

RESEARCH ARTICLE



Health Benefits and Complications Involved in Probiotics

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12th May 2014**Abstract:**

The objective of review is to outline the probiotics use in medicine and to give insight in to the benefits and complications. The use of probiotics in treatment regimen is increasing. Probiotics are live organisms and prebiotics are components of food that are not easily digested by humans and these food components essentially feed beneficial bacteria in the gut. Probiotics can be formulated to many different types of products including drugs, foods, and dietary supplements. Species of lactobacillus and bifidobacterium are most commonly used as probiotics. Probiotics are intended to assist the body's naturally occurring gut mitochondria. Some probiotic preparations have been used to prevent diarrhea caused by antibiotics or as part of treatment for antibiotic related dysbiosis. The focus of this article is on the probiotics use, clinical trials, drug interactions, duration of use, natural probiotic sources and its future.

Keywords: Probiotics use, Prebiotics use, Dietary supplements.

Introduction

A century ago, Elie Metchnikoff postulated that lactic acid bacteria (LAB) offered health benefits capable of promoting longevity¹. He suggested that intestinal auto intoxication and resultant aging could be suppressed by modifying the gut microbiota and replacing proteolytic microbes such as clostridium which produces toxic substances including phenols, indoles, and ammonia from digestion of proteins with useful microbes. In 1917 the German professor Alfred Nissle isolated a non pathogenic strain of Escherichia coli from feces of First World War soldier who did not develop enterocolitis during severe outbreak of shigellosis².

Bifidobacterium was isolated by Henry Tissier from a breast fed infant, and he named the bacterium Bacillus Bifidus communis. He claimed that Bifidobacteria would displace the proteolytic bacteria that cause diarrhea and recommended administration of bifidobacteria to infants suffering from this symptom³. The term probiotics was introduced in 1965 by Lilly and Stillwell⁴. In 1989, Roy Fuller emphasized the requirement of viability for probiotics and introduced the idea that they have beneficial effect on host⁵.

Natural probiotic sources:

Yogurt: It is a plain, low fat Greek yogurt (since it's protein-rich with no added sugar), but any yogurt with a pure, simple ingredient list that includes 'live, active' cultures will do.

Buttermilk: Buttermilk is a good source of probiotics, thanks to the live cultures added to ferment the milk sugars. Cooking with it, however, will destroy the live cultures.

Kefir: It's sort of like a drinkable yogurt, but kefir has different types of probiotics than yogurt. It's made by fermenting milk with a culture of yeasts and bacteria that are referred to as kefir 'grains.'

Cultured cottage cheese: Nancy's (Nancysyogurt.com) is the only brand of cultured cottage .It's different from regular cottage cheese in that it provides live cultures, including *L. acidophilus* and *B. bifidum*, as well as four strains of lactic cultures.

Miso: It's made by fermenting cooked soybeans with rice or barley, salt, and koji (a starter culture) to form a red, white, or dark colored paste. Miso can be used in place of salt in your favorite recipes, as well as in salad dressings, soups, marinades, dips and pesto. For maximum benefit from the live cultures, buy unpasteurized miso paste (located in the refrigerated section of grocery stores) and add to cooked dishes just before removing from heat. *Lactobacillus acidophilus* present in most miso varieties

Kombucha: It's made by fermenting yeasts and bacteria with sweetened tea, resulting in a slightly carbonated, probiotic-rich beverage.

Sauerkraut: The fermentation process means that homemade sauerkraut is a good source of live, active cultures. Essentially fermented cabbage, sauerkraut contains *Lactobacilli plantarum* that can do wonders for your immune system. It also has the ability to reduce the growth of detrimental yeasts and is one of the best nondairy sources of probiotics.

Kimchi: A popular Korean dish, kimchi is fermented and pickled cabbage, mixed with other ingredients, such as red pepper flakes, radish, ginger and onion. The freshly made kimchi found at Asian markets and restaurants is rich in probiotics⁶.

Apple: A recent study looked at rats eating a diet high in pectin, a component of the dietary fiber in apples. When compared to rats on a normal diet, the rats with the apple-rich diet had increased amounts of beneficial

bacteria. Although researchers aren't sure if apples will have the same effect in humans, investigators did conclude that by eating apples regularly, the friendly bacteria help produce short chain fatty acids that provide ideal pH conditions for ensuring a beneficial balance of microorganisms.

Soy milk: Soy naturally contains some probiotic benefits, but new soy milk products on the market have added extra live cultures⁸.

Dark chocolate: Dark chocolate contains probiotics and antioxidants to keep your stomach healthy and your sweet tooth satisfied⁶.

Olives: Olives in brine have large amounts of probiotics because the brine allows the probiotic cultures to thrive.

Pickles: The common green pickle is an excellent food source of probiotics.

Tempeh: A great substitute for meat, tempeh is a fermented, probiotic-rich grain made from soy beans⁹.

Dose:

The doses needed for probiotics varies greatly depending on strain and product. Although many OTC products deliver in range of 1-10 billion cfu/dose, some products show efficacy at low levels, while some require high levels. Dose needed for probiotics, should be based on human studies showing health benefits.

The minimum criteria that have to be met for probiotic products must be:

- ✓ Specified by genus and strain.
- ✓ Alive.
- ✓ Deliver adequate dose through end of shelf life.

✓

Immunologic Benefits:

- a. Activate local macrophages to increase antigen presentation to beta lymphocytes and increase secretory immunoglobulin A (IgA) production both locally and systemically.
- b. Modulate cytokine profiles.
- c. Induce hypo responsiveness to food antigens

Non-immunologic benefits:

- a. Digest food and compete for nutrients with pathogens.
- b. Modify pathogen derived toxins.
- c. Stimulate epithelial mucin production.
- d. Alter pH to create an unfavorable local environment for pathogens.

Duration of use:

The exact length of using probiotics is as difficult a question to answer as which forms you should use for specific ailments. According to Harvard Health Publications, daily use for one to two weeks may improve infectious or antibiotic-related diarrhea. The Dairy Council of California explains that most probiotics do not permanently adhere in the intestine; therefore daily consumption is the best way to maintain effective amounts. The short answer of duration of use is "indefinitely." The specific answer lies within a conversation between you and your physician since no standardized recommendation exists¹⁰.

Probiotics are often prescribed for 1–3 weeks longer than the duration of antibiotic treatment. They should be taken with food because the increased gastric pH is more favorable for the probiotics¹¹.

Complications:

Major

The safety of probiotic ingestion has been evaluated by examining infectivity, metabolic activity, pharmacokinetics, pathogenicity and virulence factors associated with toxicity in healthy people.

Reports of harmful effects of Probiotics ingestion are rare and Probiotics are considered safe and well tolerated.

The potential for bacterial translocation, resulting in bacteremia is a concern in patients who are immunocompromised secondary to premature birth, malignancy, HIV virus infection or a chronic debilitated state. Bacterial translocation may develop when GI tract barrier is diminished allowing bacteria to pass across mucous membrane and epithelium and be transported to mesenteric lymph nodes and others.

Probiotics are most commonly used for gastro-intestinal problems, such as inflammatory diseases and diarrhea, and for yeast and urinary tract infections. Probiotics are considered relatively safe, but they have some side effects, including infection, immune system problems and antibiotic resistance.

Infection

The risk of infection or sepsis is the most important area of concern with Probiotics use, according to the AJCN. Some Probiotics have been designed to have good adherence to the intestinal wall, which may increase bacterial translocation and virulence, causing infection. The ACJN reports that the most potent Probiotics may increase pathogenicity, or tendency to cause infection.

Drug interactions with Probiotics:

Medline Plus states that people with severely weakened immune systems may develop serious infections or bacteria in the bloodstream from taking Probiotics. The British Medical Journal cites cases of infection from Lactobacillus, a common Probiotics. A 74-year-old woman developed liver abscesses after four months on a Probiotics; a 67-year-old man who regularly took Probiotics capsules developed an infection after a tooth extraction. Most reported infection cases occur in the elderly.

Immune and metabolic effects

The AJCN says that long-term alterations of "healthy" intestinal bacteria may have adverse effects on immune development. The studies show that normal intestinal microbes are important in stimulating healthy immune development, such as in the abdominal lymphoid tissues. Ingesting Probiotics may alter this crucial micro biota, with detrimental effects on immunity. This is especially true for neonates and pregnant women. The intestinal microbiota also plays an important role in metabolic activities such as glucose regulation, lipid metabolism and complex carbohydrate digestion. There is a risk of adverse metabolic effects from the manipulation of intestinal flora with the use of Probiotics.

Antibiotic resistance

Drugs.com states that antibiotic resistance has been reported for the probiotic Lactobacillus in Europe. "Clinical Infectious Diseases" reports that many strains of lactobacilli are naturally resistant to the antibiotic vancomycin. This can occasionally render the probiotic untreatable in rare cases of infection. "Biomedical and Environmental Sciences" cites a study that found that antibiotic resistance is present in different species of probiotic strains. Most strains were resistant to the antibiotics ciprofloxacin, amikacin and gentamycin. It states that this poses a threat to food safety and that Probiotics use should be directed by guidelines and regulations.

Minor :

Fungemia, GI inflammation.

Other side effects:

Other side effects from Probiotics include abdominal discomfort or gas, drug interactions and rare neurological effects. Endocarditis, an infection in the inner lining of the heart has been reported from infection in the bloodstream caused by Probiotics use.

Products:

Most common forms for probiotic are dairy products and probiotic –fortified foods. However tablets, capsules and sachets containing the bacteria in freeze dried are available. Details are cited in Table 1.

PROBIOTIC	DRUG	RESULT	MANAGEMENT
Bifidobacteria	Antibiotics	Reduces the effectiveness of bifidobacteria	Take bifidobacteria products at least two hours before or after antibiotics
Lactobacillus	Antibiotics	Reduces the effectiveness of lactobacillus	Take lactobacillus products at least two hours before or after food.
Lactobacillus	Immunosuppressants Azathioprine, Cyclosporine, Daclizumab, Tacrolimus corticosteroids etc	Increases chances of getting sick	Management as per physicians direction for individual patients

Table 1 Information on suppliers of Probiotics

Sl. NO	Company	Description	URL
1	Bio Gaia	Lactobacillus reuteri culture comes in three different product friendly forms: freeze dried DVS (Direct Vat Set) granules and frozen pellets.	http://www.biogaia.com
2	BIO K+	Producer and seller of probiotic mix including L.acidophilus and L.casei.	http://www.biokplus.com
3	Cerbios pharma	Producer of enterococcus LAB SF 68	http://www.cerbios.com
4	Danone	Producer of several brands of fermented dairy products containing probiotics.	http://www.danone.com
5	GTC nutrition	Nutra flora short chains fructo oligo saccharides are a cane sugar of beet sugar, derived natural prebiotic fiber.	http://www.gtc.nutrion.com
6	Lallemand	A Canadian supplier delivers probiotics and biosupplements to nutraceuticals, pharmaceutical industries.	http://www.lallemand.com

Table 2 Products available in Indian market

S .No	Product	Strains	Package/(INR)	Manufacturer/ Supplier
1	VSL#3 capsule	S. thermophilus ,B.breve, B.longum ,B.infantis , L. acidophilus, L.plantarum , L.delbrueckii spp bulgaricus , L.paracasei	10's (251.65)	Sun pharma http://www.sunpharma.com
2	Prepro capsule	S.faecalis C.butyricum B.mesentericus L.acidophilus	10's (80)	Fourts india http://www.fourrts.com/premiere_product.htm
3	Vizyl capsule	B.mesentericus C.butyricum S.faecalis L.sporogenes	10's (77.05)	Unichem http://www.genericpedia.com/
4	Bifilac capsule	S.faecalis, L.clostridium butyricum, B.mesentericus	10's (86.48)	Tablets india Ltd http://www.abpl.co.in/Probiotics-PreProbiotics-Product.html
5	Becelac –PB	L.acidophilus	10's (72)	Dr.Reddy's Labs

	capsules	L.calcium pantothenate , niacinamide vitamin B12, vitamin C folic acid, vitamin B6 , vitamin B2 thiamine mononitrate		http://www.mims.com/India
6	Vibact capsules	S. faecalis, C butyricum B.mesentericus	10's (790.2)	USV http://www.mims.com/India
7	Bifilac sachet	Sfaecalis C.butyricum Mesentericus	0.5 g (9.75)	Tablets india Ltd http://www.mims.com/India
8	Econorm sachet	S.boulardii.	1's (34.8)	Dr.Reddy's Labs http://www.healthkartplus.com
9	Vizyl sachet	B.mesentericus C.butyricum S.faecalis L.sporogenes	1's (8)	Unichem http://www.medguideindia.com

Table 3
Clinical applications of Probiotics:

S.No	Disease	Strains
a.	Diarrhea	L.reuteri ATCC 55730, L.rhamnous GG , L.casei DN-114001
b.	Prevention of acute diarrhea	L.GG, L.casei DN-114001 , S.boulardii
c.	Antibiotic –associated diarrhea	S.boulardii or L.rhamnous GG L.casei DN-114001.
d.	Radiation induced diarrhea, Inflammatory bowel disease –pouchitis	L.casei, L.plantarum , L.acidophilus , L.delbrueckii , B.infantis, S.thermophilus
e.	Ulcerative colitis	E .coli nissle strain
f.	Improve abdominal pain and bloating in IBS patients. Increase immune.	<u>Bacillus coagulans</u> GBI-30

Table 4 Probiotics clinical trial reports:

SL N.O	Clinical Trials Conducted	Method of Study	Outcome
1	Probiotic administration in preterm infants .(pips) [12]	Double blind, Placebo-controlled randomized trial in 1300 children.	On Going Trial
2	Probiotics for hepatic encephalopathy. [1]	Systemic review and meta-analysis study.	probiotics be an effective treatment of hepatic encephalopathy
3	Probiotic 'functional food 'in the management of irritable bowel syndrome. [13]	Randomized controlled study.	Trial didn't provide evidence for effectiveness of a probiotic in IBS, but a significant improvement was shown by participants.
4	Probiotics for prevention and treatment of pediatric atopic dermatitis. [14]	Double blind Meta-analysis study in 3679 children	Study shows probiotics' efficacy in prevention than treatment of pediatric atopic dermatitis.

5	Probiotics In H. Pylori-Colonized Subjects. [15]	randomized, double-blind, placebo-controlled	Decreases adverse side effects, resulting in better compliance and, in some cases, improved rates of eradication.
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Table 5
 Strains and uses of individual species

<u>Strains</u>	<u>Uses</u>
1. <u>Lactobacillus plantarum</u> 299v	Affect symptoms of irritable bowel syndrome.
2. <u>Lactobacillus reuteri</u> ATCC 55730 (Lactobacillus reuteri SD2112)	Evidence for diarrhea mitigation in children, decreased crying in infantile colic, <u>H. pylori</u> infection, antibiotic-associated side-effects, fever and diarrhea in children and number of sick days in adults.
3. Lactobacillus reuteri Prodentis) for oral health	Evidence for effect on <u>gingivitis</u> and <u>periodontitis</u> , preliminary evidence for reduction of oral malodor, evidence for reduction of risk factors for caries .
4. <u>Bifidobacterium longum</u> subsp. <u>Infantis</u> 35624	Possible relief from abdominal pain/discomfort, bloating and constipation.
5. <u>Lactobacillus johnsonii</u> La1 (Lactobacillus LC1, Lactobacillus johnsonii NCC533)	Reduce incidence of <u>H. pylori</u> -caused gastritis and may reduce inflammation.

Table 6
 Strains and uses of mixed species

1. Lactobacillus rhamnosus GR-1 & Lactobacillus reuteri RC-14	In one study, oral ingestion resulted in vaginal colonisation and reduced vaginitis.
2. Lactobacillus acidophilus NCFM & Bifidobacterium bifidum BB-12	Preliminary evidence for reduced <u>C. difficile</u> -associated disease.
3. Lactobacillus acidophilus CL1285 & Lactobacillus casei LBC80R .	May affect digestive health. May reduce symptoms of lactose intolerance and immune stimulation.

Product Selection:

Probiotics are sensitive to environmental conditions including pH, moisture, temperature, air and light. As soon as probiotic is manufactured the number of viable colony-forming units begins to decrease as a part of the natural life cycle of organism.

For effective Probiotics dose it should survive in GI tract colonize and replicate. The number of viable bacteria reaching and colonizing the GI tract depends on several factors including dose, formulation, GI motility, patient's gastric acid pH and co administration of food or milk (which may aid in probiotic viability).

selection, storage, and administration of probiotics.

A probiotic should contain at least 10^8 CFU. This Dose will increase the likelihood that a sufficient amount will survive and colonize GI tract. Probiotic products available in Indian market and its clinical applications are given in Table 2 and Table 3.

Role of pharmacist:

The pharmacist role in appropriate probiotic product selection and patient education is important for positive therapeutic outcomes with multiple probiotic formulations on the market, internet distributors and misleading or confusing claims in the media. Pharmacist should educate patients about the appropriate use,

References :

Reports of clinical trial of probiotics are cited in Table 4.

Revenue generation in probiotics by pharma industries:

The new generation biotech drugs and dietary supplements developed from yeast or lactic acid bacteria (LAB), is emerging as a major opportunity in the domestic and international markets for research driven Indian drug companies. At least 39 probiotic drug brands, mainly in the area of gastroenterology, from 30 major Indian companies have already created a probiotics drug market in India worth Rs 80 crore, with a year-on-year growth of 41.1 per cent. The market was likely to grow further in the coming years as many of the major Indian pharmaceutical companies are in the process of developing and in-licensing probiotic drugs.

Darolac and Sporlac, two gastro-related drugs in this category from Aristo Pharmaceuticals and Uni-Sankyo respectively, enjoy a market share of Rs 7.9 crore each. Tablets India's Bifilac, prescribed for antibiotics induced diarrhea, is the largest brand currently in India with annual sales of Rs 9.9 Crore. US Vitamin's ViBact is another major brand in this category with a turnover of Rs 8.2 Crore, according to the data from ORG-IMS¹. Probiotic related functional foods are gaining popularity in India. Amul recently launched an innovative probiotic ice-cream with health claims. Alkem Health Foods has launched health supplements, sweeteners, ready to eat cookies and jellies. Some of strains which are under research are given in Table 5 and Table 6 which may be the future of probiotics.

Conclusion :

Pharmacists can play an integral role in the optimal use of probiotics by recommending the appropriate probiotic product to health care providers and patients through reviewing the current literature, delivering patient education, dispensing high quality products and monitoring patient outcomes. High-profile probiotic containing products have been hugely successful in Europe, Asia, and in other regions of the world .The marketing success will promote consumption, product development and research in Probiotics.

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1. Lisa S Smith , Joy B Greene . Probiotics in Gastrointestinal Disease . 2009. **83-89**.
<http://www.worldgastroenterology.org>.
2. Trevor young.shigellosis.2010March.
<http://www.austincc.edu>
3. Francisco Guarner et al. World Gastroenterology Organisation Global Guidelines. Probiotics and prebiotics 2008May.
<http://www.worldgastroenterology.org>.
4. Volker Rusch.Probiotics And Definitions: A Short Overview. <http://www.old-herborn-university>.
5. Roy Fuller.Their Development and use
<http://www.old-herborn-university>.
6. <http://www.nola.com/health> .
7. <http://www.fitsugar.com/Foods>
8. <http://www.rd.com/slideshows>.
9. <http://www.globalhealingcenter.com> .
10. <http://www.livestrong.com>.
11. <http://www.medscape.com>
12. [http://www. World Gastroenterology.org](http://www.WorldGastroenterology.org) - Organisation Global Guidelines.2011October.
13. <http://www.cimsasia.com/India/>
14. .Probiotic for Preterm neonates. 2013 July.
<http://www.karger.com>
15. RaviPrakash, Kevin.D.Mullen. Mechanisms,Diagnosis and Management of Hepatic Encephalopathy.2010 August.
<http://www.med.upenn.edu/>