1 Probiotics and Health: From History to Future (Barry R. Goldin).

1.1 Early history of the use of microorganisms for human benefit.

1.2 Overview of probiotic studies and results for the past years.

1.3 Current evidence for probiotic health benefits.

1.3.1 Lactose intolerance.

1.3.2 Inflammatory bowel disease.

1.3.3 Treatment of gastroenteritis.

1.3.4 Cholesterol lowering.

1.3.5 Treatment for urogenital infections.

1.3.6 Treatment of allergic reactions.

1.3.7 Prevention of dental caries.

1.3.8 Treatment and prevention of cancer by probiotics.

1.3.9 Additional health benefits attributed to probiotics.

1.3.10 Conclusions based on past and present use of probiotics for health applications.

1.4 Nutritional effects of probiotics.

1.5 Future development and uses of probiotics for health application.

1.5.1 Probiotics as a platform for delivery of drugs, enzymes, hormones, nutrients and micronutrients.

1.5.2 Toxin sequestration.

1.5.3 Carcinogen detoxification.

1.5.4 Antibody production.

1.5.5 Treatment for enzyme deficiencies.

1.5.6 Other potential future directions for probiotics for medical use.

1.6 Conclusions.

2 The World’s Oldest Probiotic: Perspectives for Health Claims (Tomoyuki Sako).
2.1 From theory to practice: the challenge of Dr Minoru Shirota.

2.1.1 The discovery of *Lactobacillus casei* strain Shirota.

2.1.2 Early studies in Japan: the first clinical study era for Yakult and *L. casei* Shirota.

2.1.3 Probiotic definition and the *L. casei* Shirota strain.

2.2 Health benefits of Yakult and *L. casei* Shirota.

2.2.1 Identification and characterisation of *L. casei* Shirota.

2.2.2 Beneficial modulation of the intestinal microbiota.

2.2.3 Improvement of stool consistency.

2.2.4 Protection from infection.

2.2.5 Immune modulation activity.

2.2.6 Prophylactic effect of *L. casei* Shirota on cancer development.

2.3 Safety.

2.4 Health claims for *L. casei* Shirota and the product Yakult.

2.5 Current perspectives.


3.1 Introduction.

3.2 Isolating a potential probiotic strain.

3.3 Producing probiotic strains on a large scale.

3.4 Producing products containing probiotics.

3.4.1 Fermented milk products.

3.4.2 Cheese.

3.4.3 Non-fermented milk drinks.

3.4.4 Fruit and vegetable juices.

3.4.5 Dried products.
3.5 Probiotic products and feeding trials.

3.6 Conclusion.

4 Probiotics and Health Claims: Challenges for Tailoring their Efficacy
(Christophe Chassard, Franck Grattepanche and Christophe Lacroix).

4.1 Introduction.

4.2 Current selection of probiotics: setting the scene for tailoring probiotics.

4.2.1 Safety considerations.

4.2.2 Technological considerations.

4.2.3 Functionality and health benefits.

4.3 Improving the assessment of probiosis.

4.3.1 In vitro models for the assessment of probiosis.

4.3.2 In vivo models for the assessment of probiosis.

4.3.3 Clinical trials for the assessment of probiosis.

4.4 Improving the discovery of probiotic strains

4.4.1 Exploring and isolating bacterial diversity.

4.4.2 New generations of probiotics from new bacterial genera and with new targeted functions.

4.5 Improving probiotic specificity.

4.5.1 Future therapeutic strategies: combination of strains?

4.5.2 Nutritional manipulation.

4.5.3 Genetic engineering.

4.6 Conclusions.

5 Probiotics: from Origin to Labeling from a European and Brazilian Perspective.
(Célia Lucia Ferreira, Marcos Magalhães, Miguel Gueimonde and Seppo Salminen).

5.1 Introduction.

5.2 Terminology and probiotics.
5.3 Health claim regulation in the European Union.

5.4 Health claims in Europe.

5.5 Health claim regulation in Brazil.

5.6 Defining health claims.

5.6.1 Characterization of probiotic bacteria.

5.6.2 Safety assessment.

5.6.3 Human intervention studies for health claims.

5.6.4 Totality of supporting evidence.

5.7 Specific challenges for probiotics.

5.7.1 Viability.

5.7.2 Clinical studies demonstrating efficacy of probiotics in healthy subjects.

5.7.3 Challenges in regulatory areas.

6 Substantiating Health Benefit Claims for Probiotics in the United States (Mary Ellen Sanders).

6.1 Introduction.

6.1.1 Probiotics and health benefits.

6.1.2 Probiotics: a term often misused.

6.2 Health benefit claims allowable in the United States.

6.2.1 FDA and FTC standards.

6.2.2 Structure/function claims.

6.2.3 Health claims.

6.2.4 Medical food claims.

6.3 Substantiation of health benefit claims for probiotics.

6.3.1 Overriding considerations.

6.3.2 Specific issues related to human efficacy studies.

6.3.3 Key considerations for probiotic efficacy substantiation.
6.4 Bridging the gap between the US consumer, probiotic science and commercial products.

6.5 Conclusions.

7 Health Claims and Dietary Guidance in the United States: Case “Reduced Cardiovascular Disease Risk” (Alice H. Lichtenstein).

7.1 Introduction.

7.2 Types of health claims.

7.2.1 Definition.

7.2.2 Authorized health claims.

7.2.3 Qualified health claims.

7.2.4 Structure/function claims.

7.2.5 Nutrient content claims.

7.3 Legislation governing US health claims.

7.3.1 Nutrition Labeling and Education Act (NLEA).

7.3.2 Food and Drug Administration Modernization Act (FDAMA).

7.3.3 Consumer Health Information for Better Nutrition Initiative (2003).

7.4 Dietary guidance to reduce cardiovascular disease risk.

7.4.1 Dietary Guidelines for Americans.

7.4.2 National Cholesterol Education Program.

7.4.3 Dietary Reference Intakes.

7.4.4 American Heart Association.

7.4.5 American Diabetes Association.

7.4.6 American Cancer Society.

7.4.7 Case study: evolution of Dietary Guidelines for Americans.

7.5 Current challenges.

8 Probiotics and Health Claims: a Japanese Perspective (Fang He and Yoshimi Benno).
8.1 Introduction.
8.2 FOSHU health claims.
8.2.1 History of FOSHU.
8.2.2 Specifics of FOSHU health claims.
8.2.3 Procedure for obtaining permission for FOSHU.
8.2.4 FOSHU health claim for probiotics: gastrointestinal conditions.
8.3 Non-FOSHU health claims for probiotics in Japan.

9 Regulation of Probiotics in China (Anu Lahteenmäki-Uutela).
9.1 Introduction.
9.2 Health food or medicine?
9.3 Health food regulations.
9.4 Novel food regulation.

10 Probiotics and Health Claims: an Indian Perspective (Jashbhai B. Prajapati and Nagendra P. Shah).
10.1 The background.
10.2 The status.
10.3 Animal studies.
10.3.1 Chicken.
10.3.2 Albino rats.
10.3.3 Pigs.
10.3.4 Sheep.
10.3.5 Calves.
10.3.6 Fish.
10.3.7 Post-larvae.
10.4 Human studies.
10.4.1 Probiotics in gut microbiology.
10.4.2 Probiotics in diarrheal diseases.

10.4.3 Effects on lipid profile.

10.4.4 Morbidity and nutritional status.

10.5 An Indian perspective on regulation of probiotics.

11 The Role of Meta-analysis in the Evaluation of Clinical Trials on Probiotics (Hania Szajewska).

11.1 Introduction.

11.2 What is a systematic review? What is a meta-analysis?

11.3 How to conduct a systematic review.

11.3.1 Formulation of the review question (the problem).

11.3.2 Searching.

11.3.3 Selecting studies and collecting data.

11.3.4 Assessment of methodological quality (i.e. the risk of bias in included trials).

11.3.5 Analysing the data and presenting the results.

11.4 Why perform a meta-analysis?

11.5 Heterogeneity.

11.6 How to interpret a forest plot.

11.7 Critical appraisal of a systematic review.

11.8 Published meta-analyses on the effects of probiotics.

11.8.1 Acute gastroenteritis.

11.8.2 Antibiotic-associated diarrhea.

11.8.3 Clostridium difficile-associated diarrhea.

11.8.4 Traveler’s diarrhea.

11.8.5 Necrotizing enterocolitis.

11.8.6 Helicobacter pylori infection.

11.8.7 Functional gastrointestinal disorders.
11.8.8 Irritable bowel syndrome.
11.8.9 Inflammatory bowel disease.
11.8.10 Functional constipation.
11.8.11 Allergy prevention.
11.8.12 Respiratory tract infections.
11.9 Is a meta-analytical approach appropriate for assessing the efficacy of probiotics?
11.9.1 Arguments for pooling data.
11.9.2 Arguments against pooling data.
11.10 What could be the solution?
11.11 Unpublished data.
11.12 Quality of included trials.
11.13 Inconclusive systematic reviews and meta-analyses.
11.14 Opposite conclusions.
11.15 Summary and key messages.

12.1 Introduction.
12.2 Mycotoxin problem.
12.3 Lactobacillus rhamnosus strain effectively binds aflatoxin: in vitro findings.
12.4 Animal models for studying the aflatoxin–probiotic interaction.
12.5 Field studies with Lactobacillus rhamnosus strain in aflatoxin-exposed populations.

13 Probiotics Research: the Pediatric Perspective (Karl Zwiauer).
13.1 Introduction.
13.2 Development of the gastrointestinal flora postnatally.
13.3 Probiotics in infant nutrition.
13.3.1 Growth of healthy infants.
13.3.2 Probiotics in preterm infants.
13.3.3 Safety concerns.
13.4 Clinical effect of probiotics in children.
13.4.1 Prevention of allergic disease: food hypersensitivity.
13.4.2 Atopic dermatitis.
13.4.3 Prevention of antibiotic-associated diarrhea.
13.4.4 Acute gastroenteritis and community-acquired diarrhea.
13.4.5 Irritable bowel syndrome and constipation.
13.4.6 Infantile colic.
13.4.7 Inflammatory bowel disease.
13.4.8 Oral health effects: caries.
13.4.9 Other clinical conditions.
13.5 Summary and key messages.

14 Probiotics and Health Claims Related to OTC Products and Pharmaceutical Preparations (Frank M. Unger and Helmut Viernstein).

14.1 Introduction.
14.2 Production, processing and formulation of probiotic cultures for pharmaceutical purposes.
14.3 Clinical studies.
14.3.1 Gastroenterology.
14.3.2 Gynecology.
14.3.3 Dentistry/stomatology.
14.4 Evaluation and outlook.
14.4.1 Antibiotic-associated diarrhea and Clostridium difficile disease.
14.4.2 Traveler's diarrhea.
14.4.3 *Helicobacter pylori* infection.

14.4.4 Lactose intolerance.

14.4.5 Irritable bowel syndrome.

14.4.6 Ulcerative colitis.

14.4.7 Pouchitis.

14.4.8 Crohn’s disease.

14.4.9 Bacterial vaginosis.

14.4.10 Gingivitis, reduction of plaque and alleviation of gum bleeding.

14.4.11 Selected experimental approaches to probiotic products with new properties and in new indications.

15 Probiotics and Health Claims: the Perspective of the Feed Industry (Anja Meieregger, Elisabeth Mayrhuber and Hans Peter Lettner).

15.1 Introduction and history.

15.2 Feed probiotics versus food probiotics.

15.2.1 Gram-positive non-sporulating bacteria.

15.2.2 *Bacillus* species.

15.2.3 Yeasts.

15.2.4 Filamentous fungi.

15.3 Efficacy.

15.4 Feed probiotics.

15.4.1 Fundamentals.

15.4.2 Industrial production.

15.5 Authorisation processes.

15.6 Probiotics as performance enhancers: conclusions.

16 Developing LGG®Extra, a Probiotic Multispecies Combination (Maija Saxelin, Evelliina Myllyluoma and Riitta Korpela).

16.1 Introduction.
16.2 Strain selection.

16.3 Probiotic characteristics of the strains.

16.3.1 Gastrointestinal persistence and colonisation.

16.3.2 Influence on human intestinal microbiota.

16.3.3 Immunological effects in vitro.

16.3.4 Potential for reducing dietary toxins.

16.3.5 Safety aspects.

16.4 Clinical studies on the probiotic multispecies LGG®Extra combination.

16.4.1 Relieving symptoms of irritable bowel syndrome.

16.4.2 Eradication of *Helicobacter pylori* and *Candida*

16.4.3 Other research areas.

16.5 Conclusions.

**17 Probiotics and Health Claims: How to Be Met by SMEs?** (Miguel Gueimonde and Sampo J. Lahtinen).

17.1 Introduction.

17.2 Developing proprietary probiotic strains.

17.3 Probiotic research by SMEs using strains from larger companies.

17.4 Example of successful probiotic research program by an SME company: the development of probiotic strains *Bifidobacterium longum* and *B. longum C*

**18 Probiotic Products: How Can They Meet the Requirements?** (Wolfgang Kneifel).

18.1 Introduction.

18.2 Quality criteria of probiotics.

18.2.1 Basic composition and nutrient profile.

18.2.2 Nature, identity and safety of probiotic strains.

18.2.3 Viability and probiotic viable count.

18.3 Future perspectives.

19.1 Introduction.

19.2 Identifying the hurdles.

19.2.1 Characterisation.

19.2.2 Relationship to health.

19.2.3 Scientific substantiation.

19.3 Approaching the hurdles.

19.3.1 Hurdle characterisation.

19.3.2 Relationship to health.

19.3.3 Scientific substantiation.

19.4 New perspectives.

19.4.1 General considerations.

19.4.2 Functional genomics.

19.5 Conclusions.

20 Probiotics and Innovation (Jean-Michel Antoine, Jean-Michel Faurie, Raish Oozeer, Johan van Hylckama Vlieg, Jan Knol, Herwig Bachmann and Joël Doré).

20.1 Introduction.

20.1.1 Early history.

20.1.2 Recent history.

20.2 Not all probiotics are the same: genomic perspective.

20.3 Not all probiotic foods are the same: functional perspective.

20.4 Not all probiotics are cross-talking in the same way: dialogue with the host.

20.4.1 Dialogue with the human intestinal microbiota: a logical trigger for innovation.

20.4.2 Novel functional targets for the human intestinal microbiota.

20.5 European regulatory perspective: a threat or an opportunity?
20.5.1 European regulatory perspective: a threat?

20.5.2 For innovation in probiotics, the present regulatory requirements are an opportunity.

20.6 Conclusion.