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A Guide to Probiotics and Health[1]

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The World Health Organization (WHO) defines **probiotics** as "live microorganisms which[sic], when administered in adequate amounts, confer a health benefit on the host" (WHO). In the United States, probiotics are considered dietary supplements, not food or drugs, and thus are not specifically regulated by the Food and Drug Administration (FDA). As dietary supplements, some products containing live microorganisms have been marketed as probiotics without having undergone the testing needed to confirm their health benefits. It is recommended that only microbial species that have been shown to confer health benefits in well-designed, controlled studies should be considered probiotics (Hill et al. 2014). Live cultures used in the fermentation of foods (e.g., yogurt) and that have no demonstrated health benefits are not considered probiotics.

Probiotics are beneficial for gastrointestinal wellness, immunity, and a variety of other health outcomes (Sanchez et al. 2016). There are hundreds of probiotic supplements available in the marketplace and choosing a supplement can be challenging. This review provides a summary of the health benefits of probiotics that are backed by a high level of scientific evidence.

Many bacteria and other microorganisms have been tested for their beneficial effects on health. It is important to note that these microorganisms may differ in their health effects, so each potential probiotic needs to be tested to determine if it exerts a specific health benefit. Research carried out in animals alone cannot be used to support recommendations for humans. Human research studies need to be completed on all potential probiotics. Furthermore, a positive health effect from a single human research study is not sufficient to confirm the health benefits of a probiotic. A number of well-designed studies demonstrating similar positive findings provide the strongest evidence that a probiotic is effective.

A high level of scientific evidence is considered to be a **systematic review** with **meta-analysis**. A systematic review is a structured search and review of all probiotic studies to date, examining a specific health benefit. In health research, it is common to pool and statistically analyze the results of studies, a technique known as meta-analysis. Positive findings of a systematic review with meta-analysis strongly suggests efficacy, i.e., the probiotic exerts a specific health benefit. It has been suggested that systematic reviews should be conducted on studies of a single species (McFarland 2016), although most reviews to date have combined different species. Many of the health benefits of probiotics described in this review have this strong level of scientific evidence. However, it is important to note that there are many more strains that may be effective, but have yet to be studied.

Health Benefits of Probiotics

Probiotics differ in their effects on human health. Most probiotics are from the genera *Bifidobacterium* or *Lactobacillus.* Various species of *Bifidobacterium (adolescentis, animalis, bifidum, breve, and longum)* and *Lactobacillus* (*acidophilus, casei, fermentum, gasseri, johnsonii, paracasei, plantarum, rhamnosus*) provide general health benefits (Health Canada

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2009). The dose of the probiotic taken, measured in "colony forming units" or CFUs, is important for effectiveness. A minimum dose of 1 x 10^9 (1 billion) CFUs per serving is thought to be needed to provide general health benefits (Health Canada 2009).

Probiotics exert health benefits by a number of mechanisms. Most probiotics inhibit the growth of pathogens and produce beneficial fermentation products such as short chain fatty acids (Hill et al. 2014, Oelschlaeger 2010). Many probiotic species produce vitamins and useful enzymes and help to maintain gut health. A few probiotic strains have immune, neurological, and/or other body system effects, and some probiotic strains are considered drugs because they have been shown to prevent or treat disease.

Digestive Health

Constipation

One common gastrointestinal condition is constipation. Those suffering from constipation often complain of infrequent, hard stools that are difficult to pass. A lack of dietary fiber, medical conditions, and certain medications are common causes of constipation.

One of the main functions of the colon is the removal of water. This is important for the prevention of diarrhea. However, the longer material remains in the colon, the more water that is removed. If the time spent in the colon is lengthy, the result may be constipation. **Transit time** is the time it takes for the contents of the gastrointestinal tract to move through the body. Most of this time is spent in the colon. When transit time is slow, lasting many days, the result is hard stools that are difficult to pass.

Probiotics are effective in speeding up transit time in adults and are most effective in people with constipation (Miller, Zimmermann, and Ouwehand 2016). The single-strain probiotics that have been tested may be more effective than the multi-strain probiotics. Current evidence suggests that this health benefit is strain-specific. *Bifidobacterium lactis* (*B. lactis*) strains (specifically *B. lactis* HN019 and *B. lactis* DN-173 010) have been shown to be the most effective, but other strains have also been shown to be of benefit (Miller, Zimmermann, and Ouwehand 2016). A stool consistency rating is a useful indicator of transit time (hard stools = slow transit; soft stools = normal transit; liquid stools = fast transit). Stool consistency responds to changes in transit time and may improve with certain probiotics. However, little research has explored the effects of probiotics on stool consistency (Kim et al. 2015).

Diarrhea

Diarrhea is commonly defined as frequent loose or watery stools and is often caused by pathogens. Potential probiotics have been evaluated in many studies to determine if they are effective in preventing various types of diarrhea in adults, including antibiotic-associated diarrhea and chemotherapy-induced diarrhea.

Probiotics have been shown to reduce the risk of antibiotic-associated diarrhea and, specifically, *Clostridium difficile*-associated diarrhea in hospitalized patients (Pattani et al. 2013). However, a recent meta-analysis, which separated patients by age, found that probiotic administration did not reduce the risk of antibiotic-associated diarrhea in adults over 65 years of age (Jafarnejad et al. 2016). Probiotics are safe and effective in preventing *Clostridium difficile* diarrhea, the most common antibiotic-associated diarrhea (Lau and Chamberlain 2016, Goldenberg et al. 2013). Trials using *Lactobacillus spp.*, *Saccharomyces spp.*, and combinations of probiotics show reduced risk for diarrhea (Lau and Chamberlain 2016).

Meta-analyses have also been carried out on specific strains of probiotics and their efficacy in antibiotic-associated diarrhea. *Saccharomyces boulardii, Lactobacillus casei* DN114001, a mixture of *L. acidophilus* and *Bifidobacterium bifidum,* and a mixture of *Lactobacillus acidophilus, Lactobacillus casei,* and *Lactobacillus rhamnosus* are effective in helping to prevent *Clostridium difficile* infections (McFarland 2015). *Lactobacillus rhamnosus* GG is effective in decreasing risk of antibiotic-associated diarrhea in children, but in adults, only in those receiving antibiotics for *H. pylori* eradication (see section below) was *Lactobacillus rhamnosus* GG effective (Szajewska and Kolodziej 2015a). *Saccharomyces boulardii* is effective in decreasing risk of antibiotic-associated diarrhea in adults, but not specifically *Clostridium difficile*-associated diarrhea (Szajewska and Kolodziej 2015b).

A meta-analysis has shown that probiotics tested to date decrease radiotherapy-induced diarrhea but not chemotherapy-induced diarrhea in patients with abdominal and pelvic cancer (Wang et al. 2016). However, more research is needed to determine if the benefit is a general effect or strain specific.

Irritable Bowel Syndrome (IBS)

Irritable Bowel Syndrome (IBS) is a condition of the intestinal tract that results in abdominal pain and/or discomfort with altered bowel habits (diarrhea and/or constipation).

A number of systematic reviews of the effect of probiotics on symptoms of IBS have been carried out (Zhang et al. 2016; Didari et al. 2015; Tiequn, Guanqun, and Shuo 2015). A recent review using the medical diagnostic criteria of IBS (Rome III) showed that probiotics improved overall symptom scores and quality of life in individuals with IBS (Zhang et al. 2016). Probiotic doses of $<10^{10}$ CFU and single strain probiotics may be more effective than multi-strain formulations for symptom relief. Specifically, *Lactobacillus acidophilus-SDC*, *Lactobacillus plantarum* 299v, *Bacillus coagulans,* and *Bifidobacterium bifidum* MIMBb75 improved overall symptom scores in patients with IBS, and *Bifidobacterium bifidum* MIMBb7 improved quality of life. More research is needed as there are mixed findings with respect to whether probiotics improve abdominal pain (Didari et al. 2015, Zhang et al. 2016).

Infection and Peptic Ulcer Disease

Infection with *Helicobacter pylori* (*H. pylori*), a bacterial pathogen, causes gastritis (inflammation of the stomach lining) and, if left untreated, may lead to gastric ulcers and cancer. The current recommended treatment for *H. pylori* is a combination of antibiotics with a proton-pump inhibitor (stomach acid-reducing medication) (Li et al. 2015). However, the treatment may cause nausea, vomiting, and diarrhea.

Various probiotic mixtures have been evaluated for their efficacy in improving the treatment (eradication rates) of *H. pylori* infection and preventing side effects from treatment (Lu, Yu et al. 2016; McFarland et al. 2016; Lv et al. 2015; Zhang et al. 2015; Gong, Li, and Sun 2015). In a meta-analysis examining all trials, probiotics did not, as a whole, improve eradication rates of *H. pylori*, but they did decrease the side effects of diarrhea and nausea resulting from therapy (Lu, Sang et al. 2016). For these results, all different species, strains, and mixtures were combined. However, when single strains were examined, *Saccharomyces boulardii* CNCM I-745 improved eradication rates and prevented adverse symptoms and antibiotic-associated diarrhea (McFarland et al. 2015). *Lactobacillus rhamnosus* GG demonstrated an improvement in antibiotic-associated diarrhea. These are also the strains for which the most controlled studies have been done to date. There are many more strains that have been tested in single studies. Other strains may be effective but more research is needed.

Diverticular Disease

Diverticular disease is a common gastrointestinal disease, especially in older adults. Many older adults have diverticulosis (colonic diverticula, i.e., outpouching of the colon) but are without symptoms. Others develop symptoms such as abdominal pain, discomfort, and changes in bowel habit. A minority of individuals with diverticulosis develop diverticulitis, an acute inflammation of the diverticula.

There have been very few quality studies evaluating the effect of probiotics on diverticular disease (Lahner et al. 2016). Probiotics may potentially be beneficial in the management of symptoms of diverticular disease; however, much more research is needed before recommendations can be made.

Metabolism

Body Weight

Although probiotics are most often associated with gastrointestinal health, they may also have systemic effects, including an influence on body weight. A recent systematic review with meta-analysis concluded that probiotics may reduce body weight and BMI (body mass index) (Zhang, Wu, and Fei 2015). Various combinations of *Lactobacillus* and *Bifidobacterium* species in multi-strain probiotics taken for eight weeks or longer seemed to be most effective. In addition, a greater effect was seen in overweight individuals (BMI>25). Currently, no specific recommendations can be made regarding the best strain combination and dose for body weight reduction.

Type 2 Diabetes

The goal of successful management of type 2 diabetes is to achieve near normal fasting blood glucose and hemoglobin A1c, a blood test used to estimate average blood glucose levels over a three-month period. In three recent reviews of studies evaluating probiotics in participants with type 2 diabetes, fasting blood glucose was lower with probiotic supplementation compared to the placebo (Samah et al. 2016; Zhang, Wu, and Fei 2016; Li et al. 2016). The reviews differed on their findings with respect to probiotics and A1c, with one study showing a lowering and two showing no effect. However, the studies included were only four to eight weeks in length—too short to expect changes in A1c. No recommendations can be made regarding which strain of probiotic is most effective because the studies included in the reviews used combinations of strains of *Lactobacillus* and *Bifidobacterium*. Only two studies tested a single probiotic strain (Li et al. 2016).

Cholesterol

Elevated serum total cholesterol and LDL (low density lipoprotein) cholesterol are risk factors for cardiovascular disease. Administration of probiotics resulted in significant

decreases in total and LDL cholesterol (Cho and Kim 2015). Probiotics had no effect on HDL (high density lipoprotein) cholesterol or triglycerides. *Lactobacillus acidophilus* alone and in combination with *L. lactis* and *L. plantarum* showed independent beneficial effects. As with other cholesterol trials, participants with the highest cholesterol levels showed the greatest benefits.

Infection

Urinary Tract Infections

The effects of a variety of strains, formulations, and doses of probiotics on the prevention of urinary tract infections in healthy individuals have been evaluated (Schwenger, Tejani, and Loewen 2015). No benefit was found, but most studies were small and of poor quality. More research is needed to determine if there is a relationship between probiotic consumption and urinary tract infections.

Respiratory Infections

Upper respiratory tract infections (URTI), such as the common cold, are often due to viruses. For a number of years, meta-analysis evidence has supported the role of oral intake of probiotics and potential probiotics in decreasing the incidence of acute URTI, the duration of URTI, and related antibiotic use (Hao, Dong, and Wu 2015). However, confirmatory research studies of improved quality are needed.

Periodontal Disease

Probiotics may be beneficial in the prevention and treatment of dental caries and periodontal disease. However, a recent systematic review concluded that there was insufficient evidence on probiotics and prevention of dental caries (Gruner, Paris, and Schwendicke 2016). Probiotics, *Bifidobacterium spp.* in particular, have been shown to reduce populations of *Streptococcus mutans*, a bacteria linked to dental caries and also may help manage gingivitis and periodontitis.

Probiotic Purchasing Tips

Although more research is needed to determine the health effects of many potential probiotics, it is wise to select a probiotic that has been well studied and has known health benefits. When choosing a probiotic, ensure that the probiotic is described by genus, species, and strain on the label (See Figure 1 below). When making a purchasing decision, look for the genus and species and the health benefit you are seeking. Match to the strain (named by genus, species, and strain number) if the health effect is strain-specific. The label should clearly indicate the number of viable cells (CFUs), which should exceed, at a minimum, 1 x 10^9 (1 billion). Follow the manufacturer's recommendation for storage as some probiotics require refrigeration while many others can be stored at room temperature.

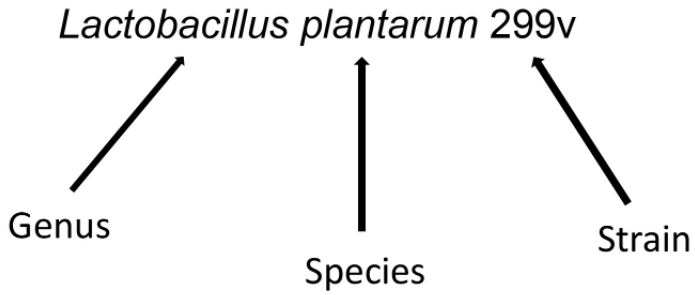

Figure 1. Example of the genus, species, and strain of a probiotic.

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