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Probiotics and constipation: mechanisms of action, evidence for effectiveness, and utilization by patients and health care professionals

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ABSTRACT

The aim of this narrative review is to assess and present the evidence on the mechanisms of action of probiotics in constipation, their effectiveness, and their utilisation by patients and health care 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, the 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 the 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 the 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.

INTRODUCTION

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 3,000 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 (GPs) 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 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, and lower health-related quality of life 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 quality of life (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 $1,912 to $7,522 per year per patient in the United States [7], whilst in the United Kingdom (UK), there are more than 1 million GP consultations and 69,054 hospital admissions per year where constipation is a diagnosis[8, 9]. Treatment failure for constipation is also associated with a total incremental cost of $2,978, 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 in chronic constipation as a potential alternative management strategy. This review aims to assess and present the evidence on the mechanisms of action of probiotics in constipation, their utilisation by patients and health care professionals and the 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 **Figure 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 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 short-chain fatty acids (SCFA), which are primary end-products of fermentation of non-digestible food components including carbohydrates (Figure 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 little evidence that probiotics affect bile acid metabolism or mucin excretion in humans [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 on 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.

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-alpha, and polymorphonuclear cell phagocytic capacity compared to placebo [48]. Hence, probiotics may have beneficial effects with regard 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 humans 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 has been investigated by many randomised controlled trials (RCTs), 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/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 two weeks in 88 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 in 228 people with chronic constipation showed no significant differences in whole GTT, gut symptoms, constipation-related quality of life, 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 in 75 people with chronic constipation showed no significant differences in whole and regional GTT, stool frequency, stool consistency, gut symptoms, quality of life, 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 20 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/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 two weeks prior to baseline, indicating a possible placebo effect [53]. Another RCT in 90 people with chronic constipation showed that four 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, 3-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 in outcomes relevant to chronic constipation, summarised in **Table 1**. Of these systematic reviews, one did not synthesize 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.

Firstly, a systematic review and meta-analysis of 11 RCTs (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 days) on gut transit time 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 days), 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 7 studies (SMD: 0.59, $p=0.01$) [(59)].

Secondly, in 2014, a systematic review and meta-analysis of two RCTs (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 (RR: 0.29, 95% CI 0.07-1.12) [(60)].

Thirdly, a systematic review and meta-analysis of 14 RCTs (n=1,182) was also published in 2014 showing that probiotics significantly reduced whole gut transit time by -12.4 h (95% CI: -22.3, -2.5 h) and increased stool frequency by +1.3 bowel movements/week (95% CI: 0.7, 1.9 bowel movements/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/week; 95% CI: 0.7, 2.3 bowel movements/week), but not following *L. casei* Shirota (mean difference: -0.2 bowel movements/week; 95% CI: -0.8, 0.9 bowel movements/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 21 RCTs (n=2,656) showed that probiotics significantly reduced gut transit time (SMD: 0.65, $p<0.001$) in people with constipation, and the mean difference in stool frequency was +0.83 bowel movements/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 to 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 days. 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 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. Firstly, although meta-analyses synthesize 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 synthesizing 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 RCTs using standardized 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 quality of life, and the effectiveness of certain probiotics in 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 (CAM), with constipation being the most cited symptom to be addressed, and probiotics being the most common CAM used [63].

The prevalence of probiotic use in constipation was also confirmed in a recent large cross-sectional study in 2,557 members of the UK general population, of whom 1,623 had self-reported constipation [64]. This study revealed that the strongest predictors for probiotic use in the general population was 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 in 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 quality of life 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. GPs, dietitians, nurses) showed that 78% of GPs advise probiotic use for their patients, with constipation being the 5th most common condition for which they are recommended [67]. However, a recent survey in 411 GPs and 365 gastroenterology specialists showed that 66% of GPs 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 GPs and 43% of GI specialists believe there is evidence for probiotic use in constipation[64], despite existing evidence from RCTs showing that certain probiotic strains may improve constipation-related symptoms[58, 61]. Interestingly, the gastroenterologist 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.

Lactobacillus casei Shirota (Yakult) and a mixed preparation of *Streptococcus, Bifidobacterium* and *Lactobacillus* (VSL#3) are the probiotics most commonly recommended by gastroenterology specialists and GPs 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 (**Figure 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]. Similarly, another survey showed that the most common sources of information for the use of CAM (including probiotics) in gastrointestinal conditions were family, newspapers, magazines, the internet and friends [63].

Taken together, the evidence shows that more people with self-reported constipation use probiotics compared to those without self-reported constipation, however, the vast majority of GPs and gastroenterologist 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 in constipation.

CONCLUSION

The 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 standardized 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 the evidence on probiotics and constipation. Education of health care 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 health care professionals to query about probiotics and discuss their use with patients and, therefore, educate them on the uncertainty in the available evidence.

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FIGURE

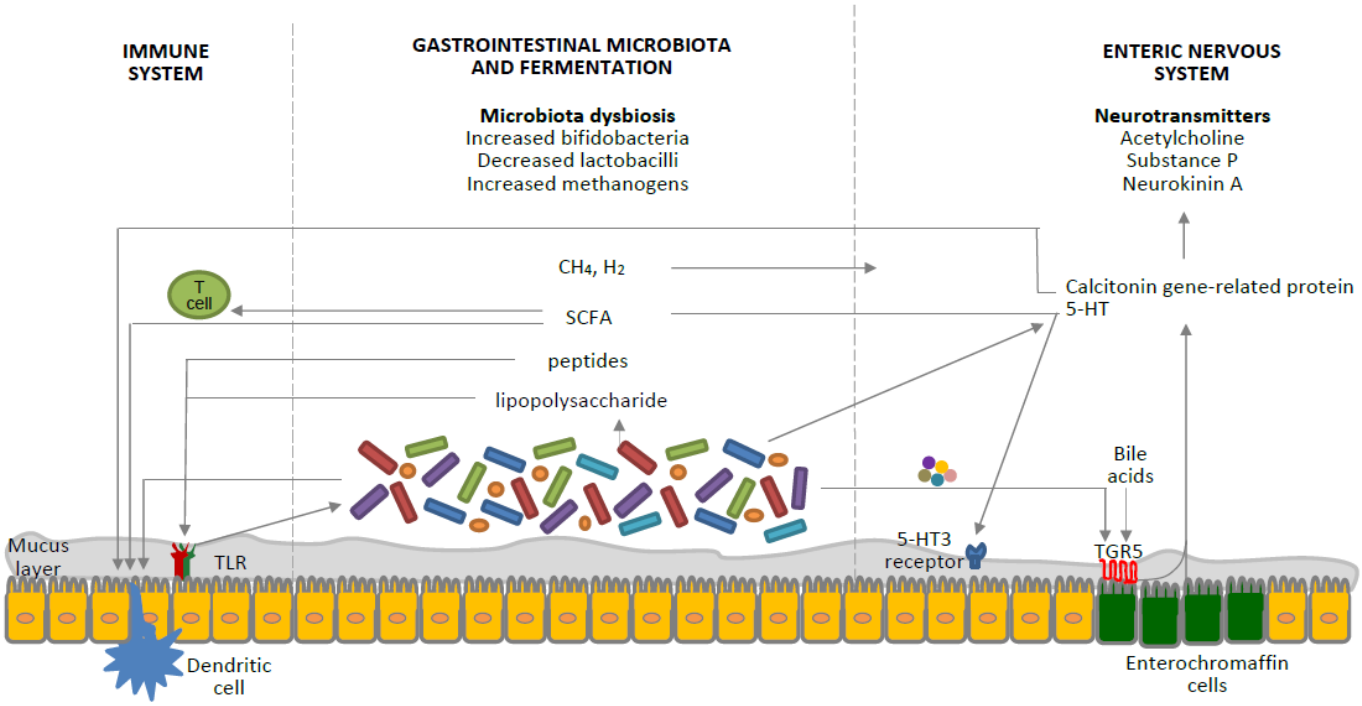

Figure 1: Interrelated factors involved in the pathophysiology of constipation as potential targets for the therapeutic role of probiotics. Probiotics affect the gastrointestinal microbiota composition, the byproducts of which interact with pattern-recognition receptors, such as TLRs, as well as with dendritic cells. SCFAs increase intestinal regulatory T cells, which limit intestinal inflammation, by reducing histone deacetylase 9 gene expression[71]. The gastrointestinal microbiota regulates 5-HT production by elevating its synthesis by host enterochromaffin cells via the release of metabolites, such as deoxycholate, which activates TGR5, expressed by enterochromaffin cells[72]. 5-HT is also released from enterochromaffin cells in response to SCFAs produced by the gastrointestinal microbiota and stimulates 5-HT3 receptors located on the vagal afferent fibers, 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]. TLRs signaling 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 genre–related peptide. Furthermore, probiotics appear to interact with the gut-brain axis via the modulation of afferent sensory nerves that influence gut motility. CH4, methane; H^2, hydrogen; TGR5, a G protein–coupled receptor; TLR, toll-like receptor; 5-HT, 5-hydroxytryptamine; 5-HT3, 5-hydroxytryptamine type 3. Taken with permission from Dimidi et al. 2017 [16].

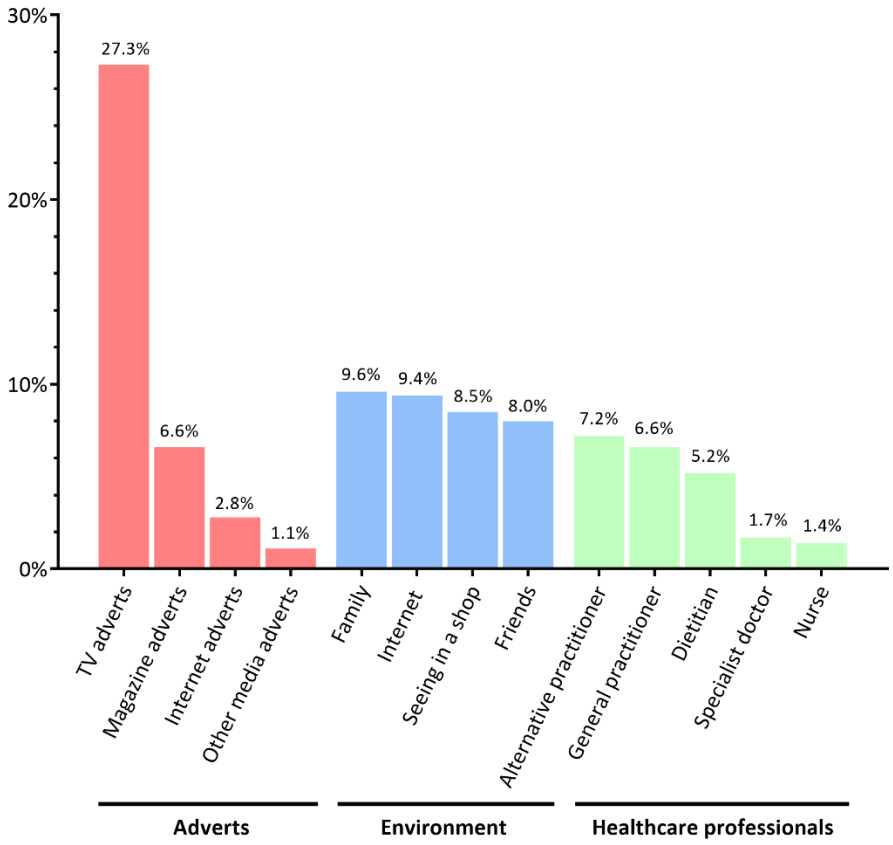

Figure 2: Sources of information for probiotic use for gut health in people with constipation based on an online survey in 346 people with self-reported constipation. GP, general practitioner (4.6% did not report a source of information for probiotic use and this is not depicted in the figure). Adapted from data presented in Dimidi et al. 2019 [64].

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

Study	Review	Characteristics of studies included in the systematic reviews				Number of studies and subjects	Main findings
		Population	Intervention	Comparison	Outcome		
Chmielewska & Szajewska, 2010 [56]	SR	Chronic constipation	Probiotics	Placebo or no intervention	Constipation-related symptoms, stool output	3 RCTs 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 unclear due to small sample size, methodological limitations and modest effect sizes.
Miller & Ouewhand, 2013[59]	SR/MA	Healthy or constipation	Probiotics. Several also with additional active ingredients (e.g. prebiotics)	Comparator group	Gut transit time	11 RCTs 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 gut transit time 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.* 2014 [61]	SR/MA	Chronic constipation	Probiotics	Placebo supplement or appropriate food comparator without probiotics	Gut transit time, stool output, constipation-related symptoms, adverse events	14 RCTs 1,182 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.

Study	Review	Characteristics of studies included in the systematic reviews				Number of studies and subjects	Main findings
		Population	Intervention	Comparison	Outcome		
Ford *et al.* 2014 [60]	SR/MA	Chronic constipation (>16 y)	Probiotics	Placebo	Dichotomous response to therapy, stool frequency, adverse events	3 RCTs 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.
Miller *et al.* 2016[57]	SR/MA	Adults. Unclear health status.	Probiotics. Several products also contained additional active ingredients (e.g. prebiotics)	Comparator group	Gut transit time	15 RCTs 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.* 2017[58]	SR/MA	Chronic constipation	Probiotics. Several products also contained additional active ingredients (e.g. prebiotics)	Comparator group	Stool frequency, gut transit time	21 RCTs 2,656 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; GTT: gut transit time; MD: mean difference; SMD: Standard Mean Difference; SR: Systematic review; SR/MA: Systematic review and meta-analysis; RR: Risk Ratio; CI: Confidence Interval; wk: week.