Symprove published research summary

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Contents

Clinical (in vivo)

Irritable bowel syndrome

Randomised clinical trial: A liquid multi-strain probiotic vs. placebo in the irritable bowel syndrome - a 12 week double-blind study

Sisson G, et al. Aliment Pharmacol Ther 2014;40(1):51–62.

Background: The importance of interactions between the host and gut microbiota in the pathogenesis of irritable bowel syndrome (IBS) is becoming increasingly apparent. Probiotics offer a potential new treatment for IBS, but current results are conflicting, largely as a result of poorly designed trials and nonstandardisation of outcome measures. **Aim:** To assess the efficacy of a liquid, multi-strain probiotic (Symprove) in IBS. **Methods:** A single-centre, randomised, double-blind, placebo-controlled trial of adult patients with symptomatic IBS. Patients received 12 weeks of treatment with the probiotic or placebo (1 mL/kg/day). The primary efficacy measure was the difference in change in the IBS symptom severity score (IBS-SSS) between probiotic vs. placebo at week 12. Secondary outcome measures included change in the IBS quality of life (IBS-QOL) score and change in the IBS-SSS symptom component scores. **Results:** A total of 186 patients were randomised and 152 patients completed the study. The mean change in IBS-SSS was -63.3 probiotic vs. -28.3 placebo. The mean difference in the IBS-SSS was statistically significant [-35.0 (95% CI; -62.03, -7.87); P = 0.01]. There was no significant improvement in the IBS-QOL. No serious adverse events were reported. **Conclusions:** The multi-strain probiotic was associated with a statistically significant improvement in overall symptom severity in patients with IBS, and was well tolerated. These results suggest this probiotic confers benefit in IBS and deserves further investigation.

A multi-strain water-based probiotic supplement in the management of irritable bowel syndrome or irritable bowel syndrome-like symptoms and quality of life: A real-world evidence study conducted in the United Kingdom

Rudland S, et al. Journal of Primary Care and General Practice 2021:4(4).

Background: Irritable bowel syndrome (IBS) is a common and burdensome functional gastrointestinal disorder of unknown etiology. Due to its complex and multifactorial nature, the delivery of effective management approaches is challenging, with modestly effective therapies and limited efficacy for many conventional drug treatments. To date, some probiotics have shown efficacy in IBS management in randomised clinical trials. The stringent inclusion criteria may not, however, be representative of the wider clinical population. The present study aimed to evaluate the effect of a multi-strain water-based probiotic (Symprove) on participant-reported change in IBS or IBS-like symptoms, and quality of life in a real-life situation. **Methods:** From 6th February to 31st March 2020, real world evidence data were collected from a total of 2301 individuals who retrospectively completed an online questionnaire, of which 1246 (54%) were trialling for IBS or IBS-like symptoms (medically- or self-diagnosed). P values were calculated using proportions Z tests and Mann-Whitney U tests (non-parametric equivalent). Differences are stated as statistically significant where $P \leq .05$. **Results:** Of the 1246, 58% (n=717) entered the medically-diagnosed pathway and 40% (n=501) entered the self-diagnosed pathway, 2% (n=28) were omitted from the final analysis. Of the final 1218, over 90% of participants in both IBS cohorts reported improvements ('completely resolved' or 'some positive difference') in IBS or IBS-like symptoms after 4 or more weeks of Symprove, including abdominal pain ($p<0.001$) bloating ($p<0.001$), urgency ($p<0.001$) and bowel habit satisfaction ($p<0.001$), in addition to quality of life ($p<0.001$). **Conclusions:** Trialling Symprove for 4 or more weeks was associated with improvements in IBS or IBS-like symptoms, in addition to quality of life. These results support the effectiveness of Symprove in patients with IBS or IBS-like symptoms and may be considered a potentially useful adjunct for patients in primary and secondary care.

Diverticular disease

A randomized double-blind placebo-controlled trial of a multi-strain probiotic in treatment of symptomatic uncomplicated diverticular disease

Kvasnovsky CL, et al. Inflammopharmcology 2017; doi: 10.1007/s10787-017-0363-y.

Background: Diverticular disease is a significant burden on healthcare systems that is managed, surgically or medically, mainly as an emergency or acute condition. There are no standardized treatment recommendations for symptomatic uncomplicated disease. We hypothesized that a probiotic would reduce abdominal pain in such patients. **Methods:** We conducted a single-center, double-blind, placebo-controlled trial of probiotic treatment (Symprove) in adult patients with moderate-to-severe chronic, non-acute symptomatic diverticular disease. 143 patients were randomized to receive 1 mL/kg/day of probiotic liquid (N = 72) or placebo (N = 71) daily for 3 months. The primary endpoint was abdominal pain severity. Secondary endpoints consisted of the change in the frequency of eight abdominal symptoms and the level of intestinal inflammation (fecal calprotectin). **Results:** 120 patients completed the trial. Abdominal pain score, the primary end point, decreased in both groups, but no significant difference between the groups was found (P = 0.11). In relation to placebo, the probiotic significantly decreased the frequency of four of the eight secondary endpoints: constipation, diarrhea, mucorrhea, and back pain (P < 0.04). No significant differences were found in frequency of abdominal pain, PR bleeding, dysuria, and bloating. **Conclusions:** Multi-strain liquid probiotic did not improve abdominal pain scores significantly, but significantly improved the frequency of four other symptoms associated with chronic, non-acute symptomatic diverticular disease.

Inflammatory bowel disease

A randomised, double-blind, placebo-controlled trial of a multi-strain probiotic in patients with asymptomatic ulcerative colitis and Crohn's disease

Bjarnason I, et al. Inflammopharmacology 2019;27(3):465–473.

Background: There is considerable interest in the possible importance of the gut microflora in the pathophysiology of the inflammatory bowel diseases (IBD) ulcerative colitis (UC) and Crohn's disease (CD). Probiotics offer a potential adjuvant treatment in these patients by modifying the intestinal milieu, but reports of their efficacy are conflicting. **Aims:** To assess the efficacy of a multi-strain probiotic (Symprove™, Symprove Ltd, Farnham, United Kingdom) in quality of life issues and intestinal inflammation in patients with asymptomatic UC and CD. **Methods:** A single-centre, randomised, double-blind, placebo-controlled trial of adult patients with asymptomatic IBD. Patients received 4 weeks of treatment with the probiotic or placebo (1 ml/kg/day). The primary efficacy measure was the difference in change in the IBD Quality of Life Questionnaire results (QOL) between probiotic vs. placebo at week 4. Secondary outcome measures included analyses of the change in laboratory findings, including faecal calprotectin (FCAL). Results: Over 500 patients were recruited to the study and 81 and 61 patients with UC and CD, respectively were randomised and completed the study. There were no significant differences in IBD-QOL scores between placebo and the probiotic groups. Similarly, there were no significant changes observed in the laboratory data. However, the differences in FCAL between patients with UC before and after probiotics versus placebo approached statistical significance with a p value of 0.076. Post-hoc analyses showed that the FCAL levels were significantly ($p < 0.015$) reduced in the UC patients receiving the probiotic as opposed to placebo. No significant changes were seen in CD. No serious adverse events were observed. **Conclusions:** This multi-strain probiotic is associated with decreased intestinal inflammation in patients with UC, but not in CD and is well tolerated. Further research is required to see if the probiotic reduces the incidence of clinical relapses in asymptomatic IBD patients.

Dermatology

The impact of using a multistrain probiotic supplement on gastrointestinal function in children and adolescents with severe recessive dystrophic epidermolysis bullosa

Yerlett N, et al. Clin Exp Dermatol 2022;00:1-5.

Background: Children and adolescents with severe recessive dystrophic epidermolysis bullosa (RDEB-S) often have severe constipation in addition to gastrointestinal dysbiosis, due to frequent antibiotic use and reduced oral diet. Constipation is treated with long-term use of high daily doses of macrogol gel (Movicol Paediatric PlainTM or Laxido™). Constipation is refractory to increases in fibre and fluids, and impacts severely on quality of life. **Aim:** To study the initial impact and efficacy of using a multistrain probiotic supplement daily for 12 weeks in patients with RDEB-S. The authors sought to determine the impact of such a supplement on gastrointestinal symptoms, stool consistency and the use of macrogol gel to treat constipation, as well as understanding patient reaction, palability and ease of use. **Methods:** Patients were identified through the epidermolysis bullosa tertiary multidisciplinary team clinic in July 2021. Patients were included if they had a diagnosis of RDEB-S, prescribed at least one sachet of macrogol gel and provided written consent to take part. Patients were provided, proprietary liquid multistrain probiotic supplement (Symprove™) with a high bacterial count, at a dose of 1 mL kg–1 once a day. Each patient completed an anonymous, nine-question, electronic survey to document symptoms and report overall findings at the start and end of a 12-week trial period. **Results:** Four patients with RDEB-S (two boys and two girls; age range 7–14 years) who met the inclusion criteria were approached to take part. All patients had chronic constipation requiring daily macrogol gel use (range 2–5 sachets per day). Three out of four (75%) completed the 12-week course. At baseline (before supplementation commenced), all three (100%) patients reported poor oral appetite, constipation, flatulence, abdominal bloating and pain, and frequent skin infections requiring oral antibiotics, with two of the three (66%) patients also having nausea. After 12 weeks of supplementation, all three patients (100%) reported a significant improvement in abdominal pain and bloating, nausea, stool consistency, stool frequency, flatulence and increased appetite. Two of the three patients (66%) were able to reduce their macrogol gel usage and the third patient (33%) was able to stop macrogol gel usage altogether during the study period. All three patients said they would choose to continue using the supplement if it was available. **Conclusion:** We have shown in this case series that giving a multistrain probiotic supplement in patients with RDEB-S has the potential to improve stool consistency and reduce or prevent the need for chronic macrogol gel use. Future larger-scale, placebo-controlled trials are needed to confirm these results.

Oncology

Mucositis reduction with probiotics in children with cancer: a randomised controlled feasibility study

Hassan H, et al. Arch Dis Child 2022;107(3):259–64.

Background: A recent systematic review and meta-analysis identified a paucity of randomised-controlled trials (RCTs) investigating the use of probiotics to reduce or prevent mucositis and infection in children with cancer. **Objective:** This study evaluated the feasibility of undertaking an RCT and investigated the efficacy of probiotics for reducing or preventing mucositis and infection in children with cancers. **Setting:** The Paediatric Oncology and Haematology department at Leeds Teaching Hospital, UK. **Patients:** Children aged 1 year or older, receiving chemotherapies likely to cause mucositis. **Interventions:** Participants were randomised to receive the probiotic or placebo on day 1-14 of a chemotherapy cycle. Participants were also required to complete a patient diary for 21 days. **Main outcome measures:** To assess whether it is feasible to recruit children diagnosed with cancer who are at risk of developing mucositis to an adequately powered RCT. **Results:** Between May and November 2019, 34 out of 39 eligible participants were approached. Ten patients were recruited (4 probiotic and 6 placebo) of which 2 participants withdrew. Seven participants partially completed the diary but only two participants completed 80% or more. Eligible participants appeared to prefer giving informal verbal feedback when in direct contact with research and healthcare professionals. **Conclusion:** This study demonstrated that recruitment needs to be improved prior to undertaking an adequately powered RCT.

Parkinsons (animal study)

Effects of a probiotic suspension Symprove™ on a rat early-stage Parkinson's disease model

Sancandi M, et al. Frontiers in Aging Neuroscience 2023;14:986127.

An increasing number of studies in recent years have focused on the role that the gut may play in Parkinson's Disease (PD) pathogenesis, suggesting that the maintenance of a healthy gut may lead to potential treatments of the disease. The health of microbiota has been shown to be directly associated with parameters that play a potential role in PD including gut barrier integrity, immunity, function, metabolism and the correct functioning of the gut-brain axis. The gut microbiota (GM) may therefore be employed as valuable indicators for early diagnosis of PD and potential targets for preventing or treating PD symptoms. Preserving the gut homeostasis using probiotics may therefore lead to a promising treatment strategy due to their known benefits in improving constipation, motor impairments, inflammation, and neurodegeneration. However, the mechanisms underlying the effects of probiotics in PD are yet to be clarified. In this project, we have tested the efficacy of an oral probiotic suspension, Symprove™, on an established animal model of PD. Symprove™, unlike many commercially available probiotics, has been shown to be resistant to gastric acidity, improve symptoms in gastrointestinal diseases and improve gut integrity in an in vitro PD model. In this study, we used an early-stage PD rat model to determine the effect of Symprove™ on neurodegeneration and neuroinflammation in the brain and on plasma cytokine levels, GM composition and short chain fatty acid (SCFA) release. Symprove™ was shown to significantly influence both the gut and brain of the PD model. It preserved the gut integrity in the PD model, reduced plasma inflammatory markers and changed microbiota composition. The treatment also prevented the reduction in SCFAs and striatal inflammation and prevented tyrosine hydroxylase (TH)-positive cell loss by 17% compared to that observed in animals treated with placebo. We conclude that Symprove™ treatment may have a positive influence on the symptomology of early-stage PD with obvious implications for the improvement of gut integrity and possibly delaying/preventing the onset of neuroinflammation and neurodegeneration in human PD patients.

Mechanistic (in vitro)

Immunomodulatory effects

A four-strain probiotic exerts positive immunomodulatory effects by enhancing colonic butyrate production in vitro

Moens F, et al. Int J Pharm 2019;555:1–10.

Poorly formulated probiotic supplements intended for oral administration often fail to protect bacteria from the challenges of human digestion, meaning bacteria do not reach the small intestine in a viable state. As a result, the ability of probiotics to influence the human gut microbiota has not been proven. Here we show how (i) considered formulation of an aqueous probiotic suspension can facilitate delivery of viable probiotic bacteria to the gut and (ii) quantitate the effect of colonisation and proliferation of specific probiotic species on the human gut microbiota, using an in-vitro gut model. Our data revealed immediate colonisation and growth of three probiotic species in the luminal and mucosal compartments of the proximal and distal colon, and growth of a fourth species in the luminal proximal colon, leading to higher proximal and distal colonic lactate concentrations. The lactate stimulated growth of lactate-consuming bacteria, altering the bacterial diversity of the microbiota and resulting in increased short-chain fatty acid production, especially butyrate. Additionally, an immunomodulatory effect of the probiotics was seen; production of anti-inflammatory cytokines (IL-6 and IL-10) was increased and production of inflammatory chemokines (MCP-1, CXCL 10 and IL-8.) was reduced. The results indicate that the probiotic species alone do not result in a clinical effect; rather, they facilitate modulation of the gut microbiota composition and metabolic activity thereby influencing the immune response.

Anti-pathogenic effects

Use of a water-based probiotic to treat common gut pathogens

Dodoo CC, et al. Int J Pharm 2019;556:136–141.

This work reports the anti-pathogenic effect of a commercially available water-based probiotic suspension, Symprove™, against three commonly encountered infectious organisms; Escherichia coli, methicillin-resistant Staphylococcus aureus (MRSA) and Shigella sonnei. An isothermal calorimetric assay was used to the monitor growth of the species individually and in binary combinations, while colony plate counting was used to enumerate viable cell numbers. It was observed that all pathogenic species were faster growing than the probiotic bacteria in Symprove™ after inoculation into growth medium yet in all instances bacterial enumeration at the end of the experiments revealed a significant reduction in the pathogen population compared with the controls. A control population between 108 and 109 CFU/ml was obtained for E. coli and S. sonnei whilst approximately 106 CFU/ml was obtained for MRSA. Upon co-incubation for 48 h, no viable counts were obtained for E. coli; a 4-log reduction was obtained for S. sonnei whilst MRSA numbers were down to less than 10 cells/ml. The results show that Symprove™ has antipathogenic activity against E. coli, S. sonnei and MRSA.

In vitro inhibition of Clostridium difficile by commercial probiotics: A microcalorimetric study

Fredua-Agyeman M, et al. Int J Pharm 2017;517(1–2):96–103.

The aim of the study was to investigate the influence of some commercial probiotics on the growth of Clostridium difficile using isothermal microcalorimetry, a technique which can monitor the real time growth of bacteria. Commercial probiotic strains and products, Lactobacillus acidophilus LA-5®, Bifidobacterium lactis BB-12®, Probio 7® and Symprove™ were co-cultured with C. difficile in Brain Heart Infusion (BHI) broth supplemented with 0.1% (w/v) l-cysteine hydrochloride and 0.1% (w/v) sodium taurocholate and monitored in the microcalorimeter. Pseudomonas aeruginosa NCIMB 8628 was also co-cultured with C. difficile and studied. The results indicated inhibition of C. difficile by the probiotics. The inhibition of C. difficile was shown to be pH-dependent using neutralized and unmodified cell free supernatant (CFS) produced by the probiotic strains. However, concentrated CFS of the probiotics also inhibited the intestinal pathogen in a non pH-dependent manner, likely due to specific antimicrobial substances produced. The results also indicated that C. difficile growth was greatly influenced by the presence of sodium taurocholate and by the pH of the medium. A medium pH of between 6.45 and 6.9 demonstrated maximum growth of the organism in the microcalorimeter.

Viability

Comparative survival of commercial probiotic formulations: tests in biorelevant gastric fluids and real-time measurements using microcalorimetry

Fredua-Agymean M, et al. Benef Microbes 2015;6(1):141–51.

The large number of probiotic products now available makes the decision about which product to choose difficult both for the consumer and for the specialist providing dietary/nutritional advice. Data on the viability of the bacteria in these products, in an in vivo situation, are therefore important. This study was designed to explore the comparative health and survival of probiotic species in various commercial formulations, using more realistic test systems. This might allow further understanding of factors that must be controlled to optimise the delivery of live healthy bacteria to the lower gut. A total of eight commercially available probiotic preparations were selected for enumeration tests and in vitro gastric tolerance tests. Tolerance assays were conducted in porcine gastric fluid (PGF) fed and fasted state (pH 3.4±0.04), simulated gastric fluid (SGF, pH adjusted to 1.2 and 3.4) and fasted state simulated gastric fluid (FaSSGF, pH adjusted to 1.6 and 3.4). Isothermal microcalorimetry was also used to measure real-time growth of probiotics after exposure to simulated gastric fluid. Results from the enumeration tests indicated that recovery of viable organisms per dose is the same as or better than the stated label claims for liquid-based formulations, but lower than the stated claim for freeze-dried products. Results from the in vitro tolerance tests overall suggest that the PGF provided a harsher environment than the simulated systems at similar pH. In general, liquid-based products tested tended to give superior results in terms of survival compared with the freeze-dried products tested. Results from tests in the fed state in PGF suggested that food greatly affects viability. Microcalorimetric data showed that for some products probiotic species were able to grow following exposure to gastric fluid, suggesting that viable bacteria reach the gut in vivo.

Parkinson's Disease (SHIME®)

Influence of probiotic bacteria on gut microbiota composition and gut wall function in an in-vitro model in patients with Parkinson's disease

Ghyselinck J, et al. Int J Pharm X 2021:3:100087.

We report here the potential role of a 4-strain probiotic suspension for use with patients with Parkinson's disease (PD). Stool samples from a group of three patients with diagnosed PD were used to create microbiotas in an in-vitro gut model. The effects of dosing with an oral probiotic suspension (Symprove) on bacterial composition and metabolic activity in the microbiotas was evaluated over 48 h and compared with healthy controls. Additionally, the effect of probiotic dosing on epithelial tight-junction integrity, production of inflammatory markers and wound healing were evaluated in cell culture models. In general, the relative proportions of the main bacterial phyla in the microbiotas of PD patients differed from those of healthy subjects, with levels of Firmicutes raised and levels of Bacteroidetes reduced. Dosing with probiotic resulted in a change in bacterial composition in the microbiotas over a 48 h period. Several other indicators of gut health changed upon dosing with the probiotic; production of short chain fatty acids (SCFAs) and lactate was stimulated, levels of anti-inflammatory cytokines (IL-6, IL-10) increased and levels of pro-inflammatory cytokines and chemokines (MCP-1 and IL-8) decreased. Tight junction integrity was seen to improve with probiotic dosing and wound healing was seen to occur faster than a control. The data suggest that if development and/or progression of PD is influenced by gut microbiota dysbiosis then supplementation of the diet with a properly formulated probiotic may be a useful adjunct to standard treatment in clinic.

Ulcerative colitis (SHIME®)

A 4-strain probiotic supplement influences gut microbiota composition and gut wall function in patients with ulcerative colitis

Ghyselinck J, et al. Int J Pharm 2020;587:119648.

Symprove, a multi-strain probiotic, has been shown to exert a mild anti-inflammatory effect in patients with ulcerative colitis (UC). We examined stool samples from 3 patients with UC in order to create microbiotas in an in-vitro gut model. The effects of Symprove on bacterial diversity and metabolic activity in the microbiotas was evaluated over 48 h. In addition, the influence of probiotic dosing on epithelial tight-junction integrity, production of inflammatory markers and wound healing were evaluated in cell culture models. The relative proportions of the main bacterial phyla in UC patients differed from those of healthy subjects studied previously; levels of Firmicutes were lowered and levels of Bacteroidetes were raised. Addition of Symprove changed the bacterial composition in the microbiotas over a 48 h period. Several other factors generally implicated in good gut health changed after dosing with probiotic; production of short chain fatty acids (SCFAs) and lactate was stimulated, levels of anti-inflammatory cytokines (IL-6, IL-10) increased, levels of pro-inflammatory cytokines and chemokines (MCP-1 and IL-8) decreased, epithelial tight junction integrity improved and wound healing occurred faster than a control. The results imply it is not the simple addition of probiotic bacteria that improves gut health. Rather, the probiotic bacteria generate lactate, which then stimulates growth of commensal gut bacteria, raising SCFA levels (particularly butyrate). The increased butyrate concentration positively influences inflammation response and time of wound healing.

Notes

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