Review Article

Probiotics and Prebiotics: Why Are They "Bugging" Us in the Pharmacy?

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OBJECTIVES Specific organisms can be added to foods to target an effect (probiotics) or non-digestible carbohydrates can be used to foster the development of a favorable flora in the intestinal tract (prebiotics). The significance of pro- and prebiotics have been studied extensively, providing many current and theoretical treatment options. The objective of this paper is to provide a brief overview of commercial products available for the practicing clinician.
METHODS The literature was evaluated for the most commonly used and studied pre- and probiotics available. In addition, information regarding each of the products was obtained from the manufacturer.
RESULTS We found that all products are not formulated the same and the content of live organisms can differ. Currently available products are relatively safe but caution should be used for any patients that may have allergies to inactive ingredients in the product or are immunocompromised.
CONCLUSIONS Many probiotics and prebiotics are commercially available to aid in promoting healthy bowel flora to resist disease. This reference can be a helpful tool for the pharmacist when answering questions or making recommendations to a patient.

KEYWORDS diet, organisms, prebiotics, probiotics, supplements

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INTRODUCTION

In the beginning of the 20th century, the concept of certain bacteria being beneficial to humans was recognized by Elie Metchnikoff.[1] Prior to that time, cultured dairy products had been used therapeutically.[2] Specific organisms can be added to foods to target an effect (probiotics) or non-digestible carbohydrates can be used to foster the development of a favorable flora in the intestinal tract (prebiotics). The significance of pro- and prebiotics have been studied extensively, providing many current and theoretical treatment options.[3,4] The goal of this paper is to provide a brief overview of commercial products available for the practicing clinician. A more thorough review of proposed physiology and mechanisms can be reviewed elsewhere.[5]

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ABBREVIATIONS FDA, Food and Drug Administration; FOS, fructooligosaccharides; GOS, galactooligosaccharides; GRAS, generally regarded as safe; NCDO, National Collection of Dairy Organisms; NEC, necrotizing enterocolitis; TNFα, tumor necrosis factor alpha; VLBW, very low birth weight

PROBIOTICS

Probiotics are dietary supplements that consist of living organisms found in normal flora that have little, if any, pathogenicity.[6] Common organisms used to produce these results include *Lactobacillus* species, *Bifidobacterium* species, and *Saccharomyces boulardii*. Lactobacilli are non-spore forming, Gram-positive rods frequently found in the mouth, gastrointestinal tract, and female genitourinary tract.[7] Lactic acid is the major end product of lactobacilli during glucose fermenta-

tion, and the most common species include *L acidophilus, L bulgaricus, L casei, L helveticus, L plantarum, L reuteri, L rhamnosus and L salivarius.* Lactobacilli are thought to prevent the growth of more pathogenic bacteria by their lactic acid production.[7] They are predominantly considered protective except in dental caries and in some immunocompromised individuals.[7] *Bifidobacterium* species are Gram-positive, non-motile, non-sporulating, non-gas producing, anaerobic, catalase-negative organisms (except *B asteroides and B indicum).*[8] The proposed mechanism of action for bifidobacteria are their antimicrobial components that may inhibit pathogenic bacteria, including organic acids, hydrogen peroxide, carbon dioxide, diacetyl, bacteriocins, and low molecular weight substances such as reuterin.[9] Some of the more common *Bifidobacterium* species *(B bifidum, B breve, B infantis, B lactis, and B longum)* predominate in human milk and are associated with a favorable microflora for the infant.[10] Of interest, *Bifidobacterium adolescentis* has been found to be colonized in infants of allergic, atopic mothers.[10] Other types of probiotics include *Lactococcus lactis,* the yogurt starter, *Streptococcus thermophilus*, and the *Saccharomyces boulardii* yeast.[2]

The proposed mechanism of action for probiotics is multifaceted. The effects seen by lactobacilli and bifidobacteria include increased production of antimicrobial agents, increased production of anti-inflammatory cytokines, improved mucosal IgA response, increased production of gastric mucus, changes in intestinal permeability, and a reduction of inflammatory mediators like TNFα.[1-5] Most recently, *Lactobacillus GG* upregulated genes associated with cytoprotective responses in anti-apoptotic pathways.[11]

Specific probiotic strains have been studied and reported in the peer-reviewed literature. For example, there are numerous animal, *in vitro*, and human studies evaluating the use of probiotics' positive results[3] related to immunity,[12] necrotizing enterocolitis (NEC)[13-15] and diarrhea.[16-18]

Lactobacillus rhamnosus (*Lactobacillus GG*, Culturelle, ConAgra Foods) has been shown to reduce the duration of the diarrheal phase of rotaviral infections by 1-3 days in infants and young children.[16] In children with diarrhea for less than 60 hours before initiation of probiotic treatment (considered early intervention), the administration of *Lactobacillus* strains can reduce the length of hospital stays by 48%.[17] A meta-analysis of the use of *Lactobacillus* therapy in children with acute diarrheal infections revealed that, in general, *Lactobacillus* species appear to reduce diarrhea duration by 0.7 days and reduce diarrhea stools by 1.6 on day 2 of treatment.[18]

A well-designed clinical study investigating the use of probiotics to prevent NEC involved 367 very low birth weight (VLBW) infants who survived beyond the seventh day after birth and had begun enteral feeds.[13] They were randomized into two groups: the treatment group received *Lactobacillus acidophilus* and *Bifidobacterium infantis* with breast milk twice daily until discharged, whereas the control group infants received breast milk only. Primary outcome measures were death or NEC greater than Bell Stage 2. Death or NEC occurred in 5% (9/180) in the treatment (probiotic) group, and in 13% (24/187) of the infants in the control group ($P = 0.009$).[13]

A second study by the same authors using a different strain of *Bifidobacterium* had similar positive effects[14] on the primary outcome (incidence of NEC stage 2 or death). Random assignment of Infloran (*L acidophilus* [10^9 colony-forming units, NCDO 1748; National Collection of Dairy Organisms] and *B bifidum* [10^9 colony-forming units, NCDO 1453; National Collection of Dairy Organisms, Reading, United Kingdom]; Laboratorio Farmaceutico, Italy) at a dose of 125 mg/kg/dose twice daily was added to breast milk or formula fed to VLBW infants.[14] There were 217 infants in the treatment group and 217 in the control (no probiotics) group. Death or NEC occurred in 4 infants in the treatment group compared to 20 infants in the control group ($P = 0.02$).[14]

Finally, preliminary data on the autism spectrum, based on studies demonstrating altered molecular characterization profiles of stool samples[19] reveal that children with autism may have higher numbers of pathogenic bacteria in their gut, including an unusual strain of *Clostridium.*[20]

PREBIOTICS

Prebiotic oligosaccharides are available through dietary sources (e.g., soybeans, oats, barley), natural sources (breast milk), and as a commercially available 70/30 Prebio (Nestle Nutrition, Vevey, Switzerland). They function to boost the activity of host protective organisms, specifically bifidobacteria and lactobacilli.

Table 1. The Current and Theoretical Uses for Enhancing the Bowel Flora Include.[1-23]

- Antibiotic associated diarrhea
- Traveler's diarrhea
- Digestive system regulation
- Infectious diarrhea/rotaviral diarrhea
- Diarrhea during Helicobacter pylori eradication treatment
- Radiation-induced diarrhea
- Diarrhea associated with tube-feedings
- HIV-associated diarrhea
- Prevention of necrotizing enterocolitis in infants with very low birth weight (< 1500g)
- Strengthening of the immune system
- Decreased respiratory tract infections in children
- Ulcerative colitis
- Irritable bowel syndrome
- Vaginal yeast infections
- Atopic diseases (atopic dermatitis, allergic rhinitis, asthma)
- Pouchitis
- Autism Spectrum Disorders (ASD)

The most common oligosaccharides are galactooligosaccharides and inulin with 5-60 fructose monomers.[21,22] Human milk contains 7-12 g/dL of oligosaccharides which is 10 to 100 times the content of other mammalian milk.[21] These sugars are very complex and consist of galactose and N-acetylglucosamine in a β-glycosidic linkage to lactose[21] which are protected from digestion in the human intestinal tract. From this core structure, additional alpha-glycosidic linkages of fructose and/or sialic acid are attached. The attachment depends on the mother's blood group status thereby making them difficult to mimic. Their benefit is to selectively stimulate the growth of bifidobacteria and lactobacilli in the intestine[16-20] and influence adhesion of pathogenic bacteria and selectins in immune function.[21,22] Bifidobacteria and lactobacilli secrete β-fructosidases which hydrolyze the β-2 linkages of prebiotics, rendering the sugars available for bacterial fermentation.[22] Commercially, galactooligosaccharides (GOS) and fructooligosaccharides (FOS) are used with success in promoting lactobacilli colonization in the human intestine in both formula and weaning food supplemented studies.[23-25]

Prebiotics have been added to adult enteral formulas for years to promote healthy microflora and prevent diarrhea, and are also available in selected pediatric oral meal replacement nutritionals. Prebiotics have been added to infant formulas, as well, in attempts to promote a healthy immune system. The current and theoretical uses of prebiotics in enhancing the bowel flora are described in Table 1.

PRODUCTS

Although the proposed uses and mechanism of action of probiotics are well documented,[5,26,27] there is not a comprehensive reference of the products available. Probiotic products are not all formulated the same and the content of live organisms can be different. Detailed information of products available is beneficial to health care personnel answering questions about probiotic and prebiotic products. Table 2 is a brief comparison of the probiotic products currently available (readers are encouraged to investigate for additional products not listed).[28-36]

SAFETY

Careful consideration should be given to the fact that these products are foods, dietary supplements, or medical foods that are not all regulated as drugs by the Food and Drug Administration (FDA). Of note, *Bifidobacterium lactis* is currently registered as GRAS (generally regarded as safe) by the FDA for use in infant formulas (Nestle Good Start; Nestle, Vevey, Switzerland). As they are not classified as drugs, these products cannot claim to have an effect on the cure, treatment, prevention, mitigation or diagnosis of a disease. Although benefits of pro- and prebiotics have consistently been shown, recommendations to patients should be made with the notion that these products are not regulated as prescription drugs. In addition, dosing of these products is organism-specific and careful consideration should be given when recommending a product to a patient.

Products currently available are relatively safe but caution should be used for any patients that may have allergies to inactive ingredients[37] in the product or patients that are immunocompromised.[6] Table 3 contains the inactive ingredients in each formulation. This information can be used to screen a patient prior to recommending a product.

Label claims and product purity are also

Table 2. Comparison of Selected Probiotic Products[30-38]

Product (Manufacturer)	Active Organism(s)	Colony Count	Package Directions
Activia yogurt (Dannon/ Danone)	*Bifidobacterium animalis* DN 173-010 (*Bifidus regularis*™), *Lactobacillus bulgaricus, Streptococcus thermophilus*	Manufactured to contain > 100 million active cultures per gm; guaranteed 10 million active cultures per gm at end of shelf life	One to three 4-oz servings daily for at least 10-14 days
Align (Proctor & Gamble)	*Bifidobacterium infantis* 35624 (Bifantis)	Manufactured to contain 1 billion live cells per 4 mg capsule	One capsule daily
Culturelle (Amerifit Brands)	*Lactobacillus GG (L rhamnosus)*	Manufactured to contain > 30 billion live cells; guaranteed 10 billion live cells when consumed	One capsule daily
DanActive (Dannon)	*Lactobacillus casei* strain DN-114-001 (L Casei Immunitas)	Manufactured to contain 10 billion cells per bottle	At least one bottle per day (100 mL)
FLORA PROBIOTIC PLUS (Golden Health Products)	15 different species of *Lactobacillus, Bifidobacterium, Lactococcus,* and *Streptococcus*	Manufactured to contain 22 billion viable cells per capsule	Capsules: Two capsules 30 minutes before breakfast with water, juice or milk for two weeks, then one capsule daily Powder: ¼ tsp mixed with liquid 30 min prior to breakfast
Flora Q 2 (Kenwood Therapeutics)	*Lactobacillus acidophilus, Bifidobacterium, Lactobacillus paracasei,* and *Streptococcus thermophilus*	375 mg	One capsule daily
Florastor Kids (Biocodex)	*Saccharomyces boulardii*	Manufactured to contain 5 billion live freeze-dried cells per 250 mg packet	Take packet contents and mix in drink or semi-solid food
Florastor (Biocodex)	*Saccharomyces boulardii*	Manufactured to contain 5 billion live freeze-dried cells per 250 mg capsule	One capsule daily; capsule contents can be mixed in drink or semi-solid food
Lactinex (Becton, Dickenson and Company)	*Lactobacillus acidophilus, L bulgaricus*	1 million cells per tablet or 100 million per packet	Four tablets 3-4 times daily
Primadophilus for Kids (Nature's Way)	*Lactobacullus rhamnosus, Bifidobacterium longum, L acidophilus*	Manufactured to contain 3 billion per tablet	For children 2-12 years; 1 tablet daily between meals (3/day)
VSL#3 (VSL Pharmaceuticals, Inc.)	*Lactobacillus acidophilus, L plantarum, L casei, L bulgaricus, Bifidobacterium breve, B infantis, B longum, Streptococcus thermophilus*	Packets: 450 billion bacteria per packet Capsules: 250 billion bacteria per 2 capsules	Bloating associated with diarrhea-predominant irritable bowel syndrome: one packet twice daily Pouchitis and ulcerative colitis: one to four packets daily, depending on number of bowel movements

Table 3. Inactive Ingredients of Available Probiotic Formulations

Product	Inactive Ingredients
Activia	cultured grade A reduced fat milk, blueberry puree, fructose syrup, sugar, modified corn starch, contains less than 1% of fructose, whey protein concentrate, kosher gelatin, natural flavor, carmine (for color), sodium citrate, malic acid *varies slightly by flavor
Align	microcystalline cellulose, hydroxypropylmethylcellulose capsule USP grade, magnesium stearate, sugar, sodium caseinate, sodium citrate dihydrate, propyl gallate, FD&C blue #2
Culturelle	microcrystalline cellulose, gelatin, contains milk protein
DanActive	cultured reduced fat milk, water, sugar, strawberry puree, contains less than 1% of dextrose, modified corn starch, natural flavor, carrot juice concentrate (for color), malic acid, sodium citrate *varies slightly by flavor
FLORA SOURCE	rice starch
Flora Q 2	Maltodextrin, microcrystalline cellulose, hyromellose, sodium alginate, silicon dioxide, magnesium stearate, titanium dioxide, and FDandC Blue 2
Florastor Kids	fructose (472 mg), lactose (33 mg), colloidal anhydrous silica, tutti-frutti flavor
Florastor	lactose (33 mg), magnesium stearate, hydroxy-propyl-methyl-cellulose, titanium dioxide (E171)
Lactinex	lactose, glucose, sucrose, milk, whey powder, soy peptone, talc (tablet), mineral oil (tablet) and sodium
Primadophilus for Kids	sorbitol, xylitol, cellulose, rice starch , citric acid, magnesium stearate, tumeric, natural oranges flavor, vanilla flavor, ascorbic acid
VSL #3	Flavored packets: maltose, natural flavorings, and silicon dioxide Unflavored packets: corn starch Capsules: microcrystalline cellulose, stearic acid, silicon dioxide
Yogurt	varies

crucial considerations when evaluating dietary supplements.[38] An independent, third party quality assurance lab such as Consumer Labs (www.consumerlabs.com) can provide invaluable information. The nonsubscriber can obtain preliminary information regarding supplements, and the subscriber (approximately US $30.00 per year) has unlimited access to all products tested in multiple categories. A posting of a "Product Review: Probiotic Supplements (Including *Lactobacillus acidophilus*, *Bifidobacterium* and Others)" appeared online on December 12, 2006, and has been updated regularly on May 27, 2007, October 9, 2007 and May 29, 2008. This is one of the best probiotic product comparisons to date, and can be accessed with subscription. Categorical information provided includes: 1) manufacturer/distributor; 2) types of organisms claimed per unit (and amounts if specified); 3) organisms in maximum suggested daily serving; 4) contained listed amount of probiotic organisms; 5) whether daily serving provides at least 1 billion bacteria ("Yes" or" No"); and, 6) if product is free of (other) microbial contamination ("Yes" or "No").

COST

A cost comparison of probiotic agents available is displayed in Table 4. It is important to note that the costs may vary by the location and store of purchase, condition being treated, and the duration of use.

PATIENT COUNSELING

Health care professionals play a vital role in providing patients with a product that is both efficacious and safe. Patients should contact their physicians prior to use if they are pregnant, breastfeeding, and/or have a weakened immune system. Since products are not equivalent, reading the package label is important to ensure patients will receive the appropriate dose of live microbes. It is advisable for health care profes-

Table 4. Cost Comparisons of Selected Products

Product	Quantity	Consumer Price*	Package Directions for Use	Estimated Daily Price
Activia	4pk-4 oz (113 g)	2.44	1 yogurt daily (minimum)	$0.61
Align	28	29.99	1 capsule daily	$1.07
Culturelle	30	14.99	1 capsule daily	$0.50
Culturelle kids	10	5.99	1 capsule daily	$0.60
DanActive	4pk-3.3 fl oz	2.58	1 bottle daily	$0.64
FLORA SOURCE	240	104 (6 mo supply)	2 daily for two weeks, 1 daily thereafter	$0.58
FLORA SOURCE	120	52 (3 mo supply)	3 daily for two weeks, 1 daily thereafter	$0.58
FLORA SOURCE	1.25 oz	29.95 (6 wk supply)	1/4 tsp of powder daily	$0.68
Florastor	10	8.93	1 capsule twice a day	$1.79
Florastor	50	32.85	1 capsule twice a day	$1.31
Florastor kids	10	9.90	1 capsule twice a day	$1.98
Lactinex	50	9.86	4 tablets 3-4 times daily	$2.37
Lactinex	12	11.44	1 packet 3-4 times daily	$2.86
Primadophilus Kids	30	6.99	1 tablet daily, between meals	$0.70
VSL #3	10	29.68	½-8 packets per day (depends on use)	$1.48 - $23.74
VSL #3	30	79.50	½-8 packets per day (depends on use)	$1.33 - $21.20
VSL #3	60	45.00	4 capsules daily	$3.00

**Prices estimated in USD from currently available on-line sources and in stores December 2007*

sionals to subscribe to independent third-party quality assurance programs (such as www.consumerlabs.com, the United States Pharmacopoeia Dietary Supplement Verification Program [www.usp.org], or the National Safety Foundation's Dietary Supplement Certification Program [www.nsf.org/dietary]) to assist patients in making judicious decisions.

CONCLUSION

Many probiotics and increasingly prebiotics are commercially available to aid in promoting healthy bowel flora to resist disease. Different label ingredients can make product selection confusing for the patient. Further research should be performed comparing efficacy and safety of these products as they are not all regulated by the FDA. This reference can be a helpful tool for the pharmacist to be used when answering questions or making recommendations to a patient.

DISCLOSURE The authors do not endorse or have any affiliations or commercial interest with these products or quality assurance programs.

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