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

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26

1 **ABSTRACT**

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

17

18

## 1 INTRODUCTION

2 Chronic constipation is a functional gastrointestinal disorder characterised by persistently difficult,  
3 infrequent or incomplete defaecation that affects approximately 14% of the general population <sup>(1,</sup>  
4 <sup>2)</sup>. It may be diagnosed using symptom-based diagnostic criteria, such as the Rome IV criteria,  
5 according to which a diagnosis is made when two or more of the following symptoms are present  
6 for at least a quarter of bowel movements: hard or lumpy stools, straining, a sense of incomplete  
7 evacuation, use of manual manoeuvres to pass stool and a sense of anorectal obstruction <sup>(1)</sup>.  
8 Nevertheless, both the general population and some doctors consider various other symptoms  
9 important for a diagnosis of constipation, including spending a long time on the toilet without  
10 achieving a bowel movement <sup>(3, 4)</sup>. Furthermore, a large cross-sectional survey in over 3,000  
11 members of the general population and doctors revealed differences in the symptoms considered  
12 important for a diagnosis of constipation between the general population, general practitioners  
13 (GPs) and gastroenterology specialists, and that there was imperfect agreement with the Rome IV  
14 criteria, highlighting the difficulties and variability in the diagnosis of chronic constipation <sup>(3,4)</sup>.

15 However chronic constipation is diagnosed, it impacts on people's lives, with straining, bloating,  
16 abdominal discomfort, abdominal pain and spending a long time on the toilet without a bowel  
17 movement being the symptoms most commonly described as being burdensome <sup>(3, 5, 6)</sup>. A  
18 multinational survey has shown a negative correlation between the total number of symptoms of  
19 constipation experienced and quality of life, and lower health-related quality of life has been  
20 reported by women, as well as by those under psychological stress, such as unemployment <sup>(5)</sup>.  
21 Chronic constipation also impacts on work productivity <sup>(6)</sup>.

22 The high prevalence of constipation, its chronicity and its impact on quality of life (QoL)  
23 contribute to the utilisation of significant healthcare resources. The direct annual cost associated  
24 with the management of constipation has been shown to range from \$1,912 to \$7,522 per year per  
25 patient in the United States <sup>(7)</sup>, whilst in the United Kingdom (UK), there are more than 1 million  
26 GP consultations and 69,054 hospital admissions per year where constipation is a diagnosis<sup>(8, 9)</sup>.  
27 Treatment failure for constipation is also associated with a total incremental cost of \$2,978, with  
28 60% being spent on medical service costs <sup>(10)</sup>, highlighting the importance of early successful  
29 management.

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

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

## 18 **POTENTIAL MECHANISMS OF ACTION OF PROBIOTICS IN CONSTIPATION**

19 Probiotics are “live microorganisms that, when administered in adequate amounts, confer a health  
20 benefit on the host” <sup>(15)</sup>. There are several mechanisms of action of probiotics relevant to  
21 constipation, including modulation of the gut microbiota and fermentation, nervous system and  
22 immune system, as shown in **Figure 1** <sup>(16)</sup>.

23 Several studies have demonstrated differences in the gut microbiota composition between people  
24 with and without constipation <sup>(16)</sup>, with a decreased concentration of bifidobacteria and lactobacilli,  
25 as well as increased numbers of *Bacteroidetes*, identified in people with constipation <sup>(16-18)</sup>. Faecal  
26 microbiota composition has been shown to correlate with colonic transit time, while the colonic  
27 mucosal microbiota composition correlates with constipation status <sup>(18)</sup>. Although the impact of  
28 probiotics on the microbiota in constipation is not well understood, a small number of trials have  
29 demonstrated significant changes in gut microbiota composition following probiotic  
30 supplementation <sup>(16)</sup>. For example, supplementation of *Bifidobacterium lactis* GCL2505 or

1 *Lactobacillus casei* Shirota increased concentration of bifidobacteria, however *B. lactis* NCC2818  
2 and VSL#3, a multi-strain probiotic, had no impact on gut microbiota composition <sup>(19-22)</sup>. These  
3 results suggest that administration of probiotics may impact on certain microbiota components,  
4 but it is yet to be determined what impact this change has on constipation, and whether effects are  
5 mediated through microbiota modification or other mechanisms.

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

19 The colonic mucus may also play a role in regulating gut motility as it acts as a lubricant and  
20 facilitates stool passage <sup>(34)</sup>, while bile acids may affect motility through luminal electrolyte and  
21 water transport regulation as demonstrated by *in vitro* and animal studies <sup>(35, 36)</sup>. However, there is  
22 currently little evidence that probiotics affect bile acid metabolism or mucin excretion in humans  
23 <sup>(37-39)</sup>.

24 Modulation of microbiota-gut-brain interactions with probiotics has been demonstrated in healthy  
25 people<sup>(40)</sup>, while *L. reuteri* has been shown to increase the excitability of myenteric neurons in rats  
26 and interact with the gut-brain axis via alterations on afferent sensory nerves that affect gut  
27 motility, indicating that that probiotics do impact on the enteric nervous system <sup>(41, 42)</sup>. Hence,  
28 probiotic-mediated modulation of microbiota-gut-brain interactions has been proposed as a  
29 potential novel therapeutic tool for the treatment of gut motility disorders, including constipation;  
30 however, there are no human studies in constipation.

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

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

## 17 **EFFECTIVENESS OF PROBIOTICS IN CONSTIPATION**

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

22 In terms of bifidobacteria, one study that investigated the effect of *B. lactis* DN-173010 revealed  
23 significant improvement in stool consistency, as well as an increase in stool frequency by +1.5  
24 bowel movements/week, compared to placebo in 135 women with chronic constipation <sup>(49)</sup>.  
25 Another triple-blind, three arm, placebo-controlled RCT that compared consumption of two  
26 different doses of *B. lactis* HN019 and placebo for two weeks in 88 people with constipation  
27 showed that the probiotic significantly decreased whole GTT in a dose-dependent manner; the  
28 high dose probiotic group experienced a reduction of -28 h in whole GTT compared to -19 h  
29 decrease and +1 h increase in the low dose and placebo group respectively ( $p < 0.001$ ) <sup>(50)</sup>.  
30 Interestingly, a subsequent double-blind RCT that investigated the effect of the same *B. lactis*

1 HN019 strain in 228 people with chronic constipation showed no significant differences in whole  
2 GTT, gut symptoms, constipation-related quality of life, stool frequency or stool consistency  
3 between the probiotic and placebo groups <sup>(51)</sup>. Similarly, a double-blind placebo-controlled RCT  
4 investigating the effect of *B. lactis* NCC2818 in 75 people with chronic constipation showed no  
5 significant differences in whole and regional GTT, stool frequency, stool consistency, gut  
6 symptoms, quality of life, and stool microbiota composition <sup>(22)</sup>. Therefore, differing results have  
7 been demonstrated even for different *B. lactis* strains, highlighting the effects of probiotics may  
8 be strain-specific.

9 In terms of lactobacilli, an RCT in 20 people with chronic constipation also showed a significant  
10 increase in stool frequency compared to controls following *L. reuteri* DSM 17938 administration,  
11 but no improvement in stool consistency <sup>(52)</sup>. *L. casei* Shirota has been shown to decrease the  
12 occurrence of hard stool compared to placebo in chronic constipation, while flatulence and  
13 bloating were unaffected <sup>(53)</sup>. It is worth noting that both the probiotic and placebo groups  
14 experienced an increase in stool frequency by +3 and +2 bowel movements/week compared to  
15 baseline, respectively, even though this difference between the two groups was significant <sup>(53)</sup>.  
16 Interestingly, an increase in stool frequency was also observed at baseline in both groups compared  
17 to the initial assessment which had taken place two weeks prior to baseline, indicating a possible  
18 placebo effect <sup>(53)</sup>. Another RCT in 90 people with chronic constipation showed that four weeks of  
19 *L. casei* Shirota administration did not improve stool consistency and quantity compared to  
20 placebo; however, a significant within-group improvement was seen following the probiotic <sup>(54)</sup>.  
21 A double-blind, 3-arm RCT in 300 people with hard stools (but not specifically with a diagnosis  
22 of constipation) reported a significant improvement in stool frequency and consistency, ease of  
23 expulsion, sense of complete evacuation and bloating following the administration of *L. plantarum*  
24 LMG P-21021 and *B. breve* DSM 16604, or *B. lactis* LMG P-21384, compared to placebo <sup>(55)</sup>.

25 Six systematic reviews have investigated the effect of probiotics in outcomes relevant to chronic  
26 constipation, summarised in **Table 1**. Of these systematic reviews, one did not synthesize data into  
27 a meta-analysis due to studies not being sufficiently similar and of sufficient quality<sup>(56)</sup>, and  
28 another<sup>(57)</sup> is similar to a subsequent systematic review published a year later by the same group<sup>(58)</sup>  
29 and therefore both are summarised in the table but not discussed here. The findings of the  
30 remaining four systematic reviews are summarised below.

1 Firstly, a systematic review and meta-analysis of 11 RCTs (n=464) that assessed the effect of  
2 probiotics (including *B. lactis*, *B. longum*, *L. casei* and *L. rhamnosus* with doses ranging from  
3  $0.48 \times 10^9$  to  $97.5 \times 10^9$  CFU/d and treatment duration from 10 to 28 days) on gut transit time in both  
4 healthy and constipated people was published in 2013 and revealed a significant decrease in GTT  
5 (Standard Mean Difference, SMD: 0.40,  $p < 0.001$ ) following probiotic (median period of  
6 consumption: 18 days), with the presence of constipation being predictive of greater GTT  
7 reductions<sup>(59)</sup>; greater reductions in GTT were seen in people with constipation compared to those  
8 without constipation in a further sub-group analysis of 7 studies (SMD: 0.59,  $p = 0.01$ )<sup>(59)</sup>.

9 Secondly, in 2014, a systematic review and meta-analysis of two RCTs (n=110) that administered  
10  $6.5 \times 10^9$  CFU/d *L. casei* Shirota for 3 weeks or  $1.25 \times 10^9$  CFU/d *B. lactis* for 2 weeks showed a  
11 significant increase in stool frequency (mean difference: +1.5 bowel movements per week, 95%  
12 CI: 1.0-2.0 bowel movements per week), but there was no significant difference in the  
13 dichotomous outcome of failure to respond to therapy compared to placebo (RR: 0.29, 95% CI  
14 0.07-1.12)<sup>(60)</sup>.

15 Thirdly, a systematic review and meta-analysis of 14 RCTs (n=1,182) was also published in 2014  
16 showing that probiotics significantly reduced whole gut transit time by -12.4 h (95% CI: -22.3, -  
17 2.5 h) and increased stool frequency by +1.3 bowel movements/week (95% CI: 0.7, 1.9 bowel  
18 movements/week)<sup>(61)</sup>. The dose of probiotics used in the individual studies ranged from  $10^8$  to  
19  $3 \times 10^{10}$  CFU/d and the treatment period varied from 2 to 8 weeks. Importantly, the sensitivity  
20 analysis showed species- and strain-specific effects of probiotics as stool frequency was  
21 significantly higher following *B. lactis* species (mean difference: +1.5 bowel movements/week;  
22 95% CI: 0.7, 2.3 bowel movements/week), but not following *L. casei* Shirota (mean difference: -  
23 0.2 bowel movements/week; 95% CI: -0.8, 0.9 bowel movements/week)<sup>(61)</sup>. Similarly, stool  
24 consistency was significantly improved following *B. lactis* administration, but not for *L. casei*  
25 Shirota<sup>(61)</sup>.

26 Fourthly, a recent systematic review and meta-analysis of 21 RCTs (n=2,656) showed that  
27 probiotics significantly reduced gut transit time (SMD: 0.65,  $p < 0.001$ ) in people with constipation,  
28 and the mean difference in stool frequency was +0.83 bowel movements/week ( $p < 0.001$ );  
29 however, after adjusting for publication bias, the difference in stool frequency was reduced to 0.3  
30 bowel movements per week (95% CI -0.01 to 0.62 bowel movements per week) which was not

1 statistically significant <sup>(58)</sup>. The dose of probiotics used in the individual studies ranged from  
2  $0.1 \times 10^9$  to  $30 \times 10^9$  CFU/d and the treatment period varied from 7 to 84 days. In addition, the  
3 probiotic products used in some of the studies also contained additional ingredients (e.g. psyllium,  
4 inulin and fructo-oligosaccharides) that did not allow for the effect of the probiotic alone to be  
5 isolated <sup>(58)</sup>. This, in addition to the increased heterogeneity among the studies, denotes that caution  
6 is needed in interpreting the results.

7 The interpretation of these findings from systematic reviews and meta-analyses is challenging due  
8 to high heterogeneity and risk of bias of the individual studies, and because species- and strain-  
9 specific effects have been identified. Firstly, although meta-analyses synthesize data from many  
10 trials in order to improve the statistical power to detect the direction, size and consistency of a  
11 clinical effect, they cannot overcome limitations in the design of individual trials. Secondly,  
12 different probiotic species and strains have different microbiological and physiological  
13 characteristics, and therefore synthesizing data from different probiotics and different doses is  
14 questionable <sup>(62)</sup>. Despite these challenges, the results provide cautious optimism for the  
15 recommendation of specific probiotic strains in the management of chronic constipation. Further  
16 adequately powered RCTs using standardized outcome measures are needed to determine which  
17 species/strains, doses and duration of probiotics are efficacious.

## 18 **USE OF PROBIOTICS IN CONSTIPATION**

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

22 A survey in 269 patients attending outpatient gastroenterology clinics identified that 44% used  
23 complementary and alternative medicines (CAM), with constipation being the most cited symptom  
24 to be addressed, and probiotics being the most common CAM used <sup>(63)</sup>.

25 The prevalence of probiotic use in constipation was also confirmed in a recent large cross-sectional  
26 study in 2,557 members of the UK general population, of whom 1,623 had self-reported  
27 constipation <sup>(64)</sup>. This study revealed that the strongest predictors for probiotic use in the general  
28 population was having constipation, although this was a population selected for such symptoms  
29 <sup>(64)</sup>. It was also shown that 60% of the general population with constipation had previously used or

1 were currently using probiotics, compared to 51% of those without constipation ( $p < 0.001$ ). In fact,  
2 self-reported constipation was associated with a 4.7 greater likelihood of current probiotic use  
3 (OR: 4.7, 95% CI 3.8-5.7,  $p < 0.001$ ). In those with self-reported constipation, significant predictors  
4 of probiotic use for either general health or gut health specifically was ‘believing probiotics have  
5 been tested in research for their effectiveness in constipation’ (OR 2.06, 95% CI 1.56-2.72,  
6  $p < 0.001$ ), having a university degree (OR: 1.76, 95% CI 1.32-2.35,  $p < 0.001$ ), being older (OR:  
7 1.02, 95% CI 1.01-1.03,  $p < 0.001$ ), and being female (OR: 0.54, 95% CI 0.35-0.81,  $p = 0.003$ )<sup>(64)</sup>.  
8 The finding that females are more likely to use probiotics than males may be explained by the fact  
9 that constipated women report significantly worse quality of life compared to constipated men<sup>(5)</sup>.  
10 Therefore, women may be more likely to seek additional or alternative treatments for their  
11 symptoms than men. Indeed, a previous study has confirmed that constipated subjects seeking  
12 medical care are most likely to be females<sup>(65)</sup>.

13 In terms of the recommendation of probiotics by doctors, probiotics seem to be commonly  
14 recommended for the management of gastrointestinal disorders, such as chronic diarrhoea and  
15 irritable bowel syndrome<sup>(66)</sup>. A UK survey of over 1500 primary care health professionals (e.g.  
16 GPs, dietitians, nurses) showed that 78% of GPs advise probiotic use for their patients, with  
17 constipation being the 5<sup>th</sup> most common condition for which they are recommended<sup>(67)</sup>. However,  
18 a recent survey in 411 GPs and 365 gastroenterology specialists showed that 66% of GPs and 74%  
19 of gastroenterology specialists do not recommend them for constipation<sup>(64)</sup>. A possible reason for  
20 this might be the perceived lack of research evidence in this area. Indeed, only 35% of GPs and  
21 43% of GI specialists believe there is evidence for probiotic use in constipation<sup>(64)</sup>, despite existing  
22 evidence from RCTs showing that certain probiotic strains may improve constipation-related  
23 symptoms<sup>(58, 61)</sup>. Interestingly, the gastroenterologist specialists who believed there is evidence for  
24 probiotics in constipation thought probiotics were more effective for the management of  
25 constipation, compared with those who did not believe there is evidence<sup>(64)</sup>. Belief in the existence  
26 of scientific evidence for probiotics among doctors is therefore likely an influencer on the belief  
27 in their impact on symptoms and on their behaviour in terms of recommending them to patients.

28 *Lactobacillus casei* Shirota (Yakult) and a mixed preparation of *Streptococcus*, *Bifidobacterium*  
29 and *Lactobacillus* (VSL#3) are the probiotics most commonly recommended by gastroenterology  
30 specialists and GPs for constipation, respectively, whereas *B. lactis* DN-173010 (Activia), *L. casei*

1 DN 114 001 (Actimel) and *L. casei* Shirota (Yakult) are the probiotics most commonly used by  
2 the general population with constipation <sup>(64)</sup>. This is in agreement with the probiotic products that  
3 patients with inflammatory bowel disease also choose to use <sup>(68)</sup>. Although there are a few reports  
4 showing beneficial results of some of these strains in constipation, these studies have various  
5 limitations, such as small sample sizes or the absence of objective outcomes <sup>(20, 54, 69, 70)</sup>.  
6 Interestingly, no study has been previously published on the effect of Actimel (*L. casei* DN 114  
7 001) on constipation. Therefore, the choice of the probiotic product used by the general population  
8 and doctors is not necessarily driven by the current scientific evidence available, but could be  
9 influenced by factors such as availability or product advertising.

10 Indeed, TV adverts were the most common source of information for probiotics in gut health,  
11 followed by family, friends and the internet in general (**Figure 2**) <sup>(64)</sup>. This is mostly in agreement  
12 with the findings of a previous survey that showed that commercial advertising was the most  
13 common source of information for probiotic use in patients with inflammatory bowel disease,  
14 followed by family and friends, and healthcare professionals <sup>(68)</sup>. Similarly, another survey showed  
15 that the most common sources of information for the use of CAM (including probiotics) in  
16 gastrointestinal conditions were family, newspapers, magazines, the internet and friends <sup>(63)</sup>.

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

## 22 CONCLUSION

23 The evidence on the effectiveness of probiotics remains varied, with certain strains exhibiting  
24 beneficial effects, while others show little effect. This highlights that the effects of probiotics may  
25 be strain-specific and that each strain needs to be tested in a high-quality RCT using standardized  
26 and validated assessment techniques in order to be able to devise clinical recommendations  
27 regarding probiotic use in constipation in the future. This, in combination with the increased  
28 probiotic usage in constipation, indicates a need to clearly communicate and raise the public's  
29 awareness on the current state of the evidence on probiotics and constipation. Education of health  
30 care professionals is also required on both the strain-specificity of the effects of probiotics, but

- 1 also on the degree of probiotic usage by the public; this may encourage health care professionals
- 2 to query about probiotics and discuss their use with patients and, therefore, educate them on the
- 3 uncertainty in the available evidence.

## 1 REFERENCES

- 2 1. Mearin F, Lacy BE, Chang L, et al. Bowel Disorders. *Gastroenterology*. 2016;150:1393-407.
- 3 2. Soares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the  
4 community: systematic review and meta-analysis. *Am J Gastroenterol*. 2011;106(9):1582-91.
- 5 3. Dimidi E, Cox C, Grant R, et al. Perceptions of constipation among the general public and people  
6 with constipation differ strikingly from those of general and specialist doctors and the Rome IV criteria.  
7 *Am J Gastroenterol*. 2019;(in press).
- 8 4. Dimidi E, Dibley L, Cotterill N, et al. Validated constipation symptom and quality-of-life measures  
9 neither reflect patient and clinician concerns nor use words familiar to patients. *Gastrointest Nurs*.  
10 2016;14(7):29-38.
- 11 5. Wald A, Scarpignato C, Kamm MA, et al. The burden of constipation on quality of life: results of a  
12 multinational survey. *Aliment Pharmacol Ther*. 2007;26(2):227-36.
- 13 6. Sun SX, Dibonaventura M, Purayidathil FW, et al. Impact of chronic constipation on health-related  
14 quality of life, work productivity, and healthcare resource use: an analysis of the National Health and  
15 Wellness Survey. *Dig Dis Sci*. 2011;56(9):2688-95.
- 16 7. Nellesen D, Yee K, Chawla A, et al. A systematic review of the economic and humanistic burden of  
17 illness in irritable bowel syndrome and chronic constipation. *J Manag Care Pharm*. 2013;19(9):755-64.
- 18 8. Health and Social Care Information Centre. National Statistics Hospital Episode Statistics,  
19 Admitted Patient Care, England - 2017-2018 [Available from: [https://digital.nhs.uk/data-and-](https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2017-18)  
20 [information/publications/statistical/hospital-admitted-patient-care-activity/2017-18](https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2017-18)].
- 21 9. Shafe AC, Lee S, Dalrymple JS, et al. The LUCK study: Laxative Usage in patients with GP-diagnosed  
22 Constipation in the UK, within the general population and in pregnancy. An epidemiological study using  
23 the General Practice Research Database (GPRD). *Therap Adv Gastroenterol*. 2011;4(6):343-63.
- 24 10. Guerin A, Carson RT, Lewis B, et al. The economic burden of treatment failure amongst patients  
25 with irritable bowel syndrome with constipation or chronic constipation: a retrospective analysis of a  
26 Medicaid population. *J Med Econ*. 2014;17(8):577-86.
- 27 11. Christodoulides S, Dimidi E, Fragkos KC, et al. Systematic review with meta-analysis: effect of fibre  
28 supplementation on chronic idiopathic constipation in adults. *Aliment Pharmacol Ther*. 2016.
- 29 12. Bharucha AE, Pemberton JH, Locke GR, 3rd. American Gastroenterological Association technical  
30 review on constipation. *Gastroenterology*. 2013;144(1):218-38.
- 31 13. Johanson JF, Kralstein J. Chronic constipation: a survey of the patient perspective. *Aliment*  
32 *Pharmacol Ther*. 2007;25(5):599-608.
- 33 14. Emmanuel A, Quigley EM, Simren M, et al. Factors affecting satisfaction with treatment in  
34 European women with chronic constipation: An internet survey. *United European Gastroenterol J*.  
35 2013;1(5):375-84.
- 36 15. Hill C, Guarner F, Reid G, et al. Expert consensus document. The International Scientific  
37 Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the  
38 term probiotic. *Nat Rev Gastroenterol Hepatol*. 2014;11(8):506-14.
- 39 16. Dimidi E, Christodoulides S, Scott SM, et al. Mechanisms of Action of Probiotics and the  
40 Gastrointestinal Microbiota on Gut Motility and Constipation. *Adv Nutr*. 2017;8(3):484-94.
- 41 17. Chassard C, Dapoigny M, Scott KP, et al. Functional dysbiosis within the gut microbiota of patients  
42 with constipated-irritable bowel syndrome. *Aliment Pharmacol Ther*. 2012;35(7):828-38.
- 43 18. Parthasarathy G, Chen J, Chen X, et al. Relationship Between Microbiota of the Colonic Mucosa vs  
44 Feces and Symptoms, Colonic Transit, and Methane Production in Female Patients With Chronic  
45 Constipation. *Gastroenterology*. 2016;150(2):367-79 e1.

- 1 19. Ishizuka A, Tomizuka K, Aoki R, et al. Effects of administration of *Bifidobacterium animalis* subsp.  
2 *lactis* GCL2505 on defecation frequency and bifidobacterial microbiota composition in humans. *J Biosci*  
3 *Bioeng.* 2012;113(5):587-91.
- 4 20. Kim SE, Choi SC, Park KS, et al. Change of Fecal Flora and Effectiveness of the Short-term VSL#3  
5 Probiotic Treatment in Patients With Functional Constipation. *J Neurogastroenterol Motil.*  
6 2015;21(1):111-20.
- 7 21. Matsumoto K, Takada T, Shimizu K, et al. The effects of a probiotic milk product containing  
8 *Lactobacillus casei* strain Shirota on the defecation frequency and the intestinal microflora of sub-optimal  
9 health state volunteers: A randomized placebo-controlled cross-over study. *Biosci Microflora.*  
10 2006;25(2):39-48.
- 11 22. Dimidi E, Zdanaviciene A, Christodoulides S, et al. Randomised clinical trial: *Bifidobacterium lactis*  
12 NCC2818 probiotic vs placebo, and impact on gut transit time, symptoms, and gut microbiology in chronic  
13 constipation. *Aliment Pharmacol Ther.* 2019;49(3):251-64.
- 14 23. Morrison DJ, Preston T. Formation of short chain fatty acids by the gut microbiota and their impact  
15 on human metabolism. *Gut Microbes.* 2016;7(3):189-200.
- 16 24. Yajima T. Contractile effect of short-chain fatty acids on the isolated colon of the rat. *J Physiol.*  
17 1985;368:667-78.
- 18 25. Cherbut C, Aube AC, Blottiere HM, et al. In vitro contractile effects of short chain fatty acids in the  
19 rat terminal ileum. *Gut.* 1996;38(1):53-8.
- 20 26. Rondeau MP, Meltzer K, Michel KE, et al. Short chain fatty acids stimulate feline colonic smooth  
21 muscle contraction. *J Feline Med Surg.* 2003;5(3):167-73.
- 22 27. Fukumoto S, Tatewaki M, Yamada T, et al. Short-chain fatty acids stimulate colonic transit via  
23 intraluminal 5-HT release in rats. *Am J Physiol Regul Integr Comp Physiol.* 2003;284(5):R1269-76.
- 24 28. Liu ZM, Xu ZY, Han M, et al. Efficacy of pasteurised yoghurt in improving chronic constipation: A  
25 randomised, double-blind, placebo-controlled trial. *Int Dairy J.* 2015;40:1-5.
- 26 29. Spanhaak S, Havenaar R, Schaafsma G. The effect of consumption of milk fermented by  
27 *Lactobacillus casei* strain Shirota on the intestinal microflora and immune parameters in humans. *Eur J*  
28 *Clin Nutr.* 1998;52(12):899-907.
- 29 30. Valerio F, Russo F, de Candia S, et al. Effects of Probiotic *Lactobacillus paracasei*-enriched  
30 Artichokes on Constipated Patients A Pilot Study. *J Clin Gastroenterol.* 2010;44:S49-S53.
- 31 31. Riezzo G, Orlando A, D'Attoma B, et al. Randomised clinical trial: efficacy of *Lactobacillus*  
32 *paracasei*-enriched artichokes in the treatment of patients with functional constipation--a double-blind,  
33 controlled, crossover study. *Aliment Pharmacol Ther.* 2012;35(4):441-50.
- 34 32. Sakai T, Makino H, Ishikawa E, et al. Fermented milk containing *Lactobacillus casei* strain Shirota  
35 reduces incidence of hard or lumpy stools in healthy population. *Int J Food Sci Nutr.* 2011;62(4):423-30.
- 36 33. Marsono Y, Illman RJ, Clarke JM, et al. Plasma lipids and large bowel volatile fatty acids in pigs fed  
37 on white rice, brown rice and rice bran. *Br J Nutr.* 1993;70(2):503-13.
- 38 34. Matsuo K, Ota H, Akamatsu T, et al. Histochemistry of the surface mucous gel layer of the human  
39 colon. *Gut.* 1997;40(6):782-9.
- 40 35. Snape WJ, Jr., Shiff S, Cohen S. Effect of deoxycholic acid on colonic motility in the rabbit. *Am J*  
41 *Physiol.* 1980;238(4):G321-5.
- 42 36. Keely SJ, Scharl MM, Bertelsen LS, et al. Bile acid-induced secretion in polarized monolayers of  
43 T84 colonic epithelial cells: Structure-activity relationships. *Am J Physiol Gastrointest Liver Physiol.*  
44 2007;292(1):G290-7.
- 45 37. Caballero-Franco C, Keller K, De Simone C, et al. The VSL#3 probiotic formula induces mucin gene  
46 expression and secretion in colonic epithelial cells. *Am J Physiol Gastrointest Liver Physiol.*  
47 2007;292(1):G315-22.

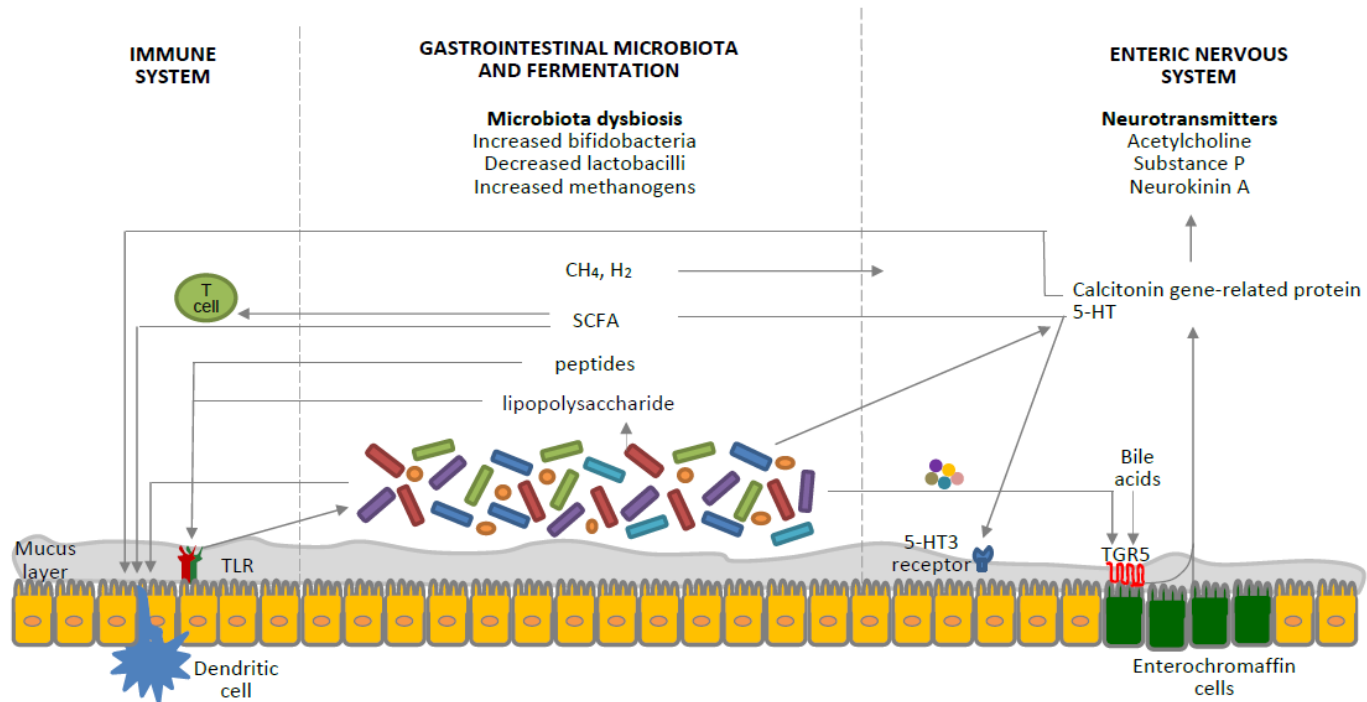
- 1 38. Ouwehand AC, Lagstrom H, Suomalainen T, et al. Effect of probiotics on constipation, fecal  
2 azoreductase activity and fecal mucin content in the elderly. *Ann Nutr Metab.* 2002;46(3-4):159-62.
- 3 39. Marteau P, Cuillerier E, Meance S, et al. Bifidobacterium animalis strain DN-173 010 shortens the  
4 colonic transit time in healthy women: a double-blind, randomized, controlled study. *Aliment Pharmacol*  
5 *Ther.* 2002;16(3):587-93.
- 6 40. Tillisch K, Labus J, Kilpatrick L, et al. Consumption of fermented milk product with probiotic  
7 modulates brain activity. *Gastroenterology.* 2013;144(7):1394-401, 401 e1-4.
- 8 41. Kunze WA, Mao YK, Wang B, et al. Lactobacillus reuteri enhances excitability of colonic AH  
9 neurons by inhibiting calcium-dependent potassium channel opening. *J Cell Mol Med.* 2009;13(8B):2261-  
10 70.
- 11 42. Wang B, Mao YK, Diorio C, et al. Lactobacillus reuteri ingestion and IK(Ca) channel blockade have  
12 similar effects on rat colon motility and myenteric neurones. *Neurogastroenterol Motil.* 2010;22(1):98-  
13 107, e33.
- 14 43. Khalif IL, Quigley EM, Konovitch EA, et al. Alterations in the colonic flora and intestinal  
15 permeability and evidence of immune activation in chronic constipation. *Dig Liver Dis.* 2005;37(11):838-  
16 49.
- 17 44. Collins SM. The immunomodulation of enteric neuromuscular function: implications for motility  
18 and inflammatory disorders. *Gastroenterology.* 1996;111(6):1683-99.
- 19 45. Guarino MP, Altomare A, Stasi E, et al. Effect of acute mucosal exposure to Lactobacillus  
20 rhamnosus GG on human colonic smooth muscle cells. *J Clin Gastroenterol.* 2008;42 Suppl 3 Pt 2:S185-  
21 90.
- 22 46. Isolauri E, Sutas Y, Kankaanpaa P, et al. Probiotics: effects on immunity. *Am J Clin Nutr.* 2001;73(2  
23 Suppl):444S-50S.
- 24 47. Ibnou-Zekri N, Blum S, Schiffrin EJ, et al. Divergent patterns of colonization and immune response  
25 elicited from two intestinal Lactobacillus strains that display similar properties in vitro. *Infect Immun.*  
26 2003;71(1):428-36.
- 27 48. Arunachalam K, Gill HS, Chandra RK. Enhancement of natural immune function by dietary  
28 consumption of Bifidobacterium lactis (HN019). *Eur J Clin Nutr.* 2000;54(3):263-7.
- 29 49. Yang YX, He M, Hu G, et al. Effect of a fermented milk containing Bifidobacterium lactis DN-173010  
30 on Chinese constipated women. *World J Gastroenterol.* 2008;14(40):6237-43.
- 31 50. Waller PA, Gopal PK, Leyer GJ, et al. Dose-response effect of Bifidobacterium lactis HN019 on  
32 whole gut transit time and functional gastrointestinal symptoms in adults. *Scand J Gastroenterol.*  
33 2011;46(9):1057-64.
- 34 51. Ibarra A, Latreille-Barbier M, Donazzolo Y, et al. Effects of 28-day Bifidobacterium animalis subsp.  
35 lactis HN019 supplementation on colonic transit time and gastrointestinal symptoms in adults with  
36 functional constipation: A double-blind, randomized, placebo-controlled, and dose-ranging trial. *Gut*  
37 *Microbes.* 2018;9(3):236-51.
- 38 52. Ojetti V, Ianiro G, Tortora A, et al. The effect of Lactobacillus reuteri supplementation in adults  
39 with chronic functional constipation: a randomized, double-blind, placebo-controlled trial. *J*  
40 *Gastrointestin Liver Dis.* 2014;23(4):387-91.
- 41 53. Koebnick C, Wagner I, Leitzmann P, et al. Probiotic beverage containing Lactobacillus casei Shirota  
42 improves gastrointestinal symptoms in patients with chronic constipation. *Can J Gastroenterol.*  
43 2003;17(11):655-9.
- 44 54. Mazlyn MM, Nagarajah LH, Fatimah A, et al. Effects of a probiotic fermented milk on functional  
45 constipation: a randomized, double-blind, placebo-controlled study. *J Gastroenterol Hepatol.*  
46 2013;28(7):1141-7.

- 1 55. Del Piano M, Carmagnola S, Anderloni A, et al. The use of probiotics in healthy volunteers with  
2 evacuation disorders and hard Stools. A double-blind, randomized, placebo-controlled Study. *J Clin*  
3 *Gastroenterol.* 2010;44:S30-S4.
- 4 56. Chmielewska A, Szajewska H. Systematic review of randomised controlled trials: probiotics for  
5 functional constipation. *World J Gastroenterol.* 2010;16(1):69-75.
- 6 57. Miller LE, Zimmermann AK, Ouwehand AC. Contemporary meta-analysis of short-term probiotic  
7 consumption on gastrointestinal transit. *World J Gastroenterol.* 2016;22(21):5122-31.
- 8 58. Miller LE, Ouwehand AC, Ibarra A. Effects of probiotic-containing products on stool frequency and  
9 intestinal transit in constipated adults: systematic review and meta-analysis of randomized controlled  
10 trials. *Ann Gastroenterol.* 2017;30(6):629-39.
- 11 59. Miller LE, Ouwehand AC. Probiotic supplementation decreases intestinal transit time: meta-  
12 analysis of randomized controlled trials. *World J Gastroenterol.* 2013;19(29):4718-25.
- 13 60. Ford AC, Quigley EM, Lacy BE, et al. Efficacy of prebiotics, probiotics, and synbiotics in irritable  
14 bowel syndrome and chronic idiopathic constipation: systematic review and meta-analysis. *Am J*  
15 *Gastroenterol.* 2014;109(10):1547-61.
- 16 61. Dimidi E, Christodoulides S, Fragkos KC, et al. The effect of probiotics on functional constipation  
17 in adults: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr.*  
18 2014;100(4):1075-84.
- 19 62. Whelan K. Editorial: The importance of systematic reviews and meta-analyses of probiotics and  
20 prebiotics. *Am J Gastroenterol.* 2014;109(10):1563-5.
- 21 63. Hung A, Kang N, Bollom A, et al. Complementary and Alternative Medicine Use Is Prevalent Among  
22 Patients with Gastrointestinal Diseases. *Dig Dis Sci.* 2015;60(7):1883-8.
- 23 64. Dimidi E, Cox C, Scott SM, et al. Probiotic use is common in constipation, but only a minority of  
24 general and specialist doctors recommend them and consider there to be an evidence base. *Nutrition.*  
25 2019;61:157-63.
- 26 65. Cheng C, Chan AO, Hui WM, et al. Coping strategies, illness perception, anxiety and depression of  
27 patients with idiopathic constipation: a population-based study. *Aliment Pharmacol Ther.* 2003;18(3):319-  
28 26.
- 29 66. Cordina C, Shaikh I, Shrestha S, et al. Probiotics in the management of gastrointestinal disease:  
30 analysis of the attitudes and prescribing practices of gastroenterologists and surgeons. *J Dig Dis.*  
31 2011;12(6):489-96.
- 32 67. Jordan D, Johnson N, Thomas L. Probiotics in primary care: A survey of health professionals.  
33 *Practice Nursing.* 2015;26(11):550-4.
- 34 68. Hedin CR, Mullard M, Sharratt E, et al. Probiotic and prebiotic use in patients with inflammatory  
35 bowel disease: a case-control study. *Inflamm Bowel Dis.* 2010;16(12):2099-108.
- 36 69. He M, Hu G, Yang Y. Effect of probiotic yogurt containing *Bifidobacterium animalis* strain DN-173  
37 010 on symptoms of constipation. *Chin J Gastroenterol* 2009;14:287-9.
- 38 70. Krammer H, von Seggern H, Schaumburg J, et al. Effect of *Lactobacillus casei* Shirota on colonic  
39 transit time in patients with chronic constipation. *Coloproctology.* 2011;33:109-13.
- 40 71. Kieffer DA, Martin RJ, Adams SH. Impact of Dietary Fibers on Nutrient Management and  
41 Detoxification Organs: Gut, Liver, and Kidneys. *Adv Nutr.* 2016;7(6):1111-21.
- 42 72. Yano JM, Yu K, Donaldson GP, et al. Indigenous bacteria from the gut microbiota regulate host  
43 serotonin biosynthesis. *Cell.* 2015;161(2):264-76.
- 44 73. Triantafyllou K, Chang C, Pimentel M. Methanogens, methane and gastrointestinal motility. *J*  
45 *Neurogastroenterol Motil.* 2014;20(1):31-40.
- 46 74. Collins SM, Bercik P. The relationship between intestinal microbiota and the central nervous  
47 system in normal gastrointestinal function and disease. *Gastroenterology.* 2009;136(6):2003-14.

- 1 75. Ng SC, Benjamin JL, McCarthy NE, et al. Relationship Between Human Intestinal Dendritic Cells,  
2 Gut Microbiota, and Disease Activity in Crohn's Disease. *Inflamm Bowel Dis.* 2011;17(10):2027-37.
- 3 76. Brun P, Giron MC, Qesari M, et al. Toll-like receptor 2 regulates intestinal inflammation by  
4 controlling integrity of the enteric nervous system. *Gastroenterology.* 2013;145(6):1323-33.

5

1 FIGURE



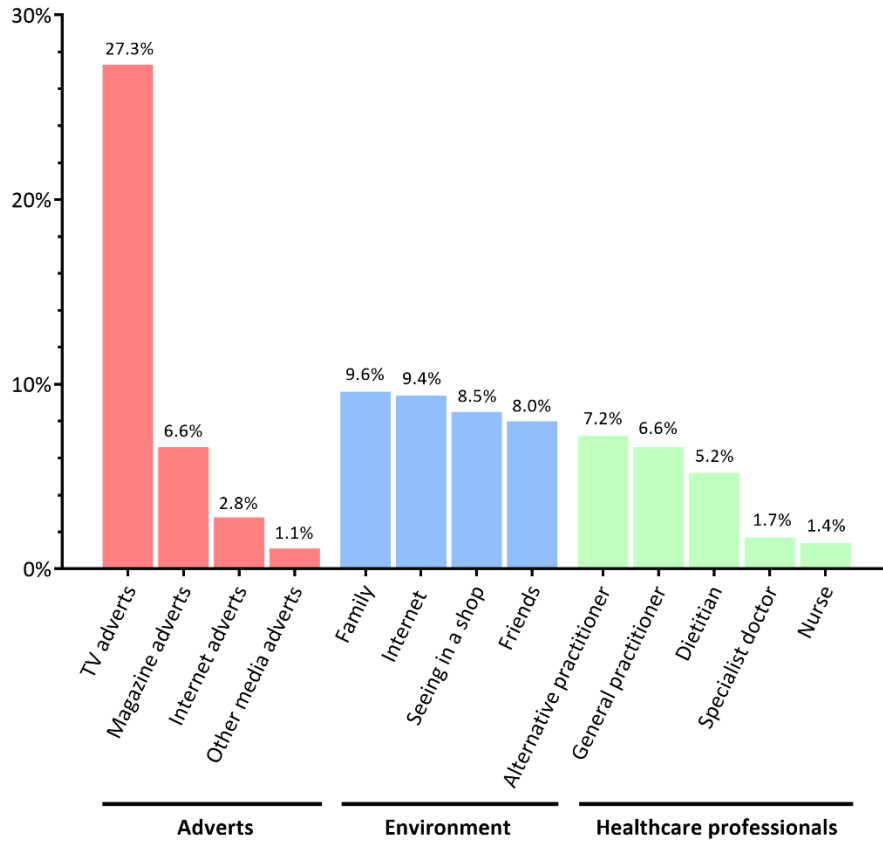
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3 **Figure 1:** Interrelated factors involved in the pathophysiology of constipation as potential targets  
 4 for the therapeutic role of probiotics. Probiotics affect the gastrointestinal microbiota composition,  
 5 the byproducts of which interact with pattern-recognition receptors, such as TLRs, as well as with  
 6 dendritic cells. SCFAs increase intestinal regulatory T cells, which limit intestinal inflammation,  
 7 by reducing histone deacetylase 9 gene expression<sup>(71)</sup>. The gastrointestinal microbiota regulates 5-  
 8 HT production by elevating its synthesis by host enterochromaffin cells via the release of  
 9 metabolites, such as deoxycholate, which activates TGR5, expressed by enterochromaffin cells<sup>(72)</sup>.  
 10 5-HT is also released from enterochromaffin cells in response to SCFAs produced by the  
 11 gastrointestinal microbiota and stimulates 5-HT<sub>3</sub> receptors located on the vagal afferent fibers,  
 12 resulting in muscle contractions<sup>(27)</sup>. Gases produced by the gastrointestinal microbiota seem to  
 13 affect gut motility via the enteric nervous system, rather than the brain-gut axis; however, the exact  
 14 mechanisms are still unknown<sup>(73)</sup>. Moreover, the gastrointestinal microbiota is key to the  
 15 development of the enteric nervous system, which is the primary regulator of gut motility, and  
 16 certain bacteria are known to produce 5-HT. Calcitonin gene-related protein, a sensory  
 17 neuropeptide, modulates dendritic cell function and may signal the presence of gastrointestinal  
 18 microbiota to the brain<sup>(74)</sup>. Components of the gastrointestinal microbiota also act via intestinal

1 dendritic cells to influence the inflammatory process<sup>(75)</sup>. TLRs signaling controls the enteric  
2 nervous system structure and neuromuscular function and hence motility<sup>(76)</sup>. Bile acids activate  
3 TGR5 expressed by enterochromaffin cells and myenteric neurons and release 5-HT and calcitonin  
4 gene-related peptide. Furthermore, probiotics appear to interact with the gut-brain axis via the  
5 modulation of afferent sensory nerves that influence gut motility. CH<sub>4</sub>, methane; H<sub>2</sub>, hydrogen;  
6 TGR5, a G protein-coupled receptor; TLR, toll-like receptor; 5-HT, 5-hydroxytryptamine; 5-HT<sub>3</sub>,  
7 5-hydroxytryptamine type 3. Taken with permission from Dimidi et al. 2017 <sup>(16)</sup>.

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2

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

7

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		
<b>Chmielewska &amp; Szajewska, 2010</b> <sup>(56)</sup>	SR	Chronic constipation	Probiotics	Placebo or no intervention	Constipation-related symptoms, stool output	3 RCTs 377 subjects	Beneficial effects reported for <i>B. lactis</i> DN-173010, <i>E. coli</i> Nissle 1917 and <i>L. casei</i> Shirota on stool frequency and consistency, however the clinical relevance unclear due to small sample size, methodological limitations and modest effect sizes.
<b>Miller &amp; Ouewhand, 2013</b> <sup>(59)</sup>	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 <i>B. lactis</i> HN019 (SMD: 0.72, 95% CI 0.27-1.18, p<0.01) and <i>B. lactis</i> 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).
<b>Dimidi et al. 2014</b> <sup>(61)</sup>	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). <i>B. lactis</i> increased stool frequency by 1.5 BM/wk (95% CI: 0.7, 2.3 BM/wk) <i>L. casei</i> Shirota did not impact stool frequency (MD: -0.2 BM/wk; 95% CI: -0.8, 0.9 BM/wk). <i>B. lactis</i> improved stool consistency (SMD: 0.46; 95% CI: 0.08, 0.85) <i>L. casei</i> 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		
<b>Ford et al. 2014</b> <sup>(60)</sup>	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.
<b>Miller et al. 2016</b> <sup>(57)</sup>	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 <i>B. lactis</i> HN019 (SMD: 0.67, 95% CI 0.37-0.97, $p<0.001$ ) and <i>B. lactis</i> DN173010 (SMD: 0.54, 95%CI: 0.16-0.92, $p<0.01$ ), compared to control. No significant impact on gut transit following <i>B. lactis</i> BB12 (SMD: 0.33, 95% CI: -0.10-0.75, $p=0.14$ ), <i>L. casei</i> CRK 431 (SMD: 0.33, 95% CI -0.10-0.75, $p=0.014$ ) or <i>L. rhamnosus</i> 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).
<b>Miller et al. 2017</b> <sup>(58)</sup>	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.

