Emerging Pharmacological Uses of Probiotics

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Abstract

Probiotics are live microbial supplements that benefit the host, and are widely available in many food products. Some probiotics are currently approved for Health Claims in Canada. There has been growing interest in the use of probiotics for pharmacological applications, including antibiotic associated diarrhea, allergic disease, and inflammatory bowel disease. In this review, the evidence supporting clinical use of probiotics for the treatment or prevention of these diseases is reviewed. Although encouraging data exists supporting the potential utility of probiotics for these purposes, larger studies are needed before routine clinical use can be recommended. While probiotics are advantageous because of their excellent safety profile and relatively low cost, there are significant challenges associated with specifying the efficacious microbial species and strains. In the future, probiotics may become a valuable clinical tool for managing many prevalent diseases.

Introduction

Probiotics are defined as live microbial supplements which beneficially affect the host,[1] and may include bacterial and fungal species. Food products containing probiotics have become widely available, and represent a multi-billion dollar industry.[2] Recently, there has been interest in the use of probiotics for pharmacological purposes.

Currently in Canada, the food industry is permitted to make Health Claims with regard to probiotic-based products.[3] Health Claims are defined by Health Canada as "any representation in labeling or advertising that states, suggests, or implies that a relationship exists between consumption of a food or food constituent (including an ingredient in the food) and a person's health".[4] When included in a minimum level of $1x10^9$ colony forming units, several species of Lactobacillus and Bifidobacterium are currently approved for such claims. [3]Advertisements may state, for example, that a probiotic contributes to healthy gut flora.

These differ from Therapeutic Claims, which state that a product treats or prevents a disease.[4] There are currently several areas where probiotics-based therapeutic strategies are being investigated. The use of probiotics for antibiotic-associated diarrhea (AAD) including *Clostrium difficile* infection (CDI), allergic disease including eczema and asthma, and inflammatory bowel disease (IBD) will be discussed here. Probiotics have also been investigated for preventing necrotizing enterocolitis,[5] and two probiotic strains have been approved by Health Canada as medical therapy for irritable bowel syndrome.[6]

Adequate treatments and preventions for AAD and CDI, allergic disease, and IBD are currently lacking or inadequate for many patients, making probiotic-based strategies an exciting concept. The intention of this review is to introduce emerging probiotic therapies and review the strength of the currently-available evidence in support of their use for these conditions.

Probiotics For Antibiotic Associated Diarrhea

AAD is defined as diarrhea occurring following the use of antibiotics with no other cause, and is often mild and self-resolving.[7] However, about 20% of AAD cases are due to *Clostridium difficile* infection, which can have severe consequences including profound electrolyte imbalance, pseudomembranous colitis, and septic shock. [8]

The incidence and mortality of CDI are increasing in Canada,[9-10] which may be attributable to a global rise in antibiotic use.[11] While CDI is a rare cause of community-acquired diarrhea, risk of *C. difficile* colonization increases proportionally with length of hospital stay.[12] The mechanism of nosocomial CDI is believed to involve (i) contact with *C. difficile* during hospital stay, and (ii) antibiotic-associated destruction of the normal gut microbiota, eliminating normal inhibition of *C. difficile*. Non-virulent bacteria in the gut are thought to prevent proliferation of virulent *C. difficile* by competing for essential nutrients and mucosal adherence sites.[13] For this reason, it is hoped that probiotics will help mitigate CDI by introducing normal gut microbes to restore microbial balance.

Current treatment strategies for CDI include correction of fluid and electrolyte abnormalities, and administration of antibiotics with known activity against *C. difficile*.[8] Such agents include vancomycin, metronidazole, and bacitracin.[14] The inciting antibiotic should be discontinued; unfortunately, this may not be feasible in situations where a serious initial infection persists and requires continued treatment.

For this reason, the prophylactic use of probiotics has been proposed where prospective risk of AAD is considerable. Multiple randomized, double-blind controlled trials (RCTs) have found *Saccharomyces boulardii*, a yeast probiotic, effective in preventing AAD.[15-17] Other trials found no preventative effect.[18-19] None reported significant safety concerns associated with probiotic administration. These trials are generally lacking in sample size and/or diverse patient

population, and larger studies will be required to adequately assess the efficacy of *S. boulardii* to prevent AAD.

Lactobacillus species (*Lactobacillus acidophilus, L. bulgaricus, L. casei, L. rhamnosus, L. reuteri*) have also been studied for the prevention of AAD. RCTs have supported their efficacy in adults[20-22] and children,[23] while another showed no effect.[24] A recent large meta-analysis that included RCTs using yeast-based, *Lactobacillus*, and other probiotics, found that probiotic use reduced the risk of AAD.[25]

Probiotics have been investigated specifically for the primary prevention of CDI. A recent meta-analysis of 20 trials involving a variety of probiotics found a protective effect against developing CDI.[26] Probiotic administration has also been proposed for the treatment of recurrent CDI. Currently, *S. boulardii* has the best evidence for this use, with some RCTs showing significant benefit over the use of antibiotics alone.[27-28]

The most recent guidelines from the Infectious Disease Society of America do not recommend probiotic administration for the prevention of primary CDI or treatment of recurrent CDI; the guidelines state "there are limited data to support this approach" and "that larger trials are required before this practice can be recommended".[29] Meta-analyses of the currently-available studies may be criticized for combining trials utilizing varied microbial contents and doses. Therefore, larger studies with standardized probiotic preparations will be necessary for evaluating the efficacy of probiotics for these purposes. As the number of Canadian deaths due to CDI rises, new approaches to treatment and prevention – such as the use of probiotics – are becoming increasingly important.

Probiotics for Allergic Diseases

Allergy is defined as "a hypersensitivity reaction initiated by specific immunological mechanisms".[30] Allergy can be antibody- or cell-mediated, and the most common antibody is the Immunoglobulin E (IgE) isotype.[31] The prevalence of many allergic diseases, such as eczema and asthma, are reportedly increasing worldwide.[32] The Hygiene Hypothesis posits[33-34] that this trend is due to reduced exposure to microbes, particularly early in life.

Normal gut flora, such as some Lactobacillus species, promote T-helper cell (Th)-1 over Th-2 cell responses.[35] Allergy is associated with exaggerated Th-2 response;[36] this includes production of Th2 cytokines such as interleukin (IL)-4, IL-5, IL-10 and IL-13.[37] These cytokines signal a switch to IgE production, leading to mast cell activation.[38] By promoting healthy gut flora through probiotic administration, it may be possible to promote normal Th-1/Th-2 balance and reduce the risk of IgE-mediated allergic disease.

Numerous RCTs have assessed the effect of prenatal and postnatal administration of Lactobacillus-based probiotics on the risk of developing eczema in early life. Some trials have found significant risk reductions associated with this strategy.[39-42] Other probiotic mixtures including Bifidobacterium species have also been effective when administered during prenatal and postnatal periods.[43-44] However, in another study, prenatal administration alone was insufficient to prevent eczema.[45]

Probiotics have also been proposed for the prevention of asthma. Unfortunately, there is currently limited evidence in support of this approach. A large RCT[46] studied a probiotic mixture given to expectant mothers whose children were considered at high risk of developing allergic disease. No significant difference in the development of allergic asthma or food allergy was found. Another study[47] found that in women with allergic symptoms, a Lactobacillus probiotic given while pregnant and breastfeeding failed to reduce risk of allergic asthma in their children. Interestingly, allergic symptoms improved in the mothers.

In addition to disease risk, many studies have measured serum IgE levels in children following prenatal and postnatal probiotic administration. A recent meta-analysis[48] of 9 RCTs involving 1103 children found that probiotics significantly lowered serum IgE. This study combined trials using various single-species and mixed-species probiotics, and found that probiotics reduced the risk of atopic sensitization overall.

With prevalence rates of many allergic diseases increasing, new methods for the primary prevention of these conditions represent an exciting prospect. While some promising evidence has emerged supporting the use of probiotics for these purposes, results have been inconsistent and further investigations will be necessary before generalized clinical use can be recommended. The 2012 position paper from the World Allergy Organization on the use of probiotics stressed a need for further basic microbiological research on gut microbiota.[49] Additionally, similar to investigations on probiotic use for AAD, future clinical trials to prevent allergic disease should focus on specific species and dosing to facilitate meta-analytical comparisons.

Probiotics for Inflammatory Bowel Disease

IBD primarily refers to two idiopathic diseases: ulcerative colitis (UC) and Crohn's disease (CD). The population prevalence of UC and CD are high, with prevalence rates of 169.7 and 198.5 per 100,000, respectively, reported from population-based data in Manitoba.[50] Prevalence rates in the United States are comparable, suggesting approximately 1 million Americans are affected by IBD.[51]

UC involves chronic inflammation of the colon, typically initiating distally (proctitis) and extending proximally in a continuous manner. Common symptoms include diarrhea, abdominal pain and rectal bleeding. Toxic megacolon and gastrointestinal hemorrhage occur less frequently, but require urgent surgical intervention when they occur.[52] Critically, risk for colorectal cancer increases dramatically for every decade with UC.[53]

CD may involve inflammation at any point of the gastrointestinal tract, and may be either continuous or discontinuous (with intervening normal tissue). Symptoms include diarrhea and abdominal pain, with the specific location dependant on the site of inflammation. Major complications can include the formation of fistulas between adjacent bowel segments, malabsorption of nutrients, and increased risk of cancer of the small or large intestine.[52]

Current treatment strategies for IBD focus on achieving and maintaining remission of symptoms. 5-aminosalicylic

acid (5-ASA) compounds are first line therapy, and corticosteroids can be used if necessary.[54] Unfortunately, these agents may be poorly tolerated due to side effects, and IBD is refractory to these treatments in many individuals. For these reasons, the use of probiotics has been proposed.

Several studies have investigated the use of the probiotic preparation VSL #3 for the treatment of UC. VSL #3 consists of 3 species of *Bifidobacterium* (*B. breve, B. longum, B. infantis*), 4 species of *Lactobacillus* (*L. acidophilus, L. plantarum, L. paracasei, L. bulgarcus*), and *Streptococcus thermophilus*.[55] Multicentre trials of over 140 participants have found VSL #3 to be effective in improving Ulcerative Colitis Disease Activity Index (UCDAI) scores in patients with active, mild-to-moderate UC.[56-57] Smaller studies have also found VSL #3 effective for inducing remission of mild-to-moderate UC in children.[58-59] The probiotic Escherichia coli strain Nissle 1917 has also been investigated, and has demonstrated equivalent efficacy to the current first-line 5-ASA treatment in maintaining remission of UC symptoms.[60-61]

The evidence in support of probiotic use for CD is less convincing. Several studies of Lactobacillus-based probiotics have failed to show efficacy in CD patients.[62-64] Probiotic preparations of *S. boulardii* were found to improve CD symptoms in small studies,[65-66] but a recent trial of much higher sample size found no significant benefit.[67] Two meta-analyses failed to find benefit of probiotic use in preventing recurrence in CD.[68-69]

Probiotics are typically very well tolerated, making them an attractive alternative to the agents currently used for the management of IBD. Further, because of the potential for serious complications that may result from poorly controlled IBD, finding new treatment strategies is critically important for patients who do not respond to existing therapies. Although larger studies will be required before routine clinical use can be recommended, much of the available data supports the efficacy of probiotics for managing UC symptoms. The quality of evidence is supported by the consistent use of the VSL #3 preparation, facilitating comparison between trials. Future studies should aim to include more participants and to demonstrate dose-responsive effects. In the future, probiotics could conceivably become an alternative strategy for the clinical management of UC.

Conclusion

Interest in probiotics has extended beyond dietary supplementary uses into an emerging strategy for the clinical management of disease. There are likely several reasons why this has occurred. In general, probiotics are associated with very few adverse effects. Across the numerous trials for the different uses of probiotics discussed above, the excellent safety profile of probiotic preparations was a consistent trend. Additionally, in comparison to other emerging pharmacological strategies such as therapeutic monoclonal antibodies, probiotics are a relatively cost-efficient strategy. Finally, interest in the therapeutic applications of probiotics has likely been fueled by our ever-expanding appreciation for the role of the gut microbiome in health and disease. The future success of probiotic therapies will depend on our continued elucidation of the complex interactions between gut microbiota and host cells.

There are also some important challenges to developing probiotic-based therapies. Notably, it may be difficult to precisely define the relevant active ingredient(s). These could include products produced by microbes, or the live microbes themselves. In the latter case, it would be necessary to define which strains of which species possess therapeutic efficacy, and at what dose. A combination of basic and translational research along with well-controlled clinical investigations will be necessary to adequately address these issues. Additionally, while probiotics are generally well-tolerated, there is nonetheless the potential for infection to occur,[29] particularly in immunocompromised patients.

In summary, AAD, allergic diseases, and IBD are emerging potential pharmacological uses for probiotics. All of these applications represent situations where current treatment strategies are either lacking or insufficient for some patients. Despite encouraging evidence in these areas, there is still a need for large, well-controlled trials, and for standardization of the microbial contents and dosing of probiotic preparations. In the future, probiotics have the potential to become a valuable tool for the management and prevention of several prevalent diseases.

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