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Review Article

Regulatory Status of Probiotics in India: A Current Scenario

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Abstract: Probiotics are employed in therapeutic settings and for consumers who are typically healthy. However, probiotic intake can have both hypothetical and real negative effects. Probiotics should be used safely and effectively, which calls for clear, doable suggestions on how to proceed in light of the introduction of new probiotic strains and products as well as the expansion of their usage among vulnerable groups. The International Scientific Association for Probiotics and Prebiotics called a meeting to discuss and develop evidence-based recommendations on potential acute and long-term risks, risks to vulnerable populations, the necessity of adverse event reporting related to probiotic use, and the importance of probiotic product quality to match the needs of vulnerable populations. In the present review we focused the ICMR-DBT guidelines for the evaluation of the probiotics and current regulatory status with reference to the probiotics.

Keywords: Probiotics, Microbes, ICMR-DBT guideline & Regulatory affairs.

INTRODUCTION

It may take several years to develop a novel medication, involving discovery, nonclinical toxicological investigations, preliminary clinical trials, and extensive pivotal studies. The Health Authority's examination of the marketing permission application is the last stage before regulatory clearance for an applicant once they have produced this extensive body of data. It takes many months for regulatory authorities to review the data and determine if the benefit/risk profile is favourable, delaying the start of treatment for patients [1]. The concept of probiotics (which means, "for life") was introduced in early 20th century by Elie Metschnikoff, it however gained momentum only recently with considerable and significant advances in functional and health food market across the world. India is also fast emerging as a potential market for probiotics in food. The global probiotic market generated US $15.9 billion in 2008 and is expected to be worth US$ 32.6 billion by 2014 with a compound annual growth rate of 12.6% from 2009 to 2014. On the other hand the probiotic product industry in India was estimated to be around Rs 20.6 million with a projected annual growth rate of 22.6% until 2015. Probiotics, especially Lactobacillus and Bifidobacterium have been suggested to be associated with alleviation of lactose intolerance ; prevention and cure of viral, bacterial and antibiotic or radiotherapy induced diarrhoeas; immunomodulation; antimutagenic and anticarcinogenic effects; and even blood cholesterol reduction. The optimism associated with probiotics is, however, counter-balanced by skepticism as many “probiotic” products in the market are unreliable in content and unproven clinically. Also, Lactobacilli and Bifidobacteria have been rarely associated with human clinical infections which are likely to be a result of opportunistic infections especially in immunocompromised individuals. Many probiotic strains in use for several decades have been validated for their safety and efficacy and are therefore, safe to use. Any new strain used as a probiotic should be evaluated for safety and efficacy [2]. However, Enterococcus is emerging as an important cause of nosocomial infections and isolates are increasingly becoming vancomycin resistant. Some side effects, though rare with probiotics are:

i) Systemic infections,
ii) Deleterious metabolic activities,
iii) Excessive immune stimulation in susceptible individuals,
iv) Gene transfer.

The absence of pathogenicity and infectivity thus is an essential pre-requisite of probiotic safety. International guidelines on probiotics in food broadly

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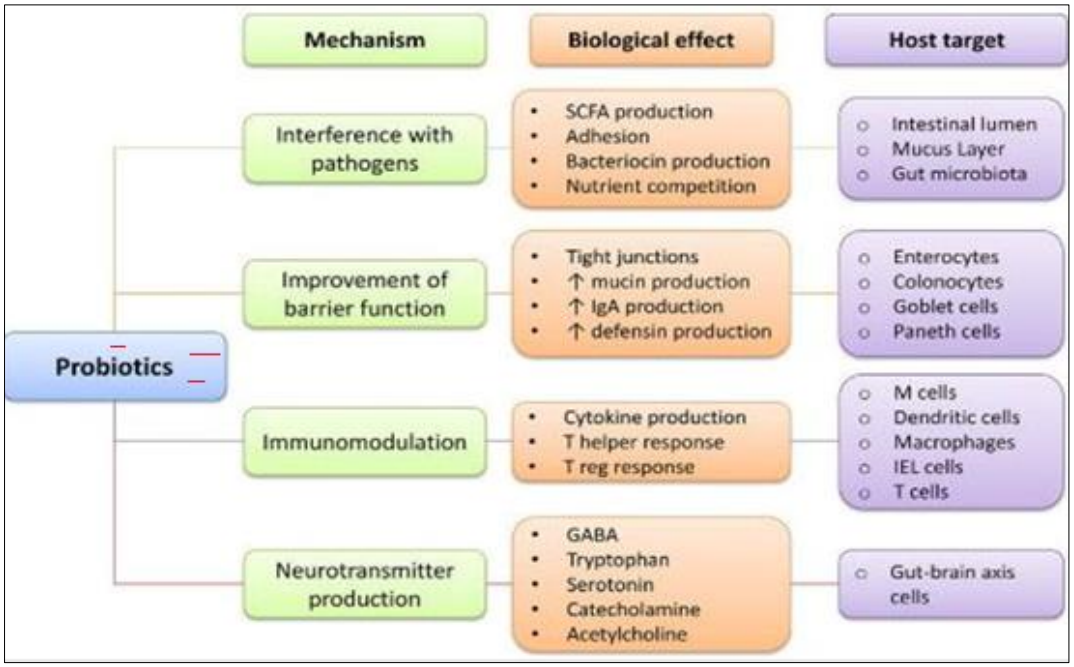
specify the kind of tests that may be required to determine the safety and to assess the health claim of a probiotic product in food. Such tests are based on the current understanding of the subject. The regulatory mechanism for probiotics differs from country to country and even within a country. In India there are no regulatory guidelines for probiotic foods. In the absence of any such standards and guidelines, there is great scope for spurious products with false claims being marketed. It, therefore, becomes imperative that these products fulfill some essential prerequisite conditions before being labeled as a 'probiotic product' [3].

Selection of bacteria used as probiotics [4]

Some principle for a lactic acid bacterium used as Probiotics:

a) Exert a beneficial effect on the host.
b) The cell number into foodstuff will become high during cell count and remain viable throughout the shelf life of the products.
c) Resistant when passage through GI tract.
d) Adhesion with human intestinal mucosa.
e) Property of antimicrobial to kill the pathogenic microorganisms.
f) Colonize in the lumen of GI tract.

Therapeutic effect of probiotics [5]



A holistic approach is therefore needed for formulating guidelines and regulations for evaluating the safety and efficacy of probiotics in India which should be in consonance with current international standards. Keeping in view the above, a Task Force was constituted by ICMR, comprising of experts from varied fields to develop guidelines for evaluation of probiotics in food in India. The Task Force took into consideration the guidelines available in different parts of the world and deliberated on the various aspects to be covered. The guidelines set forth in this document are meant to be followed for a strain or food to be termed as 'probiotic' for marketing in India.

Source of probiotics and effect on body [6-7]

Strain	Claimed potential effect in body
Bacillus coagulans GBI-30, 6086	Improve abdominal pain and bloating in IBS patients. May increase immune response to a viral challenge.
Bifidobacterium animalis subsp. lactis BB-12	May influence the gastrointestinal system.
Bifidobacterium longum subsp. infantis 35624	Possible relief from abdomenal pain/discomfort, bloating and constipation.
Lactobacillus acidophilus NCFM	Reduce the side effects of antibiotic therapy.
Lactobacillus paracasei St11 (or NCC2461) Lactobacillus johnsonii La1 (= Lactobacillus LC1, Lactobacillus johnsonii NCC533)	Reduce incidence of H. pylori-caused gastritis and may reduce inflammation.
Lactobacillus plantarum 299v	May affect symptoms of IBS.
Lactobacillus reuteri ATCC 55730	Diarrhea mitigation in children, decreased crying in infantile

Strain	Claimed potential effect in body
(Lactobacillus reuteri SD2112)	colic, H. pylori infection, antibiotic-associated side-effects, fever and diarrhea in children and number of sick days in adults.
Lactobacillus reuteri Protectis (DSM 17938, daughter strain of ATCC 55730)	Evidence for shortened duration of diarrhea in children, decreased crying in infantile colic, reduced risk of diarrhea in children, may affect constipation and functional abdominal pain in children.
Lactobacillus reuteri Prodentis (DSM 17938/ATCC 55730 and ATCC PTA 5289 in combination) for oral health	Reduction of oral malodor, evidence for reduction of risk factors for caries.
Saccharomyces boulardii	Treatment and Prevention of antibiotic-associated diarrhea and acute diarrhea.
Tested as mixture: Lactobacillus rhamnosus GR-1 & Lactobacillus reuteri RC-14	Oral ingestion resulted in vaginal colonisation and reduced vaginitis.
Tested as mixture: Lactobacillus acidophilus NCFM & Bifidobacterium bifidum BB-12	Reduced C. difficile–associated disease.

ICMR-DBT Guideline for Evaluation of Probiotics in Food [8-10]

I. Scope: The guidelines deal with the use of probiotics in food and provide requirements for assessment of safety and efficacy of the probiotic strain and health claims and labeling of products with probiotics.

II. Definition of Probiotics: Probiotics are 'live microorganisms which when administered in adequate amounts confer a health benefit on the host' (FAO/WHO, 2002).

III. Genus, species and strain identification: Strain identity is important to link a strain to a specific health effect as well as to enable accurate surveillance and epidemiological studies. Both phenotypic and genotypic tests should be done using validated standard methodology. Nomenclature of the bacteria must conform to the current, scientifically recognized names as per the International Committee on Systematic of Prokaryotes (ICPS) (available at http://www.the-icsp.org/). The current molecular techniques used for identification include PCR based techniques; 16S rRNA sequencing and DNA finger printing techniques like ribotyping and Pulsed Field Gel Electrophoresis (PFGE).

It is recommended that probiotic strains in use in India should be deposited in an internationally recognized culture collection/repository.

IV. In vitro tests to screen potential probiotic strains:

The following in vitro tests with standard methodology are recommended for screening putative probiotic strains:

1. Resistance to gastric acidity.
2. Bile acid resistance
3. Antimicrobial activity against potentially pathogenic bacteria (acid and bacteriocin production)
4. Ability to reduce pathogen adhesion to surfaces
5. Bile salt hydrolase activity

These tests are based on the hostile gut environment which they mimic under in vitro conditions. The cultures evaluated as probiotics based on these tests should be subjected to preclinical validation in appropriate animal models before clinical trials are conducted in human subjects.

V. In vivo safety studies in animal models: Assessment of the acute, subacute and chronic toxicity of ingestion of extremely large amounts of probiotics should be carried out for all potential strains. Such assessment may not be necessary for strains with established documented use.

VI. In vivo efficacy studies in animal models: To substantiate in vitro effects, appropriate, validated animal models must be used first, prior to human trials.

VII. Evaluation of safety of probiotics for human use: In recognition of the importance of assuring safety, even among group of bacteria that are Generally Recognized as Safe (GRAS), probiotics strains needs to be characterized at a minimum with the following tests:

1. Determination of antibiotic resistance patterns. It should be ascertained that any given probiotic strain is not at significant risk about transferable antibiotic resistance as well as assessment of undesirable side-effects.
2. If the strain under evaluation belongs to a species that is a known mammalian toxin producer or of hemolytic potential, it must be tested for toxin production and hemolytic activity respectively. Assessment of lack of infectivity by a probiotics strain in immunocompromised individuals would be an added measure.

VIII. Evaluation of efficacy studies in humans: The principal outcome of efficacy studies on probiotics should be proven with similar benefits in human trials, such as statistically and clinically significant improvement in condition, symptoms, signs, well-being or quality of life, reduced risk of disease or longer time to next occurrence or faster recovery from illness. Each of the parameter should have proven correlation with the probiotics tested. Probiotics delivered in food may not be tested in Phase 3 studies (effectiveness), unless the product makes a specific health claim wherein it becomes imperative to generate the required evidence

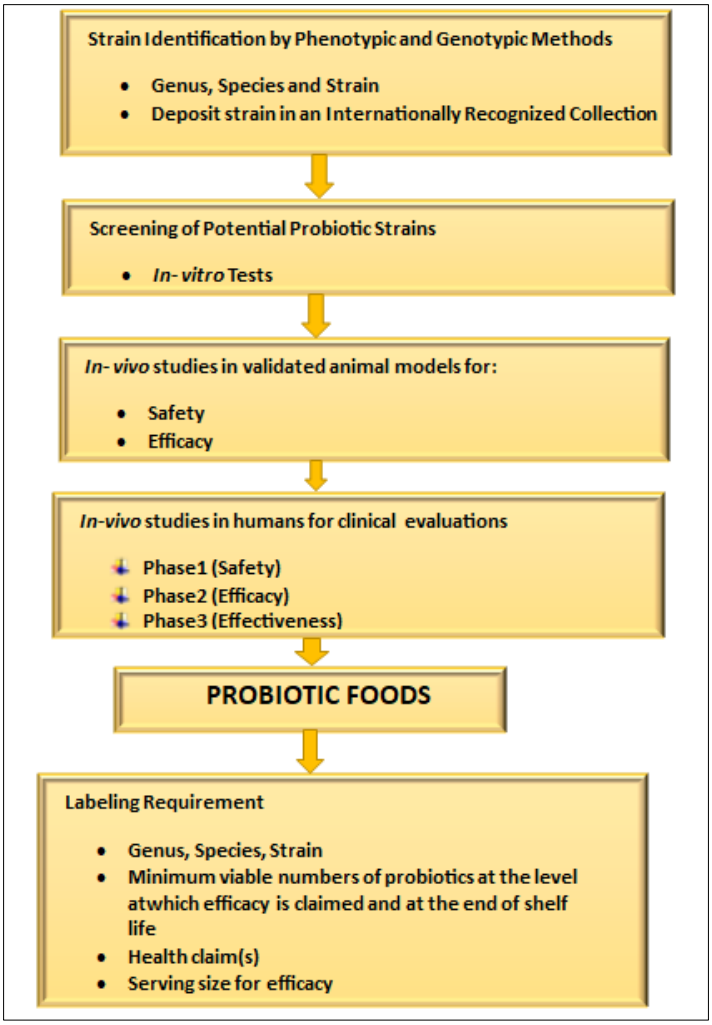
necessitating carrying out Phase 3 studies. If a probiotic food has a record of documented long and safe use outside the country, the data regarding this could be reviewed and deemed as enough to its marketing within the country. However, labeling of health benefits may require evaluation in a different manner. While considering studies done abroad, efficacy studies of probiotics (which are of proven benefit in 'other' populations) should also be conducted on Indian subjects. It is recommended that such 'bridging' human trials should comply with the principles laid down by the Drug Regulatory Authority. Adverse effects, if any, should be monitored and incidents reported to the appropriate authority.

IX. Effective dosage of probiotic strain / strains: The minimal effective dose or the level of viable cells of the probiotic strain in terms of cfu/ml/day in the carrier food that demonstrates general health promoting functions or wellbeing or specific health claims in target population should be clearly indicated.

Labeling Requirements: In addition to the general labeling requirements under the food laws, the following information should also be mentioned on the label:

- Genus, species and strain designation following the standard international nomenclature.
- The minimum viable numbers of each probiotic strain should be specified at the level at which efficacy is claimed and at the end of shelf- life.
- Evidence-based health claim(s) should be clearly stated.
- The suggested serving size to deliver the minimum effective quantity of the probiotic related to the health claim.
- Proper storage conditions to be mentioned.

Manufacturing and Handling Procedures: Adequate quality assurance programmes should be in place. Good Manufacturing Practices should be followed in the manufacture of probiotic foods. The Codex General Principles of Food Hygiene and Guidelines for Application of Hazard Analysis and Critical Control Point (HACCP) should be followed.



Guidelines for evaluation of candidate probiotic strains screening of potential probiotic strains

SUMMARY AND CONCLUSION

By controlling gastrointestinal disorders, antibiotic-induced diarrheal illnesses, lactose intolerance, irritable bowel syndrome, diabetes, cancer, and vaginal candidiasis, the above study intended to provide probiotic health advantages. A variety of sources, including dairy products, non-dairy products, and supplemental items, might yield LAB. Probiotics are also present in traditional fermented food items. Due to their abundance in bacteria such as Lactobacillus, Bifidobacterium, Saccharomyces, Enterococcus, Streptococcus, Pediococcus, Leuconostoc, Bacillus, and E. coli, these benefits may encourage the use of probiotics in food. Over the past ten years, the Indian market has seen an increased flood of probiotic goods. However, there hasn't been a methodical examination of probiotics in food to guarantee their efficacy and safety. In order to create rules for the regulation of probiotic goods in the nation, the Indian Council of Medical Research (ICMR) and the Department of Biotechnology (DBT) took the initiative. These rules outline the requirements for a product or strain to be classified as "probiotic." These comprise strain identification, probiotic characteristic in vitro screening, animal safety research, and effectiveness in vivo animal and human trials. The regulations mandate that probiotic goods be labelled with strain information and viability.

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