomous outcome of failure to respond to therapy compared to placebo (risk ratio: 0.29, 95 % CI 0.07, 1.12)[60].

Thirdly, a systematic review and meta-analysis of fourteen RCT (n 1182) was also published in 2014 showing that probiotics significantly reduced whole GTT by −12.4 (95 % CI −22.3, −2.5) h and increased stool frequency by +1.3 bowel movements per week (95 % CI 0.7, 1.9) bowel movements per week)[61]. The dose of probiotics used in the individual studies ranged from 10^8 to $3 × 10^{10}$ CFU/d and the treatment period varied from 2 to 8 weeks. Importantly, the sensitivity analysis showed species- and strain-specific effects of probiotics as stool frequency was significantly higher following *B. lactis* species (mean difference: +1.5 bowel movements per week; 95 % CI 0.7, 2.3 bowel movements per week), but not following *L. casei* Shirota (mean difference: −0.2 bowel movements per week; 95 % CI −0.8, 0.9 bowel movements per week)[61]. Similarly, stool consistency was significantly improved following *B. lactis* administration, but not for *L. casei* Shirota[61].

Fourthly, a recent systematic review and meta-analysis of twenty-one RCT (n 2656) showed that probiotics significantly reduced GTT (SMD: 0.65, $P < 0.001$) in people with constipation, and the mean difference in stool frequency was +0.83 bowel movements per week ($P < 0.001$); however, after adjusting for publication bias, the difference in stool frequency was reduced to 0.3 bowel movements per week (95 % CI −0.01, 0.62 bowel movements per week) which was not statistically significant[58]. The dose of probiotics used in the individual studies ranged from $0.1 × 10^9$ to $30 × 10^9$ CFU/d and the treatment period varied from 7 to 84 d. In addition, the probiotic products used in some of the studies also contained additional ingredients (e.g. psyllium, inulin and fructo-oligosaccharides) that did not allow for the effect of the probiotic alone to be isolated[58]. This, in

Table 1. Systematic reviews and meta-analyses of randomised controlled trials (RCT) investigating the effect of probiotics on gut transit time (GTT) and constipation in adults

Study	Population	Intervention	Comparison	Outcome	Number of studies and subjects	Main findings
Chmielewska and Szajewska[56]	Chronic constipation	Probiotics	Placebo or no intervention	Constipation-related symptoms, stool output	3 RCT 377 subjects	Beneficial effects reported for *B. lactis* DN-173010, *E. coli Nissle* 1917 and *L. casei* Shirota on stool frequency and consistency, however the clinical relevance is unclear due to small sample size, methodological limitations and modest effect sizes.
Miller and Ouewhand[59]	Healthy or constipation	Probiotics. Several products also contained additional active ingredients (e.g. prebiotics)	Comparator group	GTT	11 RCT 464 subjects	Probiotics significantly decreased GTT compared to control (SMD: 0·40, 95 % CI 0·20, 0·59, $P < 0.001$). Probiotics resulted in a greater reduction of GTT in constipation (SMD: 0·59, 95 % CI 0·39, 0·79) than in healthy adults (SMD: 0·17, 95 % CI −0·08, 0·42, $P < 0.01$). Moderate reductions in GTT following *B. lactis* HN019 (SMD: 0·72, 95 % CI 0·27, 1·18, $P < 0.01$) and *B. lactis* DN173010 (SMD: 0·54, 95 % CI:−0·15, 0·94, $P < 0.01$) compared to control. No heterogeneity among studies ($I^2 = 29$ %, $P = 0.15$). Overall, medium risk of bias (Jadad score: 3).
Dimidi *et al.*[61]	Chronic constipation	Probiotics	Placebo supplement or appropriate food comparator without probiotics	GTT, stool output, constipation-related symptoms, adverse events	14 RCT 1182 subjects	Overall, probiotics reduced whole GTT by −12·4 h (95 % CI: −22·3, −2·5 h) and increased stool frequency by +1·3 BM/wk (95 % CI: 0·7, 1·9 BM/wk). *B. lactis* increased stool frequency by 1·5 BM/wk (95 % CI: 0·7, 2·3 BM/wk). *L. casei* Shirota did not impact stool frequency (MD: −0·2 BM/wk; 95 % CI: −0·8, 0·9 BM/wk). *B. lactis* improved stool consistency (SMD: 0·46; 95 % CI: 0·08, 0·85). *L. casei* Shirota did not impact stool consistency (SMD: 0·26; 95 % CI: −0·30, 0·82). No serious adverse events reported with probiotics. There was high heterogeneity among outcomes in studies, high risks of attrition bias, lack of intention-to-treat analysis and selective reporting.
Ford *et al.*[60]	Chronic constipation (>16 years)	Probiotics	Placebo	Dichotomous response to therapy, stool frequency, adverse events	3 RCT 245 subjects	No difference between probiotics and placebo in failure to respond to therapy (RR: 0·29, 95 % CI 0·07, 1·12). Probiotics significantly increased stool frequency by +1·49 BM/wk (95 % CI: 1·02, 1·96 BM/wk). No adverse events were reported. Heterogeneity among the studies for primary outcome ($I^2 = 71$ %, $P = 0.06$) and studies were at unclear or high risk of bias.

Table 1. (*Cont.*)

Study	Population	Intervention	Comparison	Outcome	Number of studies and subjects	Main findings
			Characteristics of studies included in the systematic reviews			
Miller et al.[57]	Adults. Unclear health status	Probiotics. Several products also contained additional active ingredients (e.g. prebiotics)	Comparator group	GTT	15 RCT 675 subjects	Probiotics significantly decreased GTT compared to control (SMD: 0·38, 95 % CI 0·23, 0·53, $P < 0.001$). Probiotics resulted in a greater reduction of GTT in constipation (SMD: 0·57, 95 % CI 0·39, 0·75) than in those without constipation (SMD: 0·22, 95 % CI 0·05, 0·39, $P < 0.01$). Moderate reductions in GTT following *B. lactis* HN019 (SMD: 0·67, 95 % CI 0·37, 0·97, $P < 0.001$) and *B. lactis* DN173010 (SMD: 0·54, 95 % CI: 0·16, 0·92, $P < 0.01$), compared to control. No significant impact on gut transit following *B. lactis* BB12 (SMD: 0·33, 95 % CI: −0·10, 0·75, $P = 0.14$), *L. casei* CRK 431 (SMD: 0·33, 95 % CI −0·10, 0·75, $P = 0.014$) or *L. rhamnosus* GG (SMD: 0·10, 95 % CI −0·35, 0·55, $P = 0.67$). No significant heterogeneity among the studies ($I^2 = 20$ %, $P = 0.22$) and overall, a medium risk of bias (Jadad score: 3).
Miller et al.[58]	Chronic constipation	Probiotics. Several products also contained additional active ingredients (e.g. prebiotics)	Comparator group	Stool frequency, GTT	21 RCT 2656 subjects	Probiotics significantly increased stool frequency by +0·83 BM/wk compared to control (95 % CI 0·53, 1·1, $P < 0.001$). High heterogeneity among studies ($I^2 = 85$ %, $P < 0.001$) and significant publication bias (Egger's $P < 0.01$) was identified; after adjustment for publication bias, probiotics had no significant impact on stool frequency (95 % CI −0·01, 0·62). Probiotics significantly decreased GTT compared to control (SMD: 0·65, 95 % CI 0·33, 0·97, $P < 0.001$). High heterogeneity among studies ($I^2 = 66$ %, $P < 0.01$), but no evidence of publication bias (Egger's $P = 0.52$).

BM, bowel movements; MD, mean difference; SMD, standard mean difference; SR, systematic review; SR/MA, systematic review and meta-analysis; RR, risk ratio; wk, week.

addition to the increased heterogeneity among the studies, denotes that caution is needed in interpreting the results.

The interpretation of these findings from systematic reviews and meta-analyses is challenging due to high heterogeneity and risk of bias of the individual studies, and because species- and strain-specific effects have been identified. First, although meta-analyses synthesise data from many trials in order to improve the statistical power to detect the direction, size and consistency of a clinical effect, they cannot overcome limitations in the design of individual trials. Secondly, different probiotic species and strains have different microbiological and physiological characteristics, and therefore synthesising data from different probiotics and different doses is questionable[62]. Despite these challenges, the results provide cautious optimism for the recommendation of specific probiotic strains in the management of chronic constipation. Further adequately powered RCT using standardised outcome measures are needed to determine which species/strains, doses and duration of probiotics are efficacious.

Use of probiotics in constipation

Given the impact of constipation on QoL, and the effectiveness of certain probiotics on improving constipation-related symptoms, there is increasing interest in using probiotics as a therapeutic option.

A survey in 269 patients attending outpatient gastroenterology clinics identified that 44 % used complementary and alternative medicines, with constipation being the most cited symptom to be addressed, and probiotics being the most common complementary and alternative medicine used[63].

The prevalence of probiotic use in constipation was also confirmed in a recent large cross-sectional study in 2557 members of the UK general population, of whom 1623 had self-reported constipation[64]. This study revealed that the strongest predictors for probiotic use in the general population were having constipation, although this was a population selected for such symptoms[64]. It was also shown that 60 % of the general population with constipation had previously used or were currently using probiotics, compared to 51 % of those without constipation ($P < 0.001$). In fact, self-reported constipation was associated with a 4·7 greater likelihood of current probiotic use (OR: 4·7, 95 % CI 3·8, 5·7, $P < 0.001$). In those with self-reported constipation, significant predictors of probiotic use for either general health or gut health specifically was 'believing probiotics have been tested in research for their effectiveness on constipation' (OR 2·06, 95 % CI 1·56, 2·72, $P < 0.001$), having a university degree (OR: 1·76, 95 % CI 1·32, 2·35, $P < 0.001$), being older (OR: 1·02, 95 % CI 1·01, 1·03, $P < 0.001$), and being female (OR: 0·54, 95 % CI 0·35, 0·81, $P = 0.003$)[64]. The finding that females are more likely to use probiotics than males may be explained by the fact that constipated women report significantly worse QoL compared to constipated men[5]. Therefore, women may be more likely to seek additional or alternative treatments for their symptoms than men. Indeed, a previous study has confirmed that constipated subjects seeking medical care are most likely to be females[65].

In terms of the recommendation of probiotics by doctors, probiotics seem to be commonly recommended for the management of gastrointestinal disorders, such as chronic diarrhoea and irritable bowel syndrome[66]. A UK survey of over 1500 primary care health professionals (e.g. GP, dietitians, nurses) showed that 78 % of GP advise probiotic use for their patients, with constipation being the fifth most common condition for which they are recommended[67]. However, a recent survey in 411 GP and 365 gastroenterology specialists showed that 66 % of GP and 74 % of gastroenterology specialists do not recommend them for constipation[64]. A possible reason for this might be the perceived lack of research evidence in this area. Indeed, only 35 % of GP and 43 % of gastroenterology specialists believe there is evidence for probiotic use in constipation[64], despite existing evidence from RCT showing that certain probiotic strains may improve constipation-related symptoms[58,61]. Interestingly, the gastroenterology specialists who believed there is evidence for probiotics in constipation thought probiotics were more effective for the management of constipation, compared with those who did not believe there is evidence[64]. Belief in the existence of scientific evidence for probiotics among doctors is therefore likely an influencer on the belief in their impact on symptoms and on their behaviour in terms of recommending them to patients.

L. casei Shirota (Yakult) and a mixed preparation of *Streptococcus*, *Bifidobacterium* and *Lactobacillus* (VSL#3) are the probiotics most commonly recommended by gastroenterology specialists and GP for constipation, respectively, whereas *B. lactis* DN-173010 (Activia), *L. casei* DN 114 001 (Actimel) and *L. casei* Shirota (Yakult) are the probiotics most commonly used by the general population with constipation[64]. This is in agreement with the probiotic products that patients with inflammatory bowel disease also choose to use[68]. Although there are a few reports showing beneficial results of some of these strains in constipation, these studies have various limitations, such as small sample sizes or the absence of objective outcomes[20,54,69,70]. Interestingly, no study has been previously published on the effect of Actimel (*L. casei* DN 114 001) on constipation. Therefore, the choice of the probiotic product used by the general population and doctors is not necessarily driven by the current scientific evidence available, but could be influenced by factors such as availability or product advertising.

Indeed, TV adverts were the most common source of information for probiotics in gut health, followed by family, friends and the internet in general (Fig. 2)[64]. This is mostly in agreement with the findings of a previous survey that showed that commercial advertising was the most common source of information for probiotic use in patients with inflammatory bowel disease, followed by family and friends, and healthcare professionals[68].
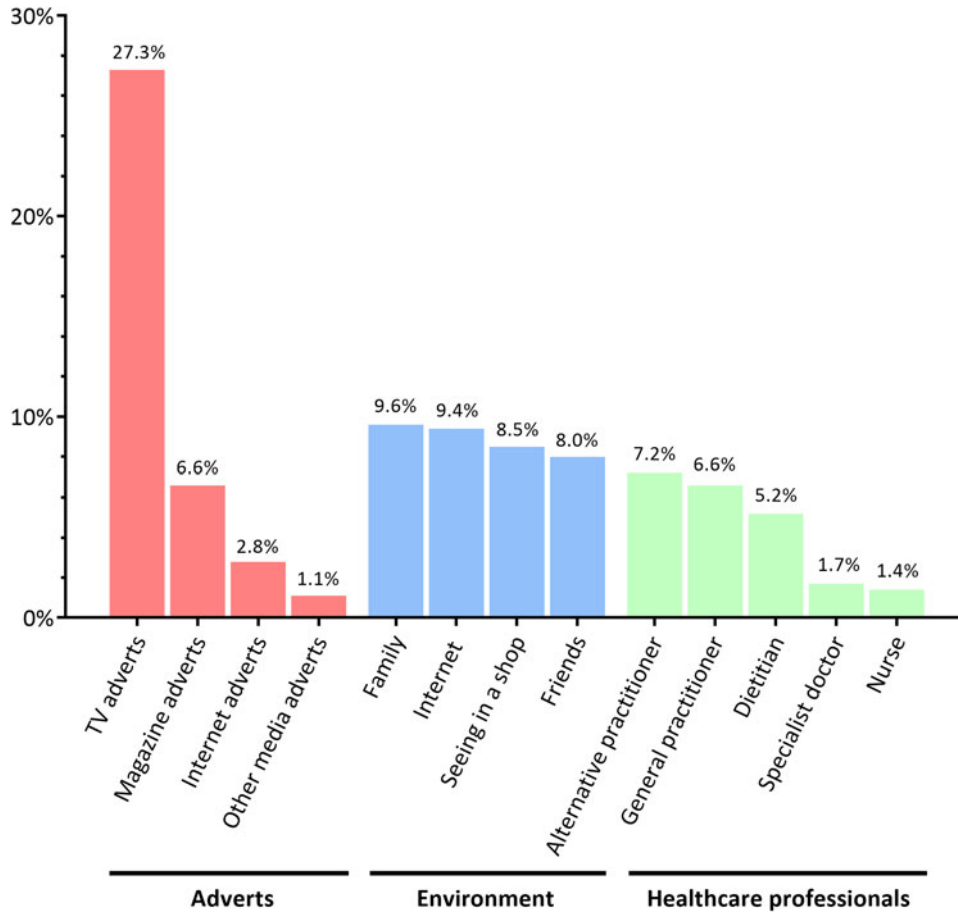
Fig. 2. (Colour online) Sources of information for probiotic use for gut health in people with constipation based on an online survey in 346 people with self-reported constipation. GP, general practitioner (4·6 % did not report a source of information for probiotic use and this is not depicted in the figure). Adapted from data presented in Dimidi *et al.*[64].

Similarly, another survey showed that the most common sources of information for the use of complementary and alternative medicines (including probiotics) in gastrointestinal conditions were family, newspapers, magazines, the internet and friends[63].

Taken together, evidence shows that more people with self-reported constipation use probiotics compared to those without self-reported constipation, however, the vast majority of GP and gastroenterology specialists do not recommend them for constipation. This could possibly be explained by the fact that the vast majority of doctors do not believe probiotics have been tested in research studies for their effect on constipation.

Conclusion

Evidence on the effectiveness of probiotics remains varied, with certain strains exhibiting beneficial effects, while others show little effect. This highlights that the effects of probiotics may be strain-specific and that each strain needs to be tested in a high-quality RCT using standardised and validated assessment techniques in order to be able to devise clinical recommendations regarding probiotic use in constipation in the future. This, in combination with the increased probiotic usage in constipation, indicates a need to clearly communicate and raise the public's awareness on the current state of evidence on probiotics and constipation. Education of healthcare professionals is also required on both the strain-specificity of the effects of probiotics, but also on the degree of probiotic usage by the public; this may encourage healthcare professionals to query about probiotics and discuss their use with patients and, therefore, educate them on the uncertainty in the available evidence.

Conflict of Interest

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Authorship

References

1. Mearin F, Lacy BE, Chang L et al. (2016) Bowel disorders. *Gastroenterology* **150**, 1393–1407.
2. Suares NC & Ford AC (2011) Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. *Am J Gastroenterol* **106**, 1582–1591.
3. Dimidi E, Cox C, Grant R et al. (2019) Perceptions of constipation among the general public and people with constipation differ strikingly from those of general and specialist doctors and the Rome IV criteria. *Am J Gastroenterol* (In the Press).
4. Dimidi E, Dibley L, Cotterill N et al. (2016) Validated constipation symptom and quality-of-life measures neither reflect patient and clinician concerns nor use words familiar to patients. *Gastrointest Nurs* **14**, 29–38.
5. Wald A, Scarpignato C, Kamm MA et al. (2007) The burden of constipation on quality of life: results of a multinational survey. *Aliment Pharmacol Ther* **26**, 227–236.
6. Sun SX, Dibonaventura M, Purayidathil FW et al. (2011) Impact of chronic constipation on health-related quality of life, work productivity, and healthcare resource use: an analysis of the National Health and Wellness Survey. *Dig Dis Sci* **56**, 2688–2695.
7. Nellesen D, Yee K, Chawla A et al. (2013) A systematic review of the economic and humanistic burden of illness in irritable bowel syndrome and chronic constipation. *J Manag Care Pharm* **19**, 755–764.
8. Health and Social Care Information Centre. National Statistics Hospital Episode Statistics, Admitted Patient Care, England – 2017–2018 [Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2017-18.
9. Shafe AC, Lee S, Dalrymple JS et al. (2011) The LUCK study: Laxative Usage in patients with GP-diagnosed Constipation in the UK, within the general population and in pregnancy. An epidemiological study using the General Practice Research Database (GPRD). *Therap Adv Gastroenterol* **4**, 343–363.
10. Guerin A, Carson RT, Lewis B et al. (2014) The economic burden of treatment failure amongst patients with irritable bowel syndrome with constipation or chronic constipation: a retrospective analysis of a Medicaid population. *J Med Econ* **17**, 577–586.
11. Christodoulides S, Dimidi E, Fragkos KC et al. (2016) Systematic review with meta-analysis: effect of fibre supplementation on chronic idiopathic constipation in adults. *Aliment Pharmacol Ther* **44**, 103–116.
12. Bharucha AE, Pemberton JH & Locke GR 3rd. (2013) American Gastroenterological Association technical review on constipation. *Gastroenterology* **144**, 218–238.
13. Johanson JF & Kralstein J (2007) Chronic constipation: a survey of the patient perspective. *Aliment Pharmacol Ther* **25**, 599–608.
14. Emmanuel A, Quigley EM, Simren M et al. (2013) Factors affecting satisfaction with treatment in European women with chronic constipation: An internet survey. *United European Gastroenterol J* **1**, 375–384.
15. Hill C, Guarner F, Reid G et al. (2014) Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol* **11**, 506–514.
16. Dimidi E, Christodoulides S, Scott SM et al. (2017) Mechanisms of action of probiotics and the gastrointestinal microbiota on gut motility and constipation. *Adv Nutr* **8**, 484–494.
17. Chassard C, Dapoigny M, Scott KP et al. (2012) Functional dysbiosis within the gut microbiota of patients with constipated-irritable bowel syndrome. *Aliment Pharmacol Ther* **35**, 828–838.
18. Parthasarathy G, Chen J, Chen X et al. (2016) Relationship between microbiota of the colonic mucosa vs feces and symptoms, colonic transit, and methane production in female patients with chronic constipation. *Gastroenterology* **150**, 367–379.
19. Ishizuka A, Tomizuka K, Aoki R et al. (2012) Effects of administration of *Bifidobacterium animalis* subsp. *lactis* GCL2505 on defecation frequency and bifidobacterial microbiota composition in humans. *J Biosci Bioeng* **113**, 587–591.
20. Kim SE, Choi SC, Park KS et al. (2015) Change of fecal flora and effectiveness of the short-term VSL#3 probiotic treatment in patients with functional constipation. *J Neurogastroenterol Motil* **21**, 111–120.
21. Matsumoto K, Takada T, Shimizu K et al. (2006) The effects of a probiotic milk product containing *Lactobacillus casei* strain Shirota on the defecation frequency and the intestinal microflora of sub-optimal health state volunteers: a randomized placebo-controlled cross-over study. *Biosci Microflora* **25**, 39–48.
22. Dimidi E, Zdanaviciene A, Christodoulides S et al. (2019) Randomised clinical trial: *Bifidobacterium lactis* NCC2818 probiotic vs placebo, and impact on gut transit time, symptoms, and gut microbiology in chronic constipation. *Aliment Pharmacol Ther* **49**, 251–264.
23. Morrison DJ & Preston T (2016) Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. *Gut Microbes* **7**, 189–200.
24. Yajima T (1985) Contractile effect of short-chain fatty acids on the isolated colon of the rat. *J Physiol* **368**, 667–678.
25. Cherbut C, Aube AC, Blottiere HM et al. (1996) In vitro contractile effects of short chain fatty acids in the rat terminal ileum. *Gut* **38**, 53–58.
26. Rondeau MP, Meltzer K, Michel KE et al. (2003) Short chain fatty acids stimulate feline colonic smooth muscle contraction. *J Feline Med Surg* **5**, 167–173.
27. Fukumoto S, Tatewaki M, Yamada T et al. (2003) Short-chain fatty acids stimulate colonic transit via intraluminal 5-HT release in rats. *Am J Physiol Regul Integr Comp Physiol* **284**, R1269–R1276.

28. Liu ZM, Xu ZY, Han M *et al.* (2015) Efficacy of pasteurised yoghurt in improving chronic constipation: A randomised, double-blind, placebo-controlled trial. *Int Dairy J* **40**, 1–5.

29. Spanhaak S, Havenaar R & Schaafsma G (1998) The effect of consumption of milk fermented by *Lactobacillus casei* strain Shirota on the intestinal microflora and immune parameters in humans. *Eur J Clin Nutr* **52**, 899–907.

30. Valerio F, Russo F, de Candia S *et al.* (2010) Effects of Probiotic *Lactobacillus paracasei*-enriched artichokes on constipated patients: a pilot study. *J Clin Gastroenterol* **44**, S49–S53.

31. Riezzo G, Orlando A, D'Attoma B *et al.* (2012) Randomised clinical trial: efficacy of *Lactobacillus paracasei*-enriched artichokes in the treatment of patients with functional constipation – a double-blind, controlled, crossover study. *Aliment Pharmacol Ther* **35**, 441–450.

32. Sakai T, Makino H, Ishikawa E *et al.* (2011) Fermented milk containing *Lactobacillus casei* strain Shirota reduces incidence of hard or lumpy stools in healthy population. *Int J Food Sci Nutr* **62**, 423–430.

33. Marsono Y, Illman RJ, Clarke JM *et al.* (1993) Plasma lipids and large bowel volatile fatty acids in pigs fed on white rice, brown rice and rice bran. *Br J Nutr* **70**, 503–513.

34. Matsuo K, Ota H, Akamatsu T *et al.* (1997) Histochemistry of the surface mucous gel layer of the human colon. *Gut* **40**, 782–789.

35. Snape WJ Jr., Shiff S & Cohen S (1980) Effect of deoxycholic acid on colonic motility in the rabbit. *Am J Physiol* **238**, G321–G325.

36. Keely SJ, Scharl MM, Bertelsen LS *et al.* (2007) Bile acid-induced secretion in polarized monolayers of T84 colonic epithelial cells: structure-activity relationships. *Am J Physiol Gastrointest Liver Physiol* **292**, G290–G297.

37. Caballero-Franco C, Keller K, De Simone C *et al.* (2007) The VSL#3 probiotic formula induces mucin gene expression and secretion in colonic epithelial cells. *Am J Physiol Gastrointest Liver Physiol* **292**, G315–G322.

38. Ouwehand AC, Lagstrom H, Suomalainen T *et al.* (2002) Effect of probiotics on constipation, fecal azoreductase activity and fecal mucin content in the elderly. *Ann Nutr Metab* **46**, 159–162.

39. Marteau P, Cuillerier E, Meance S *et al.* (2002) *Bifidobacterium animalis* strain DN-173 010 shortens the colonic transit time in healthy women: a double-blind, randomized, controlled study. *Aliment Pharmacol Ther* **16**, 587–593.

40. Tillisch K, Labus J, Kilpatrick L *et al.* (2013) Consumption of fermented milk product with probiotic modulates brain activity. *Gastroenterology* **144**, 1394–1401.

41. Kunze WA, Mao YK, Wang B *et al.* (2009) *Lactobacillus reuteri* enhances excitability of colonic AH neurons by inhibiting calcium-dependent potassium channel opening. *J Cell Mol Med* **13**, 2261–2270.

42. Wang B, Mao YK, Diorio C *et al.* (2010) *Lactobacillus reuteri* ingestion and IK(Ca) channel blockade have similar effects on rat colon motility and myenteric neurones. *Neurogastroenterol Motil* **22**, 98–107.

43. Khalif IL, Quigley EM, Konovitch EA *et al.* (2005) Alterations in the colonic flora and intestinal permeability and evidence of immune activation in chronic constipation. *Dig Liver Dis* **37**, 838–849.

44. Collins SM (1996) The immunomodulation of enteric neuromuscular function: implications for motility and inflammatory disorders. *Gastroenterology* **111**, 1683–1699.

45. Guarino MP, Altomare A, Stasi E *et al.* (2008) Effect of acute mucosal exposure to *Lactobacillus rhamnosus* GG on human colonic smooth muscle cells. *J Clin Gastroenterol* **42**(Suppl 3 Pt 2), S185–S190.

46. Isolauri E, Sutas Y, Kankaanpaa P *et al.* (2001) Probiotics: effects on immunity. *Am J Clin Nutr* **73**(2 Suppl), 444S–450S.

47. Ibnou-Zekri N, Blum S, Schiffrin EJ *et al.* (2003) Divergent patterns of colonization and immune response elicited from two intestinal *Lactobacillus* strains that display similar properties in vitro. *Infect Immun* **71**, 428–436.

48. Arunachalam K, Gill HS & Chandra RK (2000) Enhancement of natural immune function by dietary consumption of *Bifidobacterium lactis* (HN019). *Eur J Clin Nutr* **54**, 263–267.

49. Yang YX, He M, Hu G *et al.* (2008) Effect of a fermented milk containing *Bifidobacterium lactis* DN-173010 on Chinese constipated women. *World J Gastroenterol* **14**, 6237–6243.

50. Waller PA, Gopal PK, Leyer GJ *et al.* (2011) Dose-response effect of *Bifidobacterium lactis* HN019 on whole gut transit time and functional gastrointestinal symptoms in adults. *Scand J Gastroenterol* **46**, 1057–1064.

51. Ibarra A, Latreille-Barbier M, Donazzolo Y *et al.* (2018) Effects of 28-day *Bifidobacterium animalis* subsp. *lactis* HN019 supplementation on colonic transit time and gastrointestinal symptoms in adults with functional constipation: a double-blind, randomized, placebo-controlled, and dose-ranging trial. *Gut Microbes* **9**, 236–251.

52. Ojetti V, Ianiro G, Tortora A *et al.* (2014) The effect of *Lactobacillus reuteri* supplementation in adults with chronic functional constipation: a randomized, double-blind, placebo-controlled trial. *J Gastrointestin Liver Dis* **23**, 387–391.

53. Koebnick C, Wagner I, Leitzmann P *et al.* (2003) Probiotic beverage containing *Lactobacillus casei* Shirota improves gastrointestinal symptoms in patients with chronic constipation. *Can J Gastroenterol* **17**, 655–659.

54. Mazlyn MM, Nagarajah LH, Fatimah A *et al.* (2013) Effects of a probiotic fermented milk on functional constipation: a randomized, double-blind, placebo-controlled study. *J Gastroenterol Hepatol* **28**, 1141–1147.

55. Del Piano M, Carmagnola S, Anderloni A *et al.* (2010) The use of probiotics in healthy volunteers with evacuation disorders and hard Stools. A double-blind, randomized, placebo-controlled study. *J Clin Gastroenterol* **44**, S30–SS4.

56. Chmielewska A & Szajewska H (2010) Systematic review of randomised controlled trials: probiotics for functional constipation. *World J Gastroenterol* **16**, 69–75.

57. Miller LE, Zimmermann AK & Ouwehand AC (2016) Contemporary meta-analysis of short-term probiotic consumption on gastrointestinal transit. *World J Gastroenterol* **22**, 5122–5131.

58. Miller LE, Ouwehand AC & Ibarra A (2017) Effects of probiotic-containing products on stool frequency and intestinal transit in constipated adults: systematic review and meta-analysis of randomized controlled trials. *Ann Gastroenterol* **30**, 629–639.

59. Miller LE & Ouwehand AC (2013) Probiotic supplementation decreases intestinal transit time: meta-analysis of randomized controlled trials. *World J Gastroenterol* **19**, 4718–4725.

60. Ford AC, Quigley EM, Lacy BE *et al.* (2014) Efficacy of prebiotics, probiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic review and meta-analysis. *Am J Gastroenterol* **109**, 1547–1561.

61. Dimidi E, Christodoulides S, Fragkos KC *et al.* (2014) The effect of probiotics on functional constipation in adults: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr* **100**, 1075–1084.

62. Whelan K (2014) Editorial: The importance of systematic reviews and meta-analyses of probiotics and prebiotics. *Am J Gastroenterol* **109**, 1563–1565.

63. Hung A, Kang N, Bollom A *et al.* (2015) Complementary and alternative medicine use is prevalent among patients with gastrointestinal diseases. *Dig Dis Sci* **60**, 1883–1888.

64. Dimidi E, Cox C, Scott SM *et al.* (2019) Probiotic use is common in constipation, but only a minority of general and specialist doctors recommend them and consider there to be an evidence base. *Nutrition* **61**, 157–163.

65. Cheng C, Chan AO, Hui WM *et al.* (2003) Coping strategies, illness perception, anxiety and depression of patients with idiopathic constipation: a population-based study. *Aliment Pharmacol Ther* **18**, 319–326.

66. Cordina C, Shaikh I, Shrestha S *et al.* (2011) Probiotics in the management of gastrointestinal disease: analysis of the attitudes and prescribing practices of gastroenterologists and surgeons. *J Dig Dis* **12**, 489–496.

67. Jordan D, Johnson N & Thomas L (2015) Probiotics in primary care: a survey of health professionals. *Practice Nursing* **26**, 550–554.

68. Hedin CR, Mullard M, Sharratt E *et al.* (2010) Probiotic and prebiotic use in patients with inflammatory bowel disease: a case-control study. *Inflamm Bowel Dis* **16**, 2099–2108.

69. He M, Hu G & Yang Y (2009) Effect of probiotic yogurt containing *Bifidobacterium animalis* strain DN-173010 on symptoms of constipation. *Chin J Gastroenterol* **14**, 287–289.

70. Krammer H, von Seggern H, Schaumburg J *et al.* (2011) Effect of *Lactobacillus casei* Shirota on colonic transit time in patients with chronic constipation. *Coloproctology* **33**, 109–113.

71. Kieffer DA, Martin RJ & Adams SH (2016) Impact of dietary fibers on nutrient management and detoxification organs: gut, liver, and kidneys. *Adv Nutr* **7**, 1111–1121.

72. Yano JM, Yu K, Donaldson GP *et al.* (2015) Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell* **161**, 264–276.

73. Triantafyllou K, Chang C & Pimentel M (2014) Methanogens, methane and gastrointestinal motility. *J Neurogastroenterol Motil* **20**, 31–40.

74. Collins SM & Bercik P (2009) The relationship between intestinal microbiota and the central nervous system in normal gastrointestinal function and disease. *Gastroenterology* **136**, 2003–2014.

75. Ng SC, Benjamin JL, McCarthy NE *et al.* (2011) Relationship between human intestinal dendritic cells, gut microbiota, and disease activity in Crohn's disease. *Inflamm Bowel Dis* **17**, 2027–2037.

76. Brun P, Giron MC, Qesari M *et al.* (2013) Toll-like receptor 2 regulates intestinal inflammation by controlling integrity of the enteric nervous system. *Gastroenterology* **145**, 1323–1333.