ORIGINAL ARTICLE

# Probiotics and Health Benefits: A Review

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**ABSTRACT** Probiotics are live microorganisms which, when administered in adequate amounts, confer health benefits to the host. They may antagonise the pathogens by producing antimicrobial compounds; suppress inflammatory responses, in addition to improving the nutritional value of food like release of free amino acids or synthesis of vitamins. The microbial genera used as probiotics include Lactobacillus, Bifidobacterium, Streptococcus, Enterococcus, Escherichia, Bacillus, Saccharomyces, etc. Clinical studies have established that probiotic therapy can help treat several gastrointestinal disorders, delay the development of allergies in children, treat and prevent vaginal and urinary infections in women, improve lactose digestion and help in treatment of irritable bowel syndrome. Probiotics are capable of survival in the passage of gastrointestinal tract; adhere to intestinal mucosal cells for competitive exclusion of pathogens and retain stability during the intended shelf life of the product. Prebiotics differ from the probiotics as they are healthy non digestive food ingredients that reach the intestine unaffected by the digestion process and stimulate the growth of healthy bacteria in the gut and increase resistance to invading pathogen. Dietary fibre inulin is the most common type of prebiotic. Often the mixture of prebiotics and probiotics called synbiotics is used due to their combined synergic or complementary effects. Keeping the microbes alive throughout the stages of product formulation, competitive price, delivery in a viable and functional form are some of the challenges need to be dealt efficaciously for popularization of probiotic products in the market.

**Keywords:** Probiotic, Prebiotic, Synbiotic, Health benefits

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## INTRODUCTION

In the late 19th century, microbiologists identified microflora in the gastrointestinal (GI) tracts of healthy individuals that differed from those found in diseased individuals. These beneficial microflora found in the GI tract were termed probiotics - "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" (FAO/WHO, 2001). Other than health benefits, probiotics also assist in: milk preservation by the generation of lactic acid and possibly antimicrobial compounds, the production of flavour compounds and other metabolites that provide the product with organoleptic properties desired by consumer.[1]

Probiotic should essentially survive in harsh conditions of the stomach and GI tract of humans in order to ensure its efficacy and viability to exhibit wider therapeutic benefits on humans as only viable probiotics are able to colonize and adhere at the GI tract of human, providing competitive exclusion of pathogens.[2]

Prebiotics, non-digestible oligosaccharides such as inulin differ from probiotics as they stimulate the growth of potentially beneficial probiotic microorganisms. Mixture of both probiotics and prebiotics known as synbiotics has health benefits beyond providing basic.[3] In the management of gut microbiota, prebiotics help to enhance the health effects conferred by various probiotic microorganisms such as *lactobacilli, bifidobacteria*, *Roseburia* spp., *Eubacterium* spp., *Akkermansia* spp., *Christensensella* spp., *Propionibacterium* spp., and *Faecalibacterium* spp by enhancing the growth of these microorganisms through crossfeeding interactions.[4] The

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prebiotics cross the small intestine and enter the lower gut thus becoming accessible for probiotic bacteria without being utilised by other intestinal bacteria. Probiotics assist in fermentation of prebiotics, thus releasing short chain fatty acids (SCFA) which are found to regulate luminal pH, play role in mucus production, apetite regulation, glucose homestasis and more.[5] The different sources of prebiotics are chicory, onion, garlic, asparagus, artichoke, leek, bananas, tomatoes and many other plants.[6]

## Why Should We Consume Probiotics in Foods?

The natural balance in our intestinal system can be disturbed by: bacterial infections, stress, antibiotic treatment, travelling, etc. leading to diarrhoea, constipation, etc. Taking probiotics through food or supplements can help to balance the microbiota in the gut.[7] However, a sufficient amount of viable probiotics must reach the intestine in order to provide the consumer with the putative health benefits.

## HOW PROBIOTICS WORK

To know how probiotics work, physiology and microbiology of gastrointestinal tract must be clearly understood. With the entry of food to the stomach, the process of digestion starts where microbes in small and large intestine complete the digestion process. The microbes of the gastrointestinal tract may act in a favourable, neutral or in a harmful manner. Some microbes produce vitamins and are non-pathogenic and can be correlated with healthy intestinal flora. They produce lactic and acetic acids as metabolic end products resulting in lowering the pH of the intestinal contents, GI tract environment, therefore, becomes less desirable for harmful bacteria.[8]

## GENERA USED AS PROBIOTICS

Probiotics are commonly known as lactic acid bacteria due to their ability to produce lactic acid when fermented with substrate rich in sugar.[9] Most probiotics in use today belong to the genera *Lactobacillus* and *Bifidobacterium. Lactobacillus* refers to Gram-positive rods, lactic acid producing bacteria, mostly obligate and facultative anaerobes, predominantly found in the human gastrointestinal and genitourinary tracts. Most commonly used species of lactic acid bacteria in probiotic preparations include *Lactobacillus acidophilus, L.delbrueckii, L.curvatus, L.fermentum, L.lactis, L.plantarum, L.reuteri, L.brevis, Bifidobacteriumbifidum, B.animalis, B.thermophilum, Enterococcus faecalis, Streptococcus cremoris, S.salivarius, S.diacetylactus, S.intermedius.*[8] *Bifidobacteria* are among first organisms to colonise GI tract; colon being their primary habitat. These are commonly straight anaerobes, Gram-positive, nonsporing, pleomorphic rod bacteria which produce lactic and acetic acids as the product of carbohydrates fermentation.[2] The lactic acid bacteria were initially subdivided into the genera *Betabacterium, Thermobacterium, Streptobacterium, Streptococcus, Betacoccus, Tetracoccus,* and *Microbacterium* on the basis of their morphological and phenotypic features. Today, only *Streptococcus* is still retained, whereas most of the others have been renamed into *Lactobacillus, Bifidobacterium*, and *Enterococcus* sp.

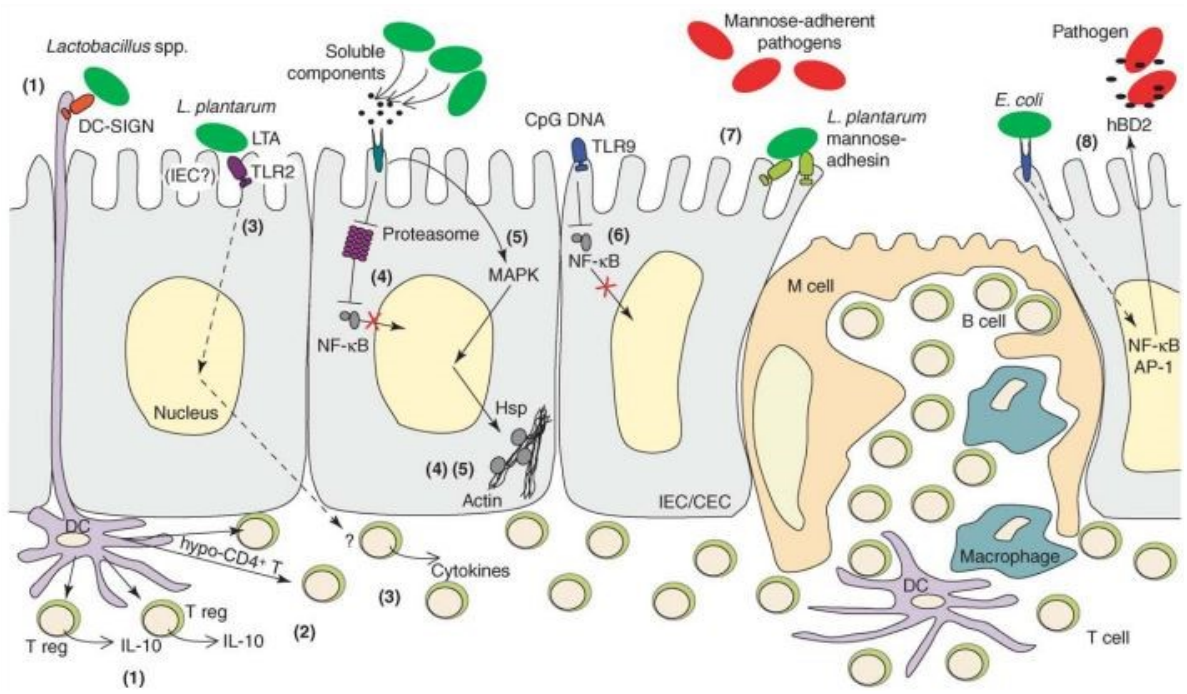
## MECHANISM OF PROBIOTIC ACTION

A number of mechanisms have been found working behind the action of probiotics. Some of which are being discussed here.

## MODULATION OF IMMUNE RESPONSE

- Dendritic cells (DCs) play a key role in early bacterial recognition and, consequently in T-cell responses.
- Several bacterial species including known probiotics (VSL#3 and *L. plantarum*299v) are shown to differentially induce in vitro maturation and cytokine expression of murine DCs, with the possibility to favor T helper 1 (Th1), Th2 or Th3 immune responses (Figure 3). These interactions with DCs appear to be at least partly mediated by Lactobacillus binding to the pattern-recognition receptor.
- VSL#3 is known to produce specific Heat Shock proteins (Hsps) in intestinal epithelial cells to maintain cytoskeletal integrity.
- Certain probiotic E.coli strains induce expression of Beta defensin 2 (hBD2)—an antimicrobial peptide (Figure 1).
- A potential probiotic effector molecule, a eukaryotic-type Serine protease inhibitor (serpin), has been identified in the genome sequence of *Bifidobacterium longum.*[10] Members of the serpin family regulate a wide range of signalling pathways in eukaryotes. Some of these are recognized for their ability to suppress inflammatory responses by inhibiting elastase activity. Recent evidence suggests that the *B. longum* serpin inhibits human elastase *in vitro.*
- Probiotic *L.plantarum* (gram positive) is involved in the anti-inflammatory activity because of its cell wall component-teichoic acid. The effects observed were TLR-2 (toll like receptors) dependent.
- DNA of some probiotics showed a systemic anti-inflammatory effect in contrast to DNA from pathogenic bacteria which induced an inflammatory reaction.[11]

**Figure 1: Potential Probiotic Effects of Bacterial and Host Effector Molecules [12]**




**Note:** DC: Dendritic cell; DC-SIGN: DC-specific intercellular adhesion molecule 3-grabbing non-integrin; IEC: Intestinal epithelial cells; CEC: Colonic epithelial cells; LTA: lipoteichoic acids; TLR: Toll-like receptor 2; MAPK: mitogen-activated protein kinases; TNF-α: tumour necrosis factor α; HSP: heat shock proteins; hBD2: antimicrobial peptide b-defensin-2; AP-1: activating protein 1. (1 and 2) DC-SIGN interaction with lactobacillus strains induces IL-10 producing T regulatory cells leading to induction of hypo responsive CD4+ T cell populations. (3) Differential modulation for production of cytokines due to LTAs. (4, 5 and 6) IEC recognizes soluble probiotic components or certain bacterial motifs such as CpG DNA by TLR9 receptors leading to inactivation of NF-kB signalling pathway. (7 and 8) Mannose adhesins or induction of hBD2 in IECs M cell helps in counteracting the pathogen attachment and growth.

## Antagonism of Pathogens

### *Production of Antimicrobial Compounds*

Probiotics can exert health benefits by producing low molecular weight compounds (<1000) like organic acids which in an undissociated form enters the bacterial cells and dissociated inside their cytoplasm. This causes lowering of intracellular pH and accumulation of the ionized form of organic acid and causes death of the pathogen.[13] Many lactic acid bacteria are also known to produce antimicrobial compounds known as bacterocins (>1000). Bacteriocins kill the target cells forming pores in cell wall or by inhibiting the synthesis of cell wall. For example, nisin forms a complex with lipid II, which is the ultimate cell wall precursor. This complex aggregates and incorporates peptides to form a pore in the cell wall hence inhibits the cell wall biosynthesis of mainly spore-forming bacilli. Other than these various other antimicrobial compounds are produced by the probiotics.[14]

### *Competitive Exclusion of Pathogenic Microorganisms*

Various bacteria use different mechanisms to exclude or to reduce the growth of other species. Interactions between different surface proteins and mucins can inhibit the colonization of pathogenic bacteria and such interactions act as an antagonistic activity by some strains of probiotics against adhesion of GI pathogens.[15]

Probiotics tend to inhibit adhesion of pathogens, produce substances and also stimulate IECs. Bacteria can also modify their surroundings and make them less favourable for other species to grow. Production of lactic acid and acetic acid is an example of such substances. Sometimes competitive exclusion can also occur when probiotic bacteria and pathogenic bacteria share binding specificities such as *lactobacilli* and *bifidobacteria* have common carbohydrate binding specificities with some enteropathogens.[14]

## Strengthening of Intestinal Barriers

### *Probiotics can have Diverse Effects on the Intestinal Epithelial Barriers*

Direct effects on the epithelium. Probiotics can increase mucin expression and secretion by goblet cells, thereby limiting bacterial movement across the mucous layer. Augmentation of â-defensin expression and secretion into the mucus by epithelial cells can prevent the proliferation of commensals

and pathogens, thus also contributing to barrier integrity (Figure 2). Probiotics can enhance tight junction stability, which decreases epithelial permeability to pathogens and their products.

Probiotics can act by enhancing mucosal immunity. They can increase levels of IgA-producing cells in the lamina propia and promote secretory IgA (sIgA) secretion into the luminal mucous layer. These antibodies limit epithelial colonization by binding bacteria and their antigens, thus contributing to gut homeostasis.

Probiotics can have effects on other surrounding or infecting bacteria. They can alter the microbiota composition and/or gene expression, leading to indirect enhancement of the barrier through the commensal bacteria. Furthermore, some probiotics can directly kill or inhibit growth of pathogenic bacteria via expression of antimicrobial factors such as bacteriocins. Probiotics can also compete with pathogens or commensals for binding sites on mucins or epithelial cells, thereby preventing detrimental colonization and contributing to barrier function.[16]

## CHARACTERISTICS OF PROBIOTICS

- Survival in the GI tract passage-Tolerance to the stomach acidic and pancreatic secretions such as bile and digestive enzymes;
- Adherence to intestinal mucosal cells-Attachment is necessary for competitive exclusion of pathogens and modulation of host cell responses;
- Non-pathogenic, nontoxic, and free of significant adverse side effects;
- Contain an adequate number of viable cells to confer the health benefit;
- Labelled in a truthful and informative manner to the consumer;
- Retain stability during the intended shelf life of the product;
- Sufficient dosage to ensure efficacy of probiotics on human health.[18]

## HEALTH AND PROBIOTICS

Numerous studies have been conducted to discuss the role of probiotics in human health and diseases.

Some of which have been summarized here as mentioned in Table 1.

## SAFETY CONSIDERATIONS

Although plenty of bacteria have been regarded as probiotics, but many do not satisfy the desirable properties. Several aspects need to be taken into consideration before considering a particular bacterial strain as potential probiotic which include safety, functional and technological characteristics. In order to ensure the safety of the probiotic products, it is essential for the probiotic microorganism to be nonpathogenic and recognized as GRAS (Generally Recognized as Safe) for human consumption by US Food

**Figure 2: Enhancement of Barrier Function by Probiotic Bacteria [17]**

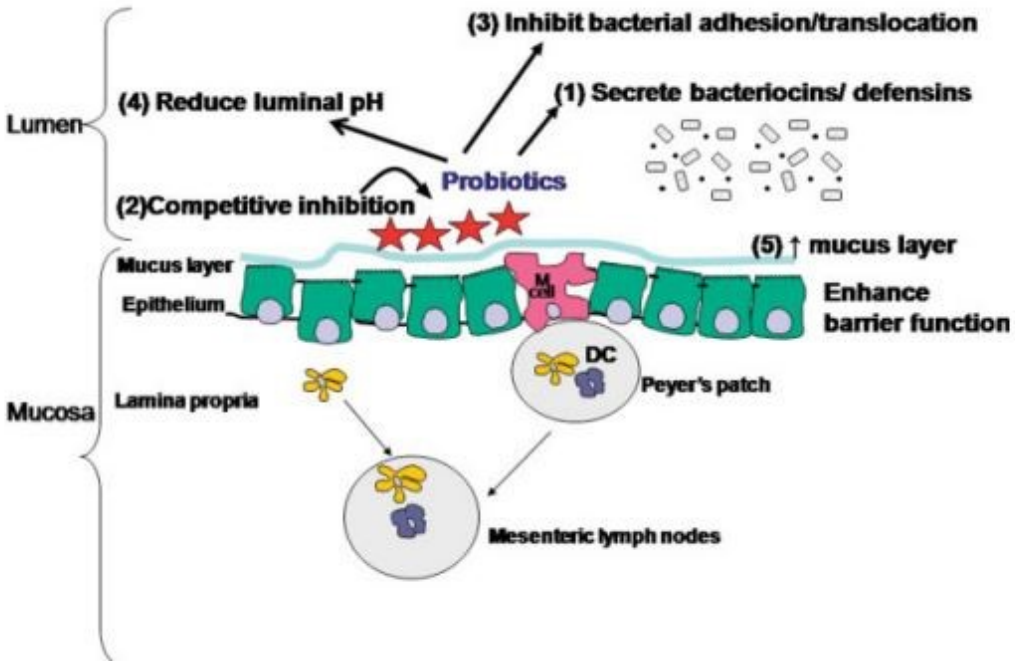


**Table 1: Impact of Probiotics on Human Health and Diseases**

| Disease | Species Name |
|---|---|
| Lowering of cholestrol levels | *Bifidobacterium* sp., *Lactobacillus* sp.,[19] |
| Improved lactose digestion | *Lactobacillus; L.acidophilus; L. bulgaricus; L.plantarum; L reuteri or L.rhamnosus, Bifidobacterium animalis, Bifidobacterium longum and Streptococcus thermophiles.*[20] |
| Decreased Diarrhoea | *Bifidobacterium breve* and *Bifidobacterium pseudocatenulatum* DSM20439 , Lactobacillus LGG, Bifidobacterium lactis HN019, *Lactobacillus rhamnosus* GG[21] |
| Inflammatory Bowel disease | Bifidobacterium longum spp. longum 35624, probiotic strain of *Faecalibacterium prausnitzii* , *Escherichia coli* Nissle, VSL #3, *Bifidobacterium breve* , *Bifidobacterium bifidum* , and *Lactobacillus acidophilus, Enterococcus faecium, Saccharomyces boulardii*[22] |
| Allergies | *Lactobacillus* GG, *E-coli,* LGG, *L. rhamnosus* LC705, *B. breve* Bb99, *P.freudenreichii* ssp shermanii JS, *L. reuteri, L. casei* DN-114001, *L. plantar um* 33, *L. acidophil us* L-92[23] |
| Oral health (Dental Caries Halitosis Gingivalis) | *L. acidophilus, L. reuteri, L. paracasei, Bifidobacterium lactis, L salivarius strain WB21 and T1271, P. gingivalis, P. intermedia*[24]. *Streptococcus salivarius* K12, *L. rhamnosus* GG (LGG) *Lactobacillus fermentum, Lactobacillus salivarius* BGHO1[25] |
| Cancer | *Lactobacillus casei ATCC 393, Bacillus polyfermenticus KU3, Enterococcus lactis IW5, Lactococcus lactis NK34, Lactococcus lactis KC24, Lactobacillus fermentum strains, Lactobacillus reuteri strains, Lactobacillus paracasei subp. paracasei X12, Lactobacillus acidophilus, Lactobacillus casei*[26] |
| Eczema | *Lactobacillus rhamnosus* , *Bifidobacterium animalis* subsp *lactis* HNO19, *Bifidobacterium bifidum* CBT BF3, *Bifidobacterium breve* CBT BR3, *Lactobacillus acidophilus* CBT LA1[27] |

and Drug Administration (FDA) or they may be given qualified presumption of safety (QPS) status by the European Food Safety Authority (EFSA).[4] These properties are important since some bacteria originated from human GI tract are also pathogenic in nature such as *Helicobacter pylori*, *Clostridium difficile*, and many more.

- As probiotics increase in popularity, it is prudent to consider whether there are any safety concerns associated with the resulting increased exposure to live microbes.
- A safety assessment must consider (arrows) the nature of the specific microbe being consumed, how it is prepared and administered, dose to be delivered, and the health status of the consumer.
- Determining the antibiotic resistance profile to avoid the transfer of antibiotic resistance to colonic microbiota. Expression of resistance to antibiotics by candidate probiotic strains should be considered from the perspective of safety.
- As *lactobacilli* and *bifidobacteria* are the common colonisers of human body their exposure is universal and persistent and is therefore their consumption as probiotic is considered safe and risk of infection by these genera is in negligible range.
- A few cases of sepsis have been associated with administration of the probiotic *S. cerevisiae* (boulardii).[28]

  It is prudent, however, to recommend that D-lactate-producing probiotics be avoided by subjects with short bowel syndrome.
- Safety is an important regulatory issue. In the United States, there are different safety standards for different regulatory categories (foods, dietary supplements, or drugs).

All ingredients used in foods must be considered GRAS generally recognized as safe, however only a few probiotic microbes are included on any official GRAS list. The emerging trend is on developing consortia (different mixtures of probiotics) of different probiotic species and strain as a number of studies have shown that probiotics deliver superior impact on human health compared to the use of single probiotic strain. Particularly in treating ulcerative colitis, irritable bowel disease, diarrhea, improving hepatic insulin resistance in diabetic patients, enhancing the immune system of the consumer, and many more.[2] However, it is important to ensure that probiotic consortia do not cross-inhibit among them as it may reduce the efficacy of the probiotic product. Therefore, controlled human studies on probiotic

products should be conducted before ensuring the effectiveness of the product.[29]

## CURRENT STATUS IN INDIA

### Pharmaceutical Products

**Table 2: Commercial Probiotic Formulations in India [30]**

| Trade Name/Dosage Form and Use | Name of Manufacturing Unit/Company | Organism Used |
|---|---|---|
| Eubioz (powder for oral solution) | Lupin (Haryana) | *Lactobacillus acidophilus* |
| | | *L. rhamnosus* |
| | | *Bifidobacterium bifidum* |
| | | *B. longum* |
| | | *Streptococcus thermophillus* |
| | | *Saccharomyces boulardii* |
| Econova (Capsules) Antidiarrhoeal | Glenmark (Himachal Pradesh) | *L. Reuteri* |
| | | *L. Rhamnosus* |
| | | *L. Reuteri* |
| | | *L. Rhamnosus* |
| Actigut (Capsules) | Alembic (Himachal Pradesh) | *L. acidophilus* |
| | | *L. rhamnosus* |
| | | *B. longum* |
| | | *B. bifidum* |
| | | *S. boulardii* |
| | | *S. thermophillus* |
| Becelac (Capsules) | Dr. Reddy Lab | *L. acidophilus* |
| Lactisyn (Injection) | Franco-Indian | *L. acidophilus* |
| | | *L. lactis* |
| | | *S. thermophillus* |
| | | *S. lactis* |
| Vi Bact (Sachet) | Unique Biotech Ltd. | *S. faecalis* |
| | | *C. butyricum* |
| | | *B. mesentericus* |
| | | *L. sporogenes* |
| Binifit (Capsules) | Rexcel (Ranbaxy Laboratories Ltd) | *C. butyricum* |
| | | *S. faecalis* |
| | | *B. mesentricus* |
| | | *L. sporogenes* |

## Food Products

- Amul - Probiotic ice creams, test-marketing pouched Lassi (sweetened curd) in Gujarat and some parts of Maharashtra.
- Yakult Danone - This is a collaborative effort of Yakult (Japan) and Danone (France). Yakult drinks have bacteria belonging to *Lactobacillus* and *Bifidobacterium* group.
- Nestle - Probiotic yoghurt (India).

  Nesvita and Actiplus (International market).
- Mother Dairy - b-Activ probiotic Dahi, b-Activ probiotic Lassi, b-Activ curd and Nutrifit (Strawberry and Mango).

## REGULATORY STATUS OF PROBIOTICS IN INDIA

Probiotics is not new to us; they are exploited for the benefit and wellbeing of humans since very long time. During the last decade probiotic products are growing tremendously but acceptance is growing slowly. Pharmaceutical formulations like Sporolac, *Saccharomyces boulardii* and yogurt are commonly used examples. In India, currently food and drugs are regulated by Prevention of Food Adulteration Act (PFA) and Food and Drug Administration (FDA) respectively. The Food Safety Standards Act of 2003 (FSSA) defines the foods for special dietary uses or functional foods, neutraceuticals or health supplements.[31] Probiotics in India are characterised as functional food and currently are regulated by food laws that regulate general food items rather than pharmaceuticals or drugs. There is further requirement of effective well defined regulations; guidelines and suitable protocols. Indian Council of Medical Research (ICMR) along with the Department of Biotechnology (DBT) formulates the guidelines and regulations for evaluating the safety and efficacy of probiotics in India. Other regulatory agencies are Food and drug administration, USA and European food safety authority.

## CONCLUSION

- Most probiotic strains marketed today were originally selected in easily measurable phenotypes (e.g., ability to tolerate bile salts or survive GI tract passage) and not necessarily selected for their unique ability to confer defined health benefits.
- If consumer support for probiotics is to continue, it will be crucial to identify the precise mechanisms by which probiotics influence human health.
- Certain considerations must be addressed viz. keeping the microbes alive throughout the stages of product formulation and the sales/distribution process; taste of the product (if in food form); competitive price; delivery in a viable and functional form to the active site in the body in addition to optimizing growth conditions for the probiotic.

Products labeled as probiotics should conform to the guidelines established by UNFAO/WHO. The emerging trend is on developing consortia (different mixtures of probiotics) of different probiotic species and strain as a number of studies have shown that probiotics deliver superior impact on human health compared to the use of single probiotic strain. Particularly in treating ulcerative colitis, irritable bowel disease, diarrhea, improving hepatic insulin resistance in diabetic patients, enhancing the immune system of the consumer, and many more.[2] However, it is important to ensure that probiotic consortia do not cross-inhibit among them as it may reduce the efficacy of the probiotic product. Therefore, controlled human studies on probiotic products should be conducted before ensuring the effectiveness of the product.[32]

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