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Review Article

The Role of Prebiotics and Probiotics in Human Health: A Systematic Review with a Focus on Gut and Immune Health

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Abstract

Probiotics, and more recently prebiotics, are the subject of increasing research for an understanding of their impact on the gut microbiota, gut health and immune health. The science is advancing, with benefits of probiotics in certain types of diarrhoea, inflammatory bowel disease, irritable bowel syndrome, and also eczema in children well established. The study of the gut microbiota is leading to the discovery of potential benefits in organs beyond the gut including the brain, cardiometabolic system, the lungs, the eyes and the oral cavity. Researchers are beginning to understand the mechanisms by which these health outcomes occur and are obtaining clinical evidence supporting these newly emerging areas. This review describes the concept of probiotics and prebiotics, explains the importance of the gut microbiota in health and disease and discusses the role of probiotics in gut and immune health as well as clinical evidence-based interventions with probiotic and prebiotic supplements.

Introduction

Growing awareness of the importance of gut health and the gut microbiome is driving an increase in interest in probiotics and prebiotics that have the potential to improve not only gut health but also overall health, including immune health [1,2].

Probiotics in the form of fermented foods and drinks have a long history of use going back centuries but the concept of probiotics as we know it today was discovered in 1907 by a Russian scientist, Elie Metchnikoff [3] of the Pasteur Institute in Paris, who, when working in Bulgaria, was intrigued to discover that some Bulgarian inhabitants lived much longer than others. He discovered that inhabitants of the Caucasus mountains drank a fermented yogurt on a daily basis. His further studies led to the discovery of the bacteria, *Lactobacillus bulgaricus,* which, he thought, may have been responsible for their long lives. Since that time, a range of gut friendly bacteria, described as probiotics for their potentially positive impacts on human health, has been identified and has been the subject of more intensive scientific study, particularly during the last 50 years.

Scientific data shows benefits of specific probiotics in certain types of diarrhoea [4] and other gastrointestinal conditions [5]. However, increasing knowledge of the role of the gut microbiome and the gut microbiota in health and the potential influence of probiotics and prebiotics on the gut microbiota, as well as health-related biochemical mediators beyond the gut, suggests that probiotics and prebiotics could have a significant impact on health more broadly. An area of emerging and current interest is the role of both probiotics and prebiotics in immune health [6], brain health [7], metabolic health [8], dental health [9] and eye health [10] as well as the overall health of the gut. The recent pandemic has also shed further light on the role of the gut in immune health, with microbial dysbiosis in the gut suggested to be an issue in respiratory tract infections [11]. Both probiotics and prebiotics are also being studied for a potential role as adjuncts in the treatment and prevention of COVID-19 [12].

This paper will consider the role of probiotics and prebiotics in human health with a focus on gut and immune health, including a consideration of the scientific data evaluating the impact of these preparations on gastrointestinal disease, eczema, allergies and respiratory tract infections. We also consider some of the emerging science evaluating the role of probiotics and prebiotics in obesity, metabolic syndrome, cardiovascular disease, cognitive and mental function and periodontal disease.

What are Probiotics and Prebiotics?

Definitions

Probiotics are defined as "live microorganisms (e.g. bacteria and yeasts) that, when administered in a viable form and adequate amounts, are beneficial to human health" [13]. This definition stipulates that a probiotic must be alive when administered, have a health benefit to the host (or person taking it) and be delivered at an effective dose. The definition implies that a probiotic must be safe for the intended use and must be a defined entity to allow for appropriate identification to the strain level.

A review paper by Sanders, et al [14] suggested there is no requirement for probiotics to demonstrate properties in pre-clinical studies such as gastrointestinal colonisation, ability to survive gastrointestinal transit, adherence to the gut mucosa, anti-pathogenic properties and ability to balance the host gastrointestinal mucosa. According to Sanders et al, the crux of the definition above is that probiotics are those live microorganisms that confer a health benefit to the individual. They add that to demonstrate a health benefit, the need is for human trials, using a well-defined intervention with well-defined microbial strains. Ideally, the impact of probiotics and prebiotics on the gut microbial population should be studied as part of such human trials [14]. These authors also expressed the view that whilst a range of tests have been used to describe probiotics in the laboratory, these tests have not been validated and the outcomes of such tests have not been linked to probiotic efficacy [14].

The concept of prebiotics is newer than that of probiotics. They were most recently defined as "a substrate that is selectively used by host micro-organisms conferring a health benefit" [15]. All compounds currently considered to be prebiotics are either carbohydrates accessible to the gut microbiota or they can be fermentable dietary fibre. Examples of such carbohydrates would be inulin and other Fructo-Oligosaccharides (FOS) that microorganisms in the gastrointestinal tract use as metabolic fuel. Other substances such as polyphenols and polyunsaturated fatty acids that can be converted to conjugated fatty acids might fit with the definition of a prebiotic [15], assuming convincing weight of evidence in the target host. Synbiotics contain a mixture of prebiotics and probiotics.

Characteristics of probiotics

Probiotics are live microorganisms, mostly bacteria and also a few yeasts. They are identified by their specific strain, which includes the genus, the species, the subspecies (if applicable), and an alphanumeric strain designation. The seven most common genuses, or genera, used in probiotic products are Bifidobacterium, Lactobacillus, Saccharomyces, Streptococcus, Enterococcus, Escherichia and Bacillus. Examples of strains reflecting appropriate nomenclature are shown in Table 1.

Genus	Species	Sub-species	Strain designation
Bifidobacterium	Animalis	Lactis	DN-173 010
Bifidobacterium	Longum	Infantis	BB-02
Lactobacillus	Plantarum	None	299v
Lactobacillus	Reuteri	None	DSM 17938
Lactobacillus	Rhamnosus	None	GG
Saccharomyces	Boulardii	None	CNCM 1-745

Table 1: Examples of nomenclature for commercial strains of probiotics.

Probiotics are measured in Colony Forming Units (CFUs), which indicate the number of viable cells (sometimes designated as live cultures). For example $1x10^9$ or 1 billion CFU and 1×10^{10} or 10 billion CFU. Many probiotic supplements contain 1 to 10 billion CFU per dose.

Strain designations are important in the clinical setting because they link clinical benefits (e.g. prevention of certain specific types of diarrhoea) with both specific strains, and mixtures of specific strains, in effective doses. Some strains have unique properties (e.g. neurological, immunological or endocrinological effects) [13] that may be linked to their specific clinical benefits. However, evidence is emerging that some mechanisms of probiotic activity are shared among different strains, species and genera. For example, the production of Short Chain Fatty Acids (SCFAs) in the colon, such as lactate and acetate and the ability to reduce gastrointestinal pH, is shared by most species of Bifidobacterium and Lactobacillus and many of their strains [14]. These SCFAs contribute to general gut health and provide a range of potential health benefits both in and beyond the gastrointestinal tract (e.g. in terms of the immune system, brain, metabolic function). In a 2017 practice guideline, the World Gastroenterology Organisation suggested that if the aim is to support digestive health, it is possible that many different probiotic preparations containing adequate amounts of single, or mixtures of well-studied, live microorganisms will be sufficient to provide a health benefit [16].

Probiotic products are available mainly in the form of dietary supplements, including tablets, capsules, powders, liquids and other formulations. Probiotics are also added to commercial yogurts and cultured milk drinks (e.g. kefir).

Fermented foods and drinks

Traditionally fermented foods such as kefir, kombucha, sauerkraut and sourdough may contain live microorganisms but the microbes may not be fully characterised in terms of the bacterial strains present, the amounts of microbes present, whether the amounts present would confer a health benefit and whether the

microbes are alive at the time of consumption. The opinion of the International Scientific Association for Probiotics and Prebiotics (ISAPP) is that these foods and drinks do not meet the definition for a probiotic product since they are largely uncharacterised and their health benefits unconfirmed [17]. The ISAPP takes the view that if a probiotic microorganism or mixture of organisms is added to a fermented food or drink then that food or drink is a probiotic product.

Nevertheless, consumption of traditionally fermented foods and drinks has been associated with health benefits. Fermented dairy products (mainly yogurt) have been associated in epidemiological studies with reduced risk of metabolic syndrome [18], reduced risk of obesity [19], reduced risk of cardiovascular disease [20] and reduced risk of colon cancer [21]. Consumption of fermented soy products, such as miso and natto, has been associated with reduced risk of high blood pressure [22] and reduced risk cardiovascular disease [23]. Conversely, in the Netherlands cohort (34,409 Dutch men and women aged 20-70 years) of the large European Prospective Investigation into Cancer and Nutrition (EPIC) study, consumption of fermented dairy foods was not associated with mortality, cancer or cardiovascular disease [24].

Characteristics of prebiotics

The key characteristic of a prebiotic is that it is selectively used by host microorganisms to confer a health benefit. Most prebiotics are a form of dietary fibre, which means they are not digested or absorbed in the small intestine, but not all dietary fibres are prebiotics. Prebiotics are commonly fermentable dietary fibre, which means they serve as growth substrates for microbes in the distal bowel or they are otherwise accessible to the microbes in the colon, where they selectively or specifically nourish microorganisms. Essentially, prebiotics act as substrates for any gut microbes that have the capacity to use them, which is primarily dependent on the structure of the prebiotic compound.

Prebiotics occur naturally in some high fibre foods such as vegetables, beans and pulses, fruits and whole grains. They are sometimes added to foods such as biscuits, cereals and dairy products. They are also available as dietary supplements in the form of tablets, capsules, powders and liquids.

Structurally, prebiotics are mixtures of Non-Starch Polysaccharides (NSPs) and oligosaccharides. Commonly used examples include: inulin (found naturally in asparagus, chicory root, Jerusalem artichoke and leeks); oligofructose (found in wheat, honey, garlic, onions and bananas); galacto-oligosaccharides (GOS) (found in legumes; hummus, cashews and pistachios, soy milk and oat milk and freekeh); xylo-oligosaccharides (found in fruits, vegetables, honey, milk and bamboo shoots); and lactulose (a synthetic disaccharide used as a medicine for the treatment of constipation and hepatic encephalopathy). Resistant starch is a type of carbohydrate that is resistant to digestion in the small intestine and ferments in the large intestine, acting as a prebiotic feeding the beneficial Bifidobacteria and Lactobacilli in the gut. Resistant starch is found in green bananas, beans, peas and lentils, whole grains, including barley and oats, and cooked then cooled potatoes and rice. Other fibres such as pectin found in apples and beta-glucan found in oats and barley have been found to demonstrate prebiotic properties. Certain other dietary compounds such as polyunsaturated fatty acids [25,26] and polyphenols (e.g. found in tea [27], cocoa [28] and red wine [29]) which are converted to respective conjugated fatty acids could be included in the definition of prebiotics as there is some evidence to suggest they promote the growth of beneficial bacteria in the gut.

Mechanisms of Action of Probiotics and Prebiotics

The mechanisms of action of both probiotics and prebiotics relate to their influence on the microbes that inhabit the gastrointestinal (GI) tract. Approximately 100 trillion microorganisms (bacteria, viruses, fungi, protozoa) of at least 1000 different species live in the GI tract [30]. Relatively few – mainly Lactobacilli and Streptococci – are found in the stomach and duodenum where gastric acid, bile and pancreatic juices inhibit or eradicate most microorganisms. Lower down in the intestine, numbers of microbes progressively increase, from 10^4 cells per gram in the jejunum to 10^9 cells per gram of contents in the distal ileum. The colon is the most heavily populated region of the GI tract – mainly with anaerobic microbes - containing to 10^{12} cells per gram of intestinal contents [16].

The diversity of gastrointestinal microbes between individuals is striking, with each individual harbouring his or her own distinctive pattern of microbial composition. This is determined by genotype, initial colonisation at birth and by dietary habits. In healthy adults, the faecal composition is stable over time. In the human gut, two bacterial divisions predominate-Bacteroidetes and Firmicutes-and account for more than 90% of microbes. However, populations of colonising microbes differ between healthy individuals and others with disease or poor health [30]. Microbial composition also appears to differ according to age, sex, race and different geographical locations [30]. However, researchers are still not entirely able to define the composition of a healthy human microbiota.

The 'gut microbiota' is the combination of microorganisms present in the GI tract. The 'gut microbiome' includes these microorganisms and also the genes associated with them and the environment that influences them [31]. The gut microbiome, which is unique to each individual, contains over 3 million genes making it 130 times more genetically varied than the human genome which consists of about 23,000 genes [31]. The gut microbiome can be considered as an organ in its own right. It produces thousands of active metabolites, which can affect human health and disease

both inside and outside of the gut.

Probiotics exhibit a variety of mechanisms of action [13], initiating their effects mainly, but not exclusively, in the GI tract. Probiotics can transiently colonise the human gut in highly individualised patterns, depending on the individual's microbiota, the probiotic strain(s), and the region of the GI tract [32]. Whilst the health benefits of probiotics have commonly been thought to arise from an ability, in healthy people, to alter the gut microbial composition, this does not always appear to be the case. Indeed, a systematic review of seven trials found little evidence that probiotics can significantly alter the structure of the gut microbiota in healthy adults [33]. This suggests that the health benefits of probiotics can occur without the need for alteration in the gut microbial population.

Evidence shows, however, that probiotics do interact with the gastrointestinal ecosystem where they inhibit the growth of pathogenic microorganisms by, for example, speeding up GI transit and reducing the ability of disease-causing bacteria to colonise and adhere to the gastrointestinal mucosa. Probiotics can also increase production of bioactive metabolites (e.g. SCFAs), so reducing the pH in the colon. Other ways in which they act include vitamin synthesis in the GI tract, bile salt metabolism, enzyme activity and toxin neutralisation [13]. Probiotics communicate with cells inside and outside of the GI tract through biochemical signalling mechanisms. This leads to improvement of gut barrier function, reduced production of pro-inflammatory markers such as cytokines [34] and improved immune function both in the gut and throughout the immune system [35]. Through all of these mechanisms, probiotics might have further wide-ranging impacts on human health and disease.

Prebiotics interact with the gut microbiota mainly by nourishing the beneficial anaerobic bacteria in the colon, principally Bifidobacteria and Lactobacilli, and increasing their number, whilst reducing the population of potentially pathogenic microorganisms. Prebiotics, which are primarily undigested dietary carbohydrates, are fermented by the colonic bacteria to produce SCFAs – acetate, propionate and butyrate - which have a variety of important roles. These include maintenance of gut barrier function, reduced levels of inflammatory markers and an influence on metabolic hormones (including stimulation of glucagon-like peptide1 (GLP-1) and Peptide Y-Y) which can reduce appetite, improve insulin sensitivity and protect against weight gain and metabolic syndrome [36]. Prebiotics also improve immunity, acting both locally in the gut and systemically by increasing anti-inflammatory cytokines and decreasing pro-inflammatory cytokines [37] and other immune function markers [38].

Clinical Applications of Probiotics and Prebiotics

The effect of probiotic supplementation has been studied in a wide range of conditions and in a large number of studies, including gastrointestinal conditions, atopic eczema in children, allergies, respiratory tract infection, obesity, metabolic disease/ type 2 diabetes, cardiovascular disease, cognitive and mental health and bone health.

Due to the large number of human studies, including Randomised Controlled Trials (RCTs), this section focuses on evidence from systematic reviews/meta-analyses. Table 2 shows a summary of the systematic reviews evaluating human studies with probiotics during the last five years. The search for these reviews was conducted on Medline using the term "probiotics" and "systematic review" or "meta-analysis". Systematic reviews including probiotics, and only those that compared these interventions with a control and, in the authors' estimations, included some moderate or high quality randomised trials (RCTs) are included in Table 2. Prebiotic research is not so well developed and is discussed separately.

Health Outcome	Number of studies	Findings	Reference
Diarrhoea			
Traveller's Diarrhoea (TD)	11 RCTs n=1227 (probiotics)	Significant efficacy in prevention of TD	[39]
Incidence of Traveller's Diarrhoea (TD)	12 RCTs in systematic review; 6 RCTs in meta-analysis (probiotics)	One of three probiotics *(Saccharomyces boulardii)* showed significant efficacy for the prevention of TD. *L. rhamnosus GG* showed a trend and *L. acidophilus* no significant effect.	[40]
Treatment of acute diarrhoea in children	12 studies n = 744 children (probiotics)	Probiotics shortened duration of diarrhoea, improved 2-day treatment efficacy and reduced hospital stay	[41]

Acute infectious diarrhoea	82 studies/ n = 12127; 11526 children;412 adults (probiotics)	Probiotics probably make little or no difference to the number of people who have diarrhoea lasting 48 hours or longer. Whether probiotics reduce duration of diarrhoea is uncertain	[42]
Prevention of antibiotic-associated diarrhoea (AAD)	33 studies n = 6352 children	Moderate protective effect of probiotics for preventing AAD	[43]
Prevention of AAD	42 studies n = 11305 (probiotics)	Probiotics are effective for preventing AAD. Secondary analyses of higher dosages and certain species have shown increased effectiveness.	[44]
AAD	37 clinical studies (including 33 RCTs) (probiotics)	The effect of probiotics on AAD is strain-specific. S. boulardii CNCM I-745 or Lactobacillus rhamnosus GG are effective	[45]
Clostridium difficile-Associated Diarrhoea (CDAD) in adults and children	39 studies n = 9995 (probiotics)	The short-term use of probiotics appears to be safe and effective when used along with antibiotics in patients who are not immunocompromised or severely debilitated.	[46]
Prevention of CDAD & AAD	10 RTCs n = 4692 (probiotics)	Probiotics especially, Lactobacilli strains, (especially *L. casei*), have a good effect on the prevention of CDAD and AAD.	[47]
Inflammatory Bowel Disease			
Induction and maintenance of Inflammatory Bowel Disease (IBD) remission	10 RCTs n= 777 with Ulcerative Colitis (UC) and Crohn's Disease (CD) (probiotics)	Probiotics can induce remission during the active period of UC, but have no obvious therapeutic advantage in maintaining CD and UC remission.	[48]
Reduction of IBD complications	21 clinical trials (probiotics, prebiotics and synbiotics)	Probiotics, as food supplements, can induce remission in IBD. Fewer reports for remission in CD	[49]
Maintenance of remission in Ulcerative Colitis (UC)	12 studies n = 1,473 (probiotics)	The effectiveness of probiotics for the maintenance of remission in ulcerative colitis is unclear	[50]
Induction and maintenance of remission in UC	14 studies n =865 (probiotics)	Probiotics may induce clinical remission in active ulcerative colitis when compared to placebo. Little or no difference in clinical remission with probiotics alone compared to 5-ASA	[51]

Induction of clinical remission in Crohn's Disease (CD)	2 studies n = 46 (probiotics)	No evidence of a difference between the use of probiotics and placebo for the induction of remission in CD) after 6 months.	[52]
IBD	38 trials (probiotics, prebiotics, synbiotics)	Pro/pre/synbiotics, (synbiotics are more effective) for treatment of IBD (especially UC). Probiotic supplements that are based on Lactobacillus and Bifidobacterium or more than one strain are more likely to be beneficial for IBD remission.	[53]
Irritable Bowel Syndrome (IBS)			
Efficacy and safety of probiotics in Irritable Bowel Syndrome (IBS)	59 studies n = 6761 (probiotics)	Probiotics are effective and safe for IBS patients. Single probiotics with a higher dose (daily dose of probiotics ≥10(10)) and shorter duration (< 8 weeks) seem to be a better choice	[54]
Management of IBS	33 RCTs n = 4321 (probiotics, prebiotics and synbiotics)	Probiotics and synbiotics improved symptoms of IBS; evidence on prebiotics is scarce	[55]
Management of IBS	42 RCTs n = 3856 participants	Six single-strain probiotics and three different types of probiotic mixtures showed significant efficacy for at least one IBS outcome measure.	[56]
Efficacy and safety of probiotics in IBS	28 studies n = 3606 (probiotics)	Particular combinations, species or strains of probiotics are effective for overall IBS symptoms.	[57]
Management of IBS	35 RCTs n = 3452 (probiotics)	Compared with placebo, patients using probiotics had a lower incidence of persistence of symptoms. Probiotics exerted a beneficial effect on global symptoms and the abdominal pain score), bloating score and flatulence score	[58]
Constipation-predominant irritable bowel syndrome:	17 RCTs n = 1469 (probiotics)	Probiotics significantly increased stool frequency by 1.29 bowel movements, and improved stool consistency. Compared with placebo, patients using probiotics experienced a shorter gut transit time by 12.36 hours	[59]
Constipation			
Constipation in adults	15 RCTs (probiotics)	Consumption of probiotics, in particular, multispecies probiotics, may substantially reduce the GTT, increase the stool frequency, and improve the stool consistency	[60]
Lactose intolerance			
Lactase deficiency; Lactose Intolerance (LI)	9 RCTs (probiotics and prebiotics)	An overall positive relationship between probiotics and LI in relation to specific strains and concentrations	[61]

Lactose intolerance	15 RCTs (probiotics)	Varying degrees of efficacy but an overall positive relationship between probiotics and lactose intolerance.	[62]
Necrotising Enterocolitis (NEC)			
Effects of probiotics in pre-term neonates	30 RCTs n- 77018 infants	Routine probiotic supplementation associated with significantly reduced NEC ≥ Stage II, late onset sepsis and all-cause mortality in neonates <37 weeks of gestation and NEC ≥ Stage II in extremely low birth weight neonates	[63]
Effect of probiotics on the risk of NEC and mortality and morbidity in very preterm or very low birth weight infants.	56 trials n = 10812 infants	Probiotics likely reduce mortality and late onset invasive infection, but analysis of 16 trials at low risk of boas showed no effect on mortality and infection. Probiotics overall had no impact on neurodevelopmental impairment	[64]
Eczema/Dermatitis/Allergies			
Prevention of atopic eczema in children	21 studies (probiotics)	Mixture of probiotic supplementation given to the mother in pregnancy and continuing while breastfeeding and also to the infant in children classified as high-risk for atopic dermatitis and non-high-risk groups is the most efficacious in reducing the risk of incidence of atopic dermatitis in children.	[67]
Prevention of atopic eczema in children	28 studies (probiotics)	Probiotic supplementation during both the prenatal and the postnatal period reduced the incidence of AD in infants and children.	[68]
Atopic Dermatitis (AD) in children	25 studies in children (14 prevention) n = 3049 (11 treatment) n = 816 (probiotics)	Probiotics potentially lower the incidence of AD and relieve AD symptoms in children, particularly when treating infants and children aged≥1 year with AD. Interventions with mixed-strain probiotics tended to have better preventive and curative effects.	[69]
Prevention of atopic eczema in children	21 studies n= 5406 (probiotics)	Certain probiotic preparations demonstrate efficacy in reducing the risk of developing atopic dermatitis when administered to pregnant women, infants, or both.	[70]
Allergies	22 studies (prebiotics)	Evidence of benefit for prebiotics preventing allergies is uncertain	[71]
Treatment of allergic rhinitis	13 RCTs n=1591 (probiotics)	8 of 9 probiotic types alleviated at least one clinical symptom of allergic rhinitis	[72]
Respiratory Tract Infection (RTI)			

Incidence of RTI	16 studies (synbiotics)	Synbiotic interventions reduced the incidence rate of RTIs by 16% (95% CI: 4%, 27%) and the proportion of participants experiencing RTIs by 16% (95% CI: 5%, 26%).	[73]
Incidence of RTI	27 trials n = 9433 (probiotics)	Probiotics could significantly increase the plasma levels of cytokines, the effect of influenza vaccine and quality of life, as well as reducing the titre of viruses and the incidence and duration of respiratory infections.	[74]
Overall health, immune health, incidence of common cold	17 studies in older people (probiotics)	Probiotic supplementation had modest effects on markers of humoral immunity, immune cell population levels and activity, as well as the incidence and duration of the common cold and other infections with some conflicting results.	[75]
Prevention of URTIs	6 RCTs n = 1551	Compared with the placebo group, the probiotics intervention group significantly reduced the incidence of URTI episodes, the episode rate of URTIs and the mean duration of one episode of URTI.	[76]
Prevention or amelioration of RTIs	18 studies (probiotics)	A combination of different probiotics, most of them in the genus Bifidobacterium sp. and Lactobacillus sp., could be a good mix to strengthen the immune system and reduce the symptoms of URTIs in the healthy working population.	[77]
RTIs	22 RCTs n = 10190 (probiotics)	PFDP have a protective effect on pneumonia and the common cold	[78]
Incidence of acute URTIs	8 RCTs in people > 60 years (probiotics)	Certain probiotic strains reduced incidence of acute URTIs in older people	[79]
Obesity			
Obesity/overweight	15 RCTs, n=957 (probiotics)	Small reduction in BMI and fat percentage	[80]
Obesity/overweight	19 RCTs n =1412 (probiotics)	Small reduction in waist circumference (WC), no effect on body weight or BMI	[81]
Obesity	23 RCTs (synbiotics)	Reduced body weight and WC. No effect on BMI and body fat	[82]

Body fat and CV risk markers in obese/overweight	26 RCTs n=1720 (probiotics)	Reduced body weight, BMI and WC, fat mass, total cholesterol, LDL-cholesterol insulin	[83]
Probiotics and synbiotics in overweight/obesity	27 studies (probiotics and synbiotics)	Weight loss in 23/27 studies	[84]
Metabolic syndrome type 2 diabetes			
Inflammatory markers and glucose homeostasis in type 2 diabetes mellitus	17 studies n = 836	Improved inflammatory markers, including C-reactive protein and TNF-alpha; improved glycaemic control	[85]
Glycaemic outcomes In adults with type 2 diabetes	9 RCTs (probiotics)	Multistrain probiotics that contain seven million to 100 billion colony forming units of Lactobacillus acidophilus, Streptococcus thermophilus, Lactobacillus bulgaricus, and/or Bifidobacterium lactis administered for 6 to 12 weeks may be efficacious for improving glycaemic control in adults with T2DM.	[86]
Glycaemic outcomes in patients with abnormal glucose metabolism	31 studies, n=1948 (probiotics)	Favourable effect on fasting plasma glucose, fasting HbAIc and fasting insulin	[87]
Cardiometabolic and anthropometric indices in metabolic syndrome	5 trials n = 1049 (synbiotics)	Reduced serum insulin, triglycerides, total cholesterol, LDL-cholesterol, waist circumference, body weight, systolic blood pressure, serum IL-6 and increased HDL-cholesterol	[88]
Blood glucose and insulin in pregnant women	20 RCTs, n=2972 (probiotics)	Reduced fasting plasma glucose, insulin, insulin resistance. Effects more pronounced in women with gestational diabetes and overweight/obese	[89]
Efficacy of probiotics/ synbiotics in diet controlled gestational diabetes	12 RCTs n= 894 (probiotics/ synbiotics)	Improved glucose and lipid metabolism, anti-inflammatory and antioxidant ability with probiotic/ synbiotic interventions	[90]
Cardiovascular disease			
Effects of probiotics on blood pressure and serum lipids in type 2 diabetes	11 RCTs n = 641 (probiotics)	Probiotics significantly reduced systolic and diastolic blood pressure, total cholesterol (TC), LDL-cholesterol, and triglycerides	[91]
Lipid profiles in adults with hypercholesterolaemia	19 RCTs n = 967 (probiotics)	Probiotics significantly lowered total cholesterol (TC) and LDL cholesterol	[92]

Serum lipid levels in non-obese healthy adults with hyperlipidaemia	16 studies n = 1429 participants (probiotics)	Intervention reduced TC and LDL cholesterol. No change in HDL cholesterol and triglycerides	[93]
Efficacy of Lactobacillus on serum lipids	15 studies n = 976 (probiotics and synbiotics)	Lactobacillus, especially *L. reuteri* and *L. plantarm*, reduced TC and LDL cholesterol significantly. Significantly beneficial effects on triglycerides and HDL-C by consuming synbiotic food, containing *L. sporogenes* and inulin.	[94]
Cognitive function and mental health			
Effect of probiotic on Mild Cognitive Impairment (MCI)	6 RCTs n = 462 (probiotics)	Favourable effects on homeostasis model assessment-insulin resistance (HOMA-IR], insulin sensitivity, VLDL and triglycerides	[95]
Effect of probiotics, prebiotics and Faecal Microbiota Transplant (FMT) on cognitive function	23 studies (probiotics/prebiotics)	Probiotics and FMT had beneficial effects on cognitive function in healthy and unhealthy subjects; prebiotics had no impact	[96]
Effect of probiotics in Alzheimer's Disease (AD), MCI and Parkinson's Disease (PD)	5 RCTs n= 342 (probiotics)	Probiotics can improve cognitive and gastrointestinal symptoms in patients with AD, MCI, and PD, which is possibly through reducing inflammatory response and improving lipid metabolism.	[97]
Effect of probiotics in AD and MCI	8 studies n= 174 patients with AD; n=446 with MCI (probiotics)	Significant effect of probiotics on cognitive function only in the studies involving people with MCI	[98]
Efficacy of probiotics on AD/ MCI	5 studies n= 297	Probiotics improved cognitive performance in AD or MCI	[99]
Effect of probiotics on cognitive function in older people	10 studies (probiotics)	No evidence for beneficial effect of probiotics on cognitive function	[100]
Effect of probiotics in AD	3 RCTs n=161 with AD receiving Lactobacillus and Bifidobacteria strains	No beneficial effect of probiotics on cognitive function	[101]

Effect of probiotics, prebiotics and fermented foods on cognitive function	22 RCTs n= 1551 probiotics (11 studies, n = 724), prebiotics (5 studies, n = 355), fermented foods (6 studies, n = 472)	No significant effect for any intervention for global cognition	[102]
Effect of probiotics in depressive symptoms	10 RCTs (probiotics)	Majority of studies found positive results that probiotics improve depressive symptoms	[103]
Bone health			
Bone health in post-menopausal women	5 RCTs n=497 (probiotics)	Significantly higher bone mineral density (BMD) in the lumbar spine; no other impacts	[108]
BMD and bone turnover in post-menopausal women	6 RCTs n=632 (probiotics)	Effects on BMD and bone turnover inconsistent	[109]
Periodontal Disease (adjunctive treatment)			
Adjunctive treatment of chronic periodontitis	7 clinical studies	The overall mean difference for clinical attachment level (CAL) between probiotics and placebo (both with root planning and scaling) was significant	[112]
Adjunctive treatment of chronic periodontitis	24 RCTs	CAL gain, probing pocket depth and bleeding on probing improved after 3 months (but no significant difference at 6 months). Improvement in plaque index and gingival index in the short term.	[114]
Adjunctive treatment of chronic periodontitis	14 clinical studies	Gain in CAL and reduced periodontal probing depth	[115]
Micronutrient status	14 RCTs (probiotics)	Positive impact on status of vitamin B12, calcium, folate, iron and zinc	[94]

Table 2: Summary of systematic reviews/RCTs valuating the impact of probiotics and synbiotics on various health outcomes.

Gastrointestinal conditions

This analysis showed substantial evidence for beneficial effects for probiotic supplementation in diarrhoea, particularly prevention of travellers' diarrhoea [39,40] and treatment of acute diarrhoea in children [41]. However, the conclusion of a Cochrane analysis of 82 studies including adults and children was that the ability of probiotics to reduce the duration of acute diarrhoea is uncertain [42]. *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* are the most commonly used probiotics associated with successful outcomes in diarrhoeal conditions.

Probiotic supplementation has also been shown to be effective in preventing Antibiotic Associated Diarrhoea (AAD) [43-45] and/or *Clostridium difficile* diarrhoea [46,47] with higher doses being the most effective in these conditions. Both *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* have been shown to reduce the risk of AAD in the studies in these meta-analyses.

Six recent meta-analyses [48-53] have shown that probiotics induce remission in Inflammatory Bowel Disease (IBD), with most evidence of effectiveness for Ulcerative Colitis (UC), but less so for Crohn's Disease (CD) [49,52]. Specific strains are likely to be important in IBD and further research is required to evaluate the place of probiotics in management of IBD and their use alongside usual care. There is also good evidence for the use of certain strains of probiotics for preventing an attack of pouchitis and in preventing further attacks after induction of remission. The effectiveness of probiotics for maintenance of remission in IBD is unclear [48,50]. Studies have used various probiotic strains and combinations including *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii*, various others strains of lactobacilli, bifidobacteria and *Streptococcus thermophilus.*

Evidence from a further six meta-analyses also shows a modest benefit with probiotics in the management of symptoms of Irritable Bowel Syndrome (IBS) [54-59], including constipation-dominant IBS in which probiotics are associated with an increased bowel frequency and stool consistency [59]. Most studies have employed strains of Lactobacilli and Bifidobacteria. In a meta-analysis of 15 RCTs, consumption of probiotics, in particular, multispecies probiotics, substantially reduced the gastrointestinal transit, increased the stool frequency, and improved the stool consistency [60]. Evidence for impact of prebiotics in IBS is scarce [56].

Variable, but generally favourable effects, have been demonstrated in two meta-analyses for probiotics [61,62], but not prebiotics [61] in lactose intolerance.

There is also evidence from systematic reviews to show that probiotics may help prevent necrotising enterocolitis in pre-term infants, although trial quality is generally poor [63,64]. There is also evidence that they contribute alongside standard treatment to the management of *Helicobacter pylori* [65], and that probiotics, prebiotics and synbiotics can alleviate Non-Alcoholic Fatty Liver Disease (NAFLD) [66].

Eczema and allergies

Research interest in probiotics and eczema in children goes back several decades. Amongst systematic reviews conducted in the last five years, four have evaluated the effect of probiotics taken during pregnancy, breast feeding and/or during infancy. All have shown the efficacy of probiotics, particularly certain strains, on reducing risk of atopic eczema in children [67-70]. Some strains of Lactobacillus, Bifidobacterium, and Propionibacterium have demonstrated beneficial outcomes in eczema whilst other strains of the same species have not.

One systematic review of 22 studies [71] evaluating the impact of prebiotics on allergies found no benefit, whilst another systematic review found benefit of probiotics on at least one symptom in allergic rhinitis [72].

Respiratory Tract Infection

An analysis of systematic reviews and meta-analyses published over the last 5 years found substantial evidence of benefit for probiotics in reducing the incidence and duration of upper respiratory tract infections in healthy people, including the common cold [73-79]. Two of these analyses [74,75] demonstrated positive impacts on immune markers and one [75] an improvement in the effect of influenza vaccine. *Lactobacillus rhamnosus* GG and *Streptococcus thermophilus* have been used with beneficial outcomes in the studies included in these analyses.

Obesity and cardiometabolic parameters

Emerging research indicates that probiotics contribute to weight loss and improve cardiometabolic parameters. Four recent systematic reviews have shown that probiotic [80-84] and symbiotic [80] consumption leads to weight loss in overweight and obese subjects, but weight loss and reduction in waist circumference and visceral fat is small [80-84]. Studies with positive outcomes in obesity have largely used Lactobacillus strains.

Probiotics can improve inflammatory markers, such as C-reactive protein, as well as glycaemic control and insulin metabolism in patients with metabolic syndrome/type 2 diabetes, [85-90] including pregnant women with gestational diabetes [85,86]. Probiotics have also been shown to improve markers for cardiovascular disease, including hypertension [91] and dyslipidaemia [92-94]. The studies in these systematic reviews tend to lack homogeneity so it is difficult to be clear about the benefits of probiotics in obesity and cardiometabolic parameters at this time. Overall research from these meta-analyses suggests that the most successful strains are *Lactobacillus*

acidophilus and *Bifidobacterium lactis*, or *Lactobacillus plantarum*.

Cognitive health

Findings from meta-analyses for probiotics and cognitive function [95-102] are somewhat inconsistent, with favourable effects of probiotics on cognitive function mostly in people with Mild Cognitive Impairment (MCI) (rather than Alzheimer's Disease (AD)), possibly related to a decrease in inflammatory and antioxidative markers. However, some systematic reviews have found no evidence of benefit for probiotics in either MCI or AD [96-98]. These inconsistencies may be related to the small size and short duration of studies, different interventions and heterogeneity in both study populations and cognitive tests. *Bifidobacteria infantis, Bifidobacteria longum, Lactobacilli acidophilus, Lactobacilli plantarum,* and *Lactobacilli casei* have been used in these studies, but much more research on doses and strains is required.

Mental health

Evidence on the use of probiotics in mental health conditions such as depression and anxiety is emerging with some positive [103] but also some null findings [104,105]. Other promising areas of research related to probiotic supplementation and conditions of the nervous system include Parkinson's disease [106] and multiple sclerosis [107].

Bone health

Another emerging area of research is probiotic supplementation and bone health, in which overall observed effects in systematic reviews to date are inconsistent [108,109], although some probiotic strains have shown beneficial effects on certain bone parameters [110,111], including serum calcium.

Periodontal disease

Probiotics have generated interest as an adjunctive treatment in periodontal disease due to the frequent colonisation by periodontal pathogens after treatment. Several systematic reviews [112-115] have found that use of probiotics reduces periodontal bacterial pathogens, the depth of periodontal pockets and periodontal tissue bleeding when used as an adjunct to standard treatment. Various strains of Lactobacilli and Streptococci have been used.

Discussion

The evidence base for use of probiotics and prebiotics and synbiotics is growing. This review has found considerable evidence that supplementation with probiotics, in particular, has beneficial outcomes for health in a range of gastrointestinal conditions, including diarrhoea, particularly for the prevention of travellers' diarrhoea [39,40] and prevention of diarrhoea associated with antibiotic administration [43-45] and *Clostridium difficile* diarrhoea in children and adults [46]. These findings confirm those of other recent reviews of clinical research studies [31,116]. Probiotics can also induce remission in ulcerative colitis, but evidence of benefit in maintenance of remission in ulcerative colitis and also for benefit in Crohn's disease is lacking. Evidence of benefit in IBS is more variable and - as for other GI conditions - is likely to be strain specific.

Gut microbiota disturbance has been noted in several gastrointestinal conditions [116] including AAD, IBD and IBS [117], *Helicobacter pylori* associated gastrointestinal disease, NAFLD and colon cancer; the potential to restore the balance of the microbiota using probiotics and/or prebiotics is promising. Both probiotics and prebiotics interact with the gut microbiota but their ability to colonise the GI tract beyond the short to medium term is not clear. However, this does not preclude their potential for gut health benefits, as evidence shows that they can prevent mucosal adhesion and colonisation of pathogenic microorganisms and enhance gut barrier function [13]. Optimisation of gut health can be achieved by use of probiotics through improved gut immune function, including increased secretion of immunoglobulin A, activation of T cells and Natural Killer (NK) cells, as well as favourably altering the balance of anti-inflammatory to pro-inflammatory cytokines [118]. In fact, modulation of the immune system is one of the most plausible mechanisms to help explain the benefits of probiotics and prebiotics, not only on gut health but also overall health [119].

The gut microbiota plays an important role in the regulation of many aspects of health and disease. This depends on the production of metabolites as a result of bacterial fermentation. Key metabolites include SCFAs, the abundance of which depends on the gut microbiota, which can be changed by diet and other environmental factors. SCFAs regulate many metabolic pathways within the gut and beyond the gut - in the liver, the adipose tissue, the muscles and the brain. These metabolites are also known to contribute to immune function and inflammation as well as influencing energy metabolism, appetite through the production of gut peptides (e.g. GLP-1 and PYY) and glucose and lipid metabolism. These mechanisms help to explain the observed effects on weight loss with probiotic supplementation [80-84], their beneficial effects on glucose and insulin metabolism, anti-inflammatory markers in type 2 diabetes [85-90] and modulation of lipid levels [91-94].

Probiotics are increasingly being studied for potential impact on brain health, including mild cognitive impairment and Alzheimer's disease. Findings to date are somewhat inconsistent but promising [95-102]. The gut microbiota can interact with the brain through various regulatory pathways between the gut and Central Nervous System (CNS) [120]. This is known as the

gut-brain axis, or put more simply, the gut talking to the brain. Shifts in the gut microbiota have been observed in patients with Alzheimer's disease, including decreased microbial diversity compared with healthy age-matched controls, reduced Firmicutes and Bifidobacterium and increase Bacteroidetes, Escherichia and Shigella [121]. Such gut dysbiosis can lead to a so-called "leaky gut" with leakage of microbial toxins (e.g. lipopolysaccharide) and inflammatory cytokines into the circulation and CNS [120]. The gut microbiota produce CNS neurotransmitters such as Gamma-Amino Butyric Acid (GABA), serotonin, catecholamines and acetylcholine, which participate in neural signalling in the brain and CNS. This illustrates the ways in which the gut can communicate with the nervous system and brain.

SCFAs (synthesised from undigested carbohydrate and resistant starch (prebiotics) by the colonic microbes) appear to be reduced in Alzheimer's disease [122]. SCFAs penetrate the blood brain barrier and can protect against inflammation in the brain, interact with brain metabolism, impact on neurotransmitter synthesis and improve the structure of the nerve synapses. They can also reduce brain β-amyloid peptide (Aβ), accumulation of which is a key feature of Alzheimer's disease [122]. Further, SCFAs prevent gut barrier damage, preventing the transport of inflammatory cytokines and interleukins into the circulation and hence to the brain and other tissues and organs [120].

Probiotics are being researched for a potential impact on musculoskeletal health. Whilst higher bone mineral density has been observed in the lumbar spine with probiotic supplementation in one systematic review [108], another systematic review concluded that evidence is so far inconsistent [109]. An altered gut microbiota may be a risk factor for poor bone health as the microflora influence, amongst other mechanisms, the activity of osteoclasts and the absorption of calcium and magnesium [123], so impacting bone formation and resorption. The influence of the gut microbiota on immune function, hormone secretion and the gut-brain axis also play a role in bone homeostasis [124]. Research also suggests that osteoarthritis, which is an inflammatory disease, has its origins in the gut as the overgrowth of pathogenic bacteria releases pro-inflammatory cytokines, which are detected in arthritic joints [125].

The benefit of probiotic supplementation in reducing the risk and duration of upper respiratory tract infections is evident from several meta-analyses [73-79] which show a positive influence on immune system and inflammatory markers. Alteration of the gut microflora has been associated with other diseases affecting the airways, including chronic obstructive airways disease, asthma and chronic bronchitis. The gut microbiota plays a role in lung health and immune function, again through the production of SCFAs, and also the production of immune cells and anti-inflammatory compounds that travel in the circulation to the lungs [126,127] in a so-called 'gut-lung axis'.

COVID-19 is a viral infection mainly affecting the respiratory tract but also affecting the gastrointestinal tract. Given that intestinal dysbiosis has been associated with severity and mortality for other respiratory infections, it seems reasonable to consider that a healthy gut microbiota might be an important protection against the SARS-CoV2 virus and whether probiotic supplementation could contribute to such protection [128]. So far, few clinical trials have been conducted but a randomised controlled trial provided a specific probiotic formula or placebo to 300 adults with symptomatic COVID-19 disease. The probiotic reduced intestinal and non-intestinal symptoms and viral load in the upper respiratory tract. No significant changes were detected in the composition of the faecal microbiota between probiotic and placebo, but probiotic supplementation significantly increased specific IgM and IgG against SARS-CoV2 compared to placebo, leading the authors to conclude that this probiotic primarily acts by interacting with the host's immune system rather than changing colonic microbiota composition [129]. Research looking at the impact of probiotics in the prevention or adjunctive treatment of COVID-19 is in its infancy and more findings need to be established with regards to dose and specific strains, as well as safety, in different patient groups (e.g. immunocompromised patients).

Gut dysbiosis may also be linked to the development of inflammatory eye diseases such as glaucoma, age-related macular degeneration, uveitis [130,131] and dry eye [132]. This is an emerging research area and probiotics are being considered as candidates for the prevention of these eye conditions.

Much more research is needed to establish whether these links between the gut microbiota and other areas of the body such as the brain, lungs and eyes can be translated into beneficial health outcomes with the use of probiotics and prebiotics. However, this review has highlighted the increasing scientific evidence that the gut microbiota contributes to health and disease throughout the body. These effects are mediated by various regulatory pathways associated with immune function, inflammation, and neuroendocrine and hormone activity, with SCFA production from the colonic bacteria playing a key role.

Health effects of prebiotics are evolving but currently suggested benefits from the scientific literature include benefits in the gastrointestinal tract (e.g. inhibition of pathogens, immune stimulation), cardiometabolic effects (e.g. reduction in blood lipid levels, effects upon insulin resistance), mental health (e.g. production of metabolites that influence brain function, energy and cognition) and bone (e.g. mineral bioavailability) [13,31].

In the context of the current evidence, it would seem reasonable to recommend that probiotics and prebiotics are included

as part of the dietary intake. This could include supplements. Whilst it is unclear the extent to which a probiotic will alter the gut microbiota, health benefits have been observed without significant changes in the microbiota as probiotics produce benefits in the gut and other organs through other mechanisms. Many high fibre foods contain prebiotic compounds but fibre intake falls below the recommended intake of 30 g daily in the UK. The UK National Diet and Nutrition Survey shows that mean daily intakes of dietary fibre in 19-64 and 65-74 year old adults are 19.7 g [133]. Although research on the benefits of prebiotics is not so well established as that for probiotics, increasing the intake of prebiotic compounds as part of dietary intake would seem sensible.

Conclusion

Probiotics have a well-established evidence base in the prevention and management of gastrointestinal diseases such as traveller's diarrhoea, antibiotic associated diarrhoea and *Clostridium difficile* diarrhoea. Other bowel conditions where they have a demonstrable clinical impact include ulcerative colitis, specifically in remission rather than maintenance, with less evidence of benefit in Crohn's disease. They have also been shown to tackle some symptoms of irritable bowel syndrome, lactose intolerance and constipation. Systematic reviews have also demonstrated the benefit of probiotics in preventing eczema in children, whether taken by the pregnant and/or breast-feeding mother or the infant. Although the health effects of prebiotics are emerging, they have been shown to be beneficial for the health of the gastrointestinal tract, inhibiting pathogens and stimulating immune function.

Emerging evidence indicates that probiotics positively impact brain health with data from RCTs and systematic reviews indicating benefits in dementia, depression, Parkinson's disease, in cardiometabolic health and obesity, and in respiratory health, reducing the risk of upper respiratory tract infection, asthma, bronchitis and chronic obstructive airways disease. People with gut dysbiosis who have contracted COVID-19 seem to be at higher risk of more severe disease and death, suggesting that probiotics could be considered for the purpose of maintaining a healthy gut microbiota. These effects on organs distant from the gut arise as a result of communication between the gut microbiota and these organs through immune cells, inflammatory mediators, neurotransmitters and hormones. These findings, whilst requiring much more research in terms of health outcomes, represent exciting possibilities for the future of probiotics and prebiotics.

Competing Interests Statement

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