



Probiotics Usage and Safety Concerns - A Review

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ABSTRACT

Probiotics use has gained popularity in recent years for the treatment of chronic as well as non- chronic diseases, however, the safety of such products and their adherence to protocols is still questionable. Recently many cases of secondary diseases like fungemia or Bacteremia have been reported in patients receiving probiotics as a supportive agent. The main concern of this review is to focus on safety perspectives of probiotics and rational use of such products. More so because the market is flooded with a variety of such products while the regulations pertaining to these are quite weak. Growing health concerns, complexity of diseases and health awareness has led to indiscriminate use of these products. Further the cost of these products being on higher side poses an additional burden on the overall economy of the treatment.

Keywords: Bacteremia, Fungemia, Probiotics, Regulations, Safety.

INTRODUCTION

Probiotic is a living non- pathogenic microorganism which on consumption provides a beneficial effect to the host. The "Probiotic" terms were first used by Lilly and Stillwell¹ and redefined as "A product produced by one microorganism stimulating the growth of another microorganism". Fuller defined the term as "a non-pathogenic microorganism which when ingested, give a positive result on the host health."²

The latest definition of probiotic is given by FDA and WHO jointly, states that they are "live microorganism which when administered in adequate amount confers a health benefit to the host". An expert consensus documents published in 2013 which terms the use of probiotics and the scope of probiotics. The panel found that the definition of a probiotic advanced by the FAO/WHO³ in 2001 is sufficiently broad to enable a wide range of products to be developed, and sufficiently narrow to impose some core requirements.⁴

Probiotics are just live bacteria and yeasts that are beneficial in several health conditions. They are commonly ingested as supplements, popularly known as "good bacteria". They restore the balance of gut flora upon ingestion when disturbed due to long term exposure to antibiotics or gastrointestinal problems.⁵ A wide range of microbes and their application are included in this definition of probiotics. After this definition, they easily distinguish between live microbes which are used as processing aids or sources of useful compounds and those which are noticed primarily for their health benefits. Also, one can differentiate between commensal microorganisms and probiotics by this definition. Although commensal presents in the gut are mainly the source of probiotics strains, but before their isolation and characterization, a convincing evidence for their proven

health benefits must be available before they can be termed as 'probiotics'. Even after thirteen years of this known definition, various researches have been conducted to challenge the limits of probiotics concept, ranging from fecal microbiota transplants (FMT) to live microbial culture present in fermented foods. The terms 'probiotics' has also been embezzled for e.g., on a product such as shampoos, disinfectants, mattress, and aftershaves for which effectiveness and maintenance of viability of the microbes used are not established.⁶

The taxonomy of the probiotics candidate must be well defined. It has proven that the efficacy of probiotics is strain specific and cannot be observed from other strain of same genus or species. This introduces two terms which are genotype and phenotype used for the precise identification of the isolated strain.⁶

According to the 2002 FAO/WHO guidelines, the safety of the potential probiotics should be assessed by the following minimum required tests.⁷⁻¹³

Antibiotics resistance patterns must be determined.

- Evaluation of some metabolic activities (e.g. bile salt deconjugation, D- lactate production)
- Side effects evolution during human studies.
- Epidemiological observation of unfortunate incidents in consumers (aftermarket).
- Test for toxin production is required if the species of the strain is known to produce toxins in mammals. One scheme for testing toxin production has been suggested by the EU scientific committee on animal nutrition.



- Tests for hemolytic activity is required if the strain under evaluation belong of a species which have a hemolytic potential.

Most commonly used probiotics are from the species of *Lactobacillus* and *Bifidobacterium*, although some species of *E.coli* and *Bacillus* and the yeast (*Saccharomyces cerevisiae*) are also used as probiotics.

The *Lactobacillus* or Lactic acid bacterial strain was used for the fermentation of the food and formation of various consumable products which show some effects to the human body. The consumption of fermented milk was first noted in the Old Testament, and the ancient carvings show that the humans for their benefits inoculated the milk containing cultures to produce Yogurts as early as 2250 BC.¹⁴

The Russian scientist Elie Metchnikoff contributed their efforts in the 1900s on making of fermented milk which on consumption shows beneficial effects to the hosts.¹⁵ The fermented milk developed also had the medicinal effects. Metchnikoff also claimed that consumption of yogurt containing lactobacilli led to reduction of harmful bacteria in the gut and helped to re-establish the healthy gut flora.

Metchnikoff hypothesis led to the development of the dairy industry in France, the first of its kind in the European country for producing fermented milk using *Bacillus bulgaricus*.

Approximately every civilization has developed fermentation of food of various types. Many scientists have found the production of beverage as early as 7000 BC, and in Asian countries, the fermented beverages were prepared from the fermentation from rice, wheat, and ripe fruits. (Table 1)

Table 1: Some Historical Fermented Foods

Origin food	Region	Years of introduction
Fermented Milk	Middle East	10,000 BC
Fermented Milk Products	Egypt, Greece and Italy	7000-5000 BC
Fermented Rice	China, Asia	2000 BC
Fermented Honey	North America, Middle East	2000 BC
Fermented malted cereals: Beer	North Africa, China and Middle East	2000 BC
Fermented meats	Middle East	1500 BC
Wine	North Africa, Europe, Middle East	3000 BC

Prebiotics

Prebiotics are non-digestible food ingredients in fiber form which provide the good effect on the host by stimulating the growth and activity of beneficial or good bacteria in the colon reported.⁵

The terms prebiotics was given by Gibson and Roberfiord who exchanges “pro” for “pre” which means “before” and “for”. They defined Prebiotics “as non- digestible food ingredients that probiotics can feed off”. They are selectively utilized in the gut to increase healthy bacteria, aid digestion and enhance the production of valuable vitamins. Good bacteria play a significant role in regulating immune system, inhibiting the growth of pathogens (disease-causing bacteria) and digesting food. Galacto-oligosaccharides (GOS) is the most advanced form of Prebiotic which belong to a group of particular nutrient fibers that feed and encourage the growth of good bacteria in the gut. Prebiotic alter the colonic microbiota in favors of a healthier composition.¹⁶

Synbiotics

A *synbiotic* is a supplement that contains both probiotics and prebiotics. The two works in tandem to ensure availability of enough of the healthy, beneficial bacteria.¹⁷ The synbiotic formulation includes probiotic like *Lactobacilli*, *Bifidobacterium* spp, *S.boulardii*, *Bacillus clausii*, etc. and prebiotics like Fructo-oligosaccharide (FOS), GOS, xylo-oligosaccharides (XOS), Inulin and some other naturally obtained like chicory and yacoon roots, etc. Following are the health benefits obtained by consuming symbiotic.¹⁸

Increase in the level of good bacteria in the colon.

- Improvement in balancing the microbial gut flora.
- Improved liver functioning, in cirrhotic patients.
- Improvement in immunomodulating activity.
- Preventing the nosocomial infections in surgery patients.

MODE OF ACTION OF PROBIOTICS

On ingestion in certain numbers, probiotics provide health benefits which are beyond inherent general nutrition. Mechanism of action is as shown in figure1. There is enough evidence that some specific strains of *Lactobacillus* and *Bifidobacterium* can influence immune function through many different pathways such as effects on enterocytes, antigen presenting cells (including both circulating monocytes and local dendrite cells), effectors T and B cells, regulating T cells. It is not known to what extent a finding using a certain bacterial strain is related for other strains even if they belong to same species because there are very few studies in which several allegedly probiotics strains have been compared. There are only a few strains to date, which are limited to *lactobacilli*, which have been also reasonably well documented and defined in clinical studies, mostly against infectious gastroenteritis and

lactose intolerance. Locally in the gut, there is an affirmation that at least one probiotic strain has the potential to maintain the nobility of the intestinal barrier, potentially minimizing systemic antigen load and commensally gut bacteria help reduce local inflammation.¹⁹ The mechanism of action is defined in Figure 1.

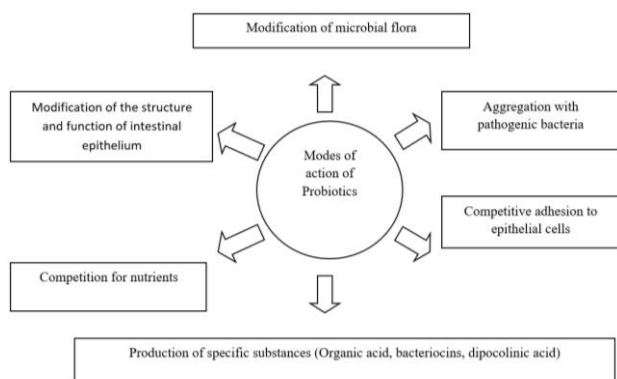


Figure 1: Mechanisms of action of Probiotics

ADVANTAGES OF PROBIOTICS

The balance or imbalance of bacteria in the digestive system is directly related to overall health and wellbeing of an individual. Probiotics by increasing the number of good bacteria of gut results in a range of benefits like weight loss, digestive health, immune function, etc.

Balancing the Friendly Bacteria of Digestive System

Prolonged medical illness, antibiotic therapy, poor diet may all lead to an imbalance between “good” and “bad” micro flora of the gut. The consequences may include allergies, mental health problems, obesity, digestive issues, and more. Probiotics given as medicine or supplements restore this imbalance by elevating the proportion of “good” bacteria by direct and indirect means.⁴

Preventing and Treating Diarrhea

Diarrhea is a common side effect of excessive antibiotic usage. According to some studies, the use of probiotics is linked with diminished risk of antibiotics associated diarrhea. Probiotics can also help in curing other forms of diarrhea which are not associated with antibiotics. In a large review of 35 studies, it was concluded that certain strains of probiotics could reduce the duration of infectious diarrhea to as short as 24hrs. Efficacy of probiotics for preventing diarrhea from other causes is 26% in adults and 57% in children. This efficiency depends on the dose and type of the probiotics taken, commonly known anti-diarrheal probiotic strains are *Lactobacillus casei*, *Lactobacillus rhamnosus* and the yeast *Saccharomyces boulardii*.²⁰

Improving Mental Health Conditions

Several studies have depicted a direct link of gut health with mood and mental health of individuals. Probiotics supplements showed improved mental health in animal

and human subjects. In a review of 15 human studies, it was shown that supplementing with *Bifidobacterium* and *Lactobacillus* strains for 1-2 months can reduce anxiety, depression, autism, OCD and aids in memory. One study followed 70 chemical workers for 6 weeks in which those who consumed 100 grams of probiotic yogurt per day or took a daily probiotic capsule experienced benefits for general health, depression, anxiety and stress).²¹ Thus it can be concluded that probiotics can significantly reduce symptoms of mental health disorders such as depression, anxiety, stress, and memory.

Maintenance of Healthy Heart

Probiotics reduce the level of LDL (“bad”) cholesterol and blood pressure, diminishing the risk of artery or vein blockage and heart stroke. Bile is a fluid (made up of cholesterol) which occurs naturally in the body, helps indigestion. There are certain lactic acids producing bacteria which breaks the bile in the gut and hence reduce the cholesterol so by breaking down bile, probiotics can prevent it from being reabsorbed in the gut, where it can enter the blood as cholesterol as reported.²² Prebiotic consumption may also lower blood pressure.

Decrease the Severity of Some Allergies and Eczema

According to a study a significant drop in incidences and severity of eczema was seen in infants and children fed on probiotics supplemented milk when compared to infants and children fed on milk without probiotics.¹⁹ In another study, probiotics were given to women during pregnancy as a result; children had an 83% lower risk of developing eczema in the first two years of life.²³ Some probiotics are also known to reduce inflammatory responses in people with milk or dairy allergies such as lactose intolerant people. However, the evidence is weak and further studies are needed.

Reducing Symptoms of Certain Digestive Disorders

In US more than 1 million people suffer from inflammatory bowel disease. Many types of probiotics from the *Bifidobacterium* and *Lactobacillus* strains have shown improved symptoms in people with mild ulcerative colitis. Astoundingly, one study found that supplementing with the probiotic *E.coli* either in the form of capsules or in the daily diet; was enormously effective in maintaining revocation in people with ulcerative colitis.²⁴ Early research suggests that they may help in reducing the symptoms of irritable bowel syndrome (IBS). Probiotics have also been shown to diminish the risk of severe necrotizing by 50% so; one can easily conclude that consumption of probiotics will have a recognizable effect on digestive problems in a better way which will further show a good impact on their mood as our food is directly linked to our mood.

Boosting the Immune System

Probiotics improve the immune system and retards the growth of harmful gut bacteria by promoting the synthesis of natural antibodies. Studies reveal that immune cells like

IgA- producing cells, T lymphocytes and natural killer cells are markedly increased by probiotics. A case study revealed that consuming probiotics reduces the occurrence and duration of respiratory infections. In another study on 570 children, it was found that taking lactobacillus GG reduced the frequency and seriousness of respiratory infections by 17%.²⁵ In women on the consumption of probiotic *Lactobacillus crispatus*, there is a reduction in risk of urinary tract infections (UTIs) by 50%.

Weight Management

There are a number of different mechanisms by which probiotics help in weight and belly fat reduction. Evidences suggest that probiotics prevent absorption of dietary fats in the intestines. The fats, rather than being stored in the body get excreted out through the faeces. Probiotics may also give a feeling of fullness for longer; it helps in burning more calories and storing less fat.²⁶ This is partly caused by the increasing level of certain hormones, such as GLP (a hormone that stimulates insulin secretion in response to meals).²⁷ In a study, women lost 50% weight when supplemented with *Lactobacillus rhamnosus* for 3 months.²⁸

In Lactose Intolerance

Probiotics stains have also proved to solve the problem of lactose intolerance. There is an enzyme called lactase or β -galactosidase which is responsible for breaking the milk sugar or a disaccharide in milk i.e., lactose into glucose and

galactose. So people lacking the ability to produce lactase enzyme or β -galactosidase enzyme are known as lactose intolerant. These individuals are not able to digest milk and it mostly poses a problem in newborn infants. People who are suffering from lactose intolerance problems experience cramps, flatulence, abdominal discomfort, diarrhea, nausea, vomiting, etc.; *Lactobacillus* produces the lactase enzyme, among others. So, by consuming *L. acidophilus* and *L.casei*, it helps to breakup lactose and delivers it in a much more digestible form (in the form of glucose and galactose).²⁹

Active against Certain Vaginal Infection and *Candida Albicans*

An imbalance in the intestinal flora has an effect on the whole body, particularly the vaginal systems. This includes an extreme growth of pathogen which converts into vaginal bacterial or yeast infections, such as *C. albicans*. *L. acidophilus*, a commensal bacteria of vagina maintains a low pH and produce bacteriocins in vagina making the environment hostile to pathogens. It produces hypothiocyanate and hydrogen peroxide which retards the growth of *C. albicans*.³⁰

COMMERCIALLY AVAILABLE PREPARATIONS IN INDIA

In India lot of probiotic brands are available which are used frequently in OTCs or are highly prescribed by physician with antibiotic treatment and chronic illness. Few brands with their parent companies are shown in Table 2.

Table 2: Probiotic Brands Available in Indian Market

S.No.	Brand Name	Company	Bacteria/Specie	Claimed Counts
1.	VSL#3	Sun Pharmaceutical	Live Freeze Dried Lactic Acid Bacteria and Bifidobacterium	112.5 Billion
2.	Enterogermina	Sanofi India Ltd.	<i>Bacillus Clausii</i>	2 Billion
3.	Darolac	Aristo Pharmaceutical Pvt. Ltd.	<i>Bacillus Clausii UBBC-07</i>	2 Billion
4.	Bifilac	Tablet India	<i>Streptococcus faecalis</i> <i>Clostridium butyricum</i> <i>Bacillus mesentericus</i> <i>Lactic acid Bacillus (LAB)</i>	30million 2 million 1 million 50million
5.	Econorm	Dr.Reddy Laboratories Ltd.	<i>Saccharomyces Boulardi</i>	250 mg
6.	Vizylac	Unichem laboratories Ltd.	<i>Lactic acid bacillus (LAB)</i>	120million
7.	Sporlac	Sanzyme Ltd	<i>Lactic acid bacillus (LAB)</i>	120million
8.	Valgut	Eris life Science Pvt Ltd.	<i>Bifidobacterium species</i> <i>Sachromyces boulardi</i> <i>Lactobacillus species</i>	5 billion
9.	Flora BC	Mankind Pharma	<i>Lactobacillus acidophilus</i> <i>Lactobacilus Rhamnosus</i> <i>Lactobacillus casei</i> <i>Lactobacillus plantarum</i> <i>Lactibacillus bulgaricus</i> <i>Bifidobacterium longum</i> <i>Bifidobacterium infantis</i> <i>Bifidobacterium breve</i> <i>Streptococcus thermophilus</i> <i>Saccharomyces boulardi</i>	350million 200million 150million 150million 150million 150million 150million 150million 200million 0.05billion
10.	Entero Plus	GSK	<i>Lactobacillus rhamnosus</i>	3 billion

COMMON PROBLEMS ASSOCIATED WITH PROBIOTIC USAGE

Bacteremia

Bacteremia is a disease associated with the presence of bacteria in the blood. Cases have been reported where the consumption of *Lactobacillus* strain has caused bacteremia in the patient. Severe sepsis was also reported which is caused by another *Lactobacillus* strain i.e. *L.helveticus*.³¹⁻³⁵ *L. rhamnosus* was one of the most common characterized strains in bacteremia. The risk of sepsis was more in immune- deficient and post-surgical patients.

Fungemia

Fungemia is a most prevalent observed side effect of the probiotics in critically ill ICU patient. Many case reports showed that in patients on long term antibiotic therapy, *S.boulardii* was the main causative agent of fungemia when treated with probiotics was for 14 to 56 days of periods. It was seen that central venous catheter (CVC) was used in these cases and *S.boulardii* was the initiator of fungemia.³⁶

CASE REPORTS RECORDED

Esaassen E *et al.*, (2016) reported bacteremia in three pre-term infants taking *Bifidobacterium longum* in probiotic therapy. Such systemic infections caused by probiotic microorganism may have severe clinical course in preterm infants and need proper diagnosis and management.³⁷

Meini S. *et al.*, (2015) reported bacteremia in an adult patient having severe active ulcerative colitis, associated with use of *Lactobacillus rhamnosus* probiotic therapy.³⁸

Krawzenko S *et al.*, 2014 reported bacterial infection in a newborn having intrauterine growth restriction disease when treated with *Lactobacillus rhamnosus* probiotic therapy.³⁹

Doern CD *et al.*, (2014) reported an episode of respiratory syncytial virus (RSV) bronchiolitis with bacterial super infection secondary to administration of *Lactobacillus rhamnosus* in an 11-month-old female with trisomy.⁴⁰

Jenke A *et al.*, (2012) reported septicaemia in an extremely low-weight infant taking *Bifidobacterium* in a probiotic therapy.³⁶

Lolis N *et al.*, (2008) reported fungaemia in an intensive care unit patient taking *Saccharomyces boulardii* probiotic therapy.⁴¹

Land MH *et al.*, (2005) observed sepsis in two infant having cardiac stenosis and autoimmune autistic disorder (AAD) taking *Lactobacillus* species as probiotic.⁴²

Munoz P *et al.*, (2005) observed fungaemia in a patient taking *Saccharomyces boulardii* in probiotic therapy.⁴³

Kunz A.N *et al.*, (2004) reported bacteremia in two infants with short gut syndrome and gatrochsis taking *Lactobacillus* species in probiotic treatment.⁴⁴

Henry *et al.*, (2004) reported fungemia in 65 years old male patient having head and neck cancer taking *Saccharomyces boulardii* in probiotic treatment.⁴⁵

Cherifi S *et al.*, *et al.*, (2004) observed fungemia in a 89 years old patient having severe diarrhoea taking *Saccharomyces boulardii* in probiotic treatment.⁴⁶

Lungarotti MS *et al.*, (2003) isolated *Saccharomyces* and candida from the concurrent blood sample of a male infant taking *S.boulardii* capsule to prevent bacterial growth.⁴⁷

Lestin F (2003), reported fungaemia in a 48 year old patient having diabetes with multiple co-morbidities, taking oral treatment with *Saccharomyces boulardii*.⁴⁸

Cassone M *et al.*, (2003)., observed fungaemia in a 34 years old man having head and thoracic trauma, taking *S.boulardii* in probiotic therapy.⁴⁹

Presterl E *et al.*, (2001) observed the occurrence of endocarditis in a young man who ate a large amount of probiotic yogurt containing *Lactobacillus rhamnosus*.⁵⁰

Rijnders B *et al.*, (2000) reported fungemia in 74 years old male patient having subarachnoidal haemotoma and diarrhoea taking *Saccharomyces boulardii* in probiotic therapy.⁵¹

Niault M *et al.*, (1999) observed fungaemia in a 78 years old woman having chronic obstructive pulmonary disease taking *Saccharomyces boulardii* in probiotic therapy.⁵²

SUSPECTED CAUSE OF INCIDENCES OF ADVERSE EFFECTS OF PROBIOTICS

- A weak regulatory frame work in terms of categorization of probiotics.
- Cross contamination of probiotic products.
- Failure to maintain the claimed CFU by the time of end use.
- Poor maintenance of cold chain during storage and transport.
- False labeling/ false claims.
- Universal recommendation without assessing the patient's acceptability.

RECOMMENDED MEASURES TO ENSURE SAFETY OF PROBIOTICS

Regulatory Frame Work

European Food Safety Authority (EFSA) detailed current practices and review content in safety assessment was published by the European Union. There is no formal safety test protocol guidelines established within the European Union. The EFSA was established in 2002 to introduce the importance and complex scientific and technical issues in relation to food and feed safety (Regulation No.178/2002). However, the probiotics have their historical use or used as an additive which follows the outside the scope of the novel food regulation. The intended use of probiotics for



humans strictly followed the European Union regulation concern the safety of microbes based feed additives.⁵³⁻⁵⁵

Regulatory frame work in India, the food and regulatory affairs are regulated by Prevention of food adulteration Act (PFA) and FDA. In India the probiotics were introduced as a functional food rather than pharmaceutical preparations and are regulated by food laws that regulate the general food items in term of dietary supplements. The FSSA i.e. Food safety and standard act was formulated in India to regulate the different varieties of eatables covering the Nutraceutical, foods and dietary supplements. According to FSSA, Functional foods are defined legally but categorization of food categories, such as nutraceutical, biotherapeutics agents is still unclear. The PFA regulates the labeling and packaging of food and nutraceutical in order to give the maximum information including the ingredients, date of expiry, manufacturer information, nutrition information etc. as reported by Aggarwal *et al.*, (2012); Sharma *et al.*, (2013).^{56,57}

Critical Designing of Clinical Trials for Probiotics

To monitor the safety of probiotic we need to conduct population based scrutiny for the isolation of probiotic bacteria from the patients having the infection. Before conducting clinical trial whole strain profile must be reported.^{58, 59} There should be molecular methods to compare the ability of isolated strain with the probiotic strain. Any trial employing a probiotic strain should have active observation for cases of infection associated with such use and should have active observation for the occurrence of other adverse effects. Although some caution may be necessary in any trial of probiotics, concerns about toxicity should not preclude their study. Rather, each study should be evaluated on a case by case basis, examining the risk, benefit and potential toxicity. There is a list of patients for whom caution might be warranted, such as those with immune compromise, premature infants, those with short bowel syndrome, and those with central venous catheter, elderly patients, and those with cardiac valve disease. However, the presence of any of these factors may not necessarily, preclude a clinical trial. Each study should be evaluated on a study by study basis, with the appropriate involvement of a human investigation review committee and a data safety monitoring committee, as well as specific hypothesis to be tested and observed for bloodstream infection with the probiotic strain.

CONCLUSIONS

Probiotics are extensively prescribed by health professionals due to their ability to treat, prevent or mitigate diseases. Despite their large health effects, the necessity to ensure safe use of probiotics cannot be ignored. Although probiotic consumption among the healthy individuals is safe, but there is a need to ensure safety in case of critically ill patients, in immunocompromised individuals, patient with short bowel syndrome, premature infants, patient with central

venous catheters, and patient with cardiac valve diseases. Also different strains may have different effects in healthy and diseased conditions, thus the effects of one strain cannot be generalized to other strains. Strict surveillance, better regulatory framework, critically designed clinical trials along with careful assessment of patient acceptability are required to ensure the rationality in applications of these products.

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