Wei Chen · Arjan Narbad

Lactic Acid Bacteria in Foodborne Hazards Reduction

Physiology to Practice

Springer

Lactic Acid Bacteria in Foodborne Hazards Reduction

Wei Chen • Arjan Narbad

Lactic Acid Bacteria in Foodborne Hazards Reduction

Physiology to Practice

Springer

Wei Chen
School of Food Science and Technology
Jiangnan University
Wuxi, Jiangsu, China

Arjan Narbad
Quadram Institute Bioscience
Norwich, Norfolk, UK

ISBN 978-981-13-1558-9 ISBN 978-981-13-1559-6 (eBook)
https://doi.org/10.1007/978-981-13-1559-6

Library of Congress Control Number: 2018959743

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Contents

1 Introduction 1
1.1 Background 2
1.2 The Habitats of Lactic Acid Bacteria 4
1.3 The Current Taxonomy of Lactic Acid Bacteria 5
1.4 The Safety of Lactic Acid Bacteria 7
1.5 The Role and Importance of Lactic Acid Bacteria 10
1.6 Lactic Acid Bacteria, to the Future and Beyond 14
References 15

2 Genomic Analysis of Lactic Acid Bacteria and Their Applications 21
2.1 Introduction 22
2.2 DNA Sequencing and Its Application on Genomic Analyses of Lactic Acid Bacteria 22
2.3 Plasmids of LAB and Their Functions 25
2.3.1 New Developments in the Area of LAB Plasmids 26
2.3.2 The Function of LAB Plasmids and Their Relevance to Research 28
2.3.3 The Relevance to Food Industry 29
2.4 The Gene-Based Techniques for Rapid Identification of LAB Strains 30
2.4.1 16S Ribosomal DNA Sequencing and Genetic Fingerprinting 30
2.4.2 Fluorescent In Situ Hybridization 35
2.5 Exploiting Genetic Information to Explore the Functions of LAB 36
2.5.1 LAB in the Gut 37
2.5.2 LAB as Probiotics for Human Health 38
References 40

3 Proteins and Exopolysaccharides of Lactic Acid Bacteria 51
3.1 Introduction 52
3.2 Bacteriocins 52

3.2.1 The Classification and Chemical Structure of Bacteriocins 52
3.2.2 The Genetics and Regulation of Bacteriocins 60
3.2.3 The Applications of Bacteriocins Derived from LAB 62
3.3 Exopolysaccharide (EPS) 66
3.3.1 The Classification and Chemical Structure of EPS 66
3.3.2 The Biosynthesis and Genetics of EPS in LAB 70
3.3.3 The Physiological Functionality of EPS 72
3.3.4 The Technological Functionality of EPS 75
References 76

4 Metabolites of Lactic Acid Bacteria 87
4.1 Introduction 88
4.2 Aromatic Metabolites 89
4.2.1 The Formation of Flavor Compounds 89
4.2.2 Representative Flavor Compounds 90
4.3 Organic Acid 92
4.3.1 Lactic Acid 92
4.3.2 Acetic Acid 95
4.3.3 Gamma-Aminobutyric Acid (GABA) 96
4.3.4 Conjugated Linoleic Acid 96
4.4 Bacteriocins and Bacteriocin-Like Peptides and Proteins 99
4.4.1 Classification of Bacteriocins 99
4.4.2 Applications of LAB Bacteriocins 101
4.5 Other Metabolites 103
4.5.1 Vitamins 103
4.5.2 Hydrogen Peroxide 106
4.6 Conclusions 107
References 107

5 Environmental Stress Responses of Lactic Acid Bacteria 115
5.1 Response of Lactic Acid Bacteria to Acid Stress 116
5.1.1 Introduction 116
5.1.2 The Metabolic Responses to Acid Stress by LAB 117
5.1.3 Signal Transduction 118
5.2 Responses of Lactic Acid Bacteria to Bile Stress 119
5.2.1 Introduction 119
5.2.2 The Mechanism Responses to Bile Stress in Lactic Acid Bacteria 120
5.2.3 Bile Salt Hydrolases of LAB 121
5.2.4 Scope of Bile Salt Hydrolases of LAB 122
5.3 Responses of Lactic Acid Bacteria to Osmotic Stress 122
5.3.1 Introduction 122
5.3.2 Fundamental Principles of Responses to Osmotic Stress in Lactic Acid Bacteria 123
5.3.3 Regulatory Mechanisms in the Osmotic Responses of Lactic Acid Bacteria 124

5.4 Responses of Lactic Acid Bacteria to Oxidative Stress 125
5.4.1 Introduction 125
5.4.2 Metabolic Responses to Oxidative Stress in Lactic Acid Bacteria 126
5.4.3 Regulatory Mechanisms in the Oxidative Stress of Lactic Acid Bacteria 127
5.5 Responses of Lactic Acid Bacteria to Cold Stress 127
5.5.1 Introduction 127
5.5.2 Regulatory Mechanisms in the Cold Responses of Lactic Acid Bacteria 129
References 133

6 Lactic Acid Bacteria-Based Food Fermentations 141
6.1 Biodiversity of Fermented Products 142
6.2 Fermented Dairy Products 143
6.2.1 Biochemistry of Fermented Dairy Products 145
6.2.2 Microbiology of Fermented Dairy Products 150
6.3 Fermented Cereal Products 156
6.3.1 Introduction 156
6.3.2 LAB in Cereal-Based Products 156
6.3.3 Function of Lactic Acid Bacteria Communities in Cereal-Based Products 158
6.4 Fermented Vegetable Products 164
6.4.1 History and Development of Fermented Vegetable 164
6.4.2 LAB Microflora in Fermented Vegetable 165
6.4.3 Function of LAB Microflora in Fermented Vegetable 166
6.4.4 Effects of Lactic Acid Bacteria on the Probiotic Properties of Fermented Vegetable 168
6.4.5 Lactic Acid Bacteria and Safety of Fermented Vegetable 168
6.5 Functional Fermented Products 170
References 170

7 Lactic Acid Bacteria and Foodborne Pathogens 183
7.1 Introduction 184
7.1.1 Foodborne Pathogens and Hazards 185
7.1.2 Strategy of Controlling Foodborne Pathogens 187
7.1.3 The Potential of Probiotics to Prevent Foodborne Pathogens 189
7.2 Probiotics to Control Foodborne Pathogens 189
7.2.1 Probiotics to Control Bacterial Pathogens 190
7.2.2 Probiotics to Control Fungus and Viral Pathogens 195
7.2.3 The Mechanism of Probiotics Inhibiting Pathogenic Bacteria 197
7.2.4 Prebiotics 199

7.3 The Application of Probiotics for Animal Health 203
7.3.1 Probiotics in Treatment of Animal Diseases 203
7.3.2 The Application of Probiotics in Feed 205
7.4 Conclusion and Future Perspectives 206
References 207

8 Applications of Lactic Acid Bacteria in Heavy Metal Pollution Environment 213
8.1 Introduction 214
8.2 Heavy Metal Removal by Lactic Acid Bacteria In Vitro 217
8.2.1 Heavy Metal Tolerance 217
8.2.2 Heavy Metal Binding 219
8.2.3 Heavy Metal Removal from Fruit and Vegetable Juices 225
8.3 Heavy Metal Toxicity Alleviation by Lactic Acid Bacteria In Vivo 227
8.3.1 Decrease of Heavy Metal Accumulation 227
8.3.2 Recovery of Heavy Metal-Induced Dysfunction 230
8.3.3 Alleviation of Heavy Metal-Induced Oxidative Stress 233
References 236

9 Lactic Acid Bacteria and Food-Based Allergy 249
9.1 Food Allergy 250
9.1.1 Symptoms and Severity 251
9.1.2 The Mechanism of Allergic Reactions 252
9.1.3 Oral Tolerance and the Prevention of Food Allergy 254
9.2 Lactic Acid Bacteria and Immune System 256
9.2.1 Mucosal Immune System 256
9.2.2 Effects of LAB on the Immune Response 257
9.3 Lactic Acid Bacteria and Allergy 260
9.3.1 Regulation of Cellular Immunity 261
9.3.2 Regulation of Humoral Immunity 262
9.4 Mucosal Vaccines for Food Allergy 263
9.4.1 Expression Systems of *L. lactis* 263
9.4.2 Engineered *L. lactis* for the Production Heterologous Proteins 265
9.4.3 Engineered *L. lactis* as Vaccine Delivery System 266
References 267

10 Lactic Acid Bacteria and Biotoxins 275
10.1 Biotoxins and the Hazards to Human Health 276
10.1.1 Introduction 276
10.1.2 Aflatoxin and the Harm on Human Health 276
10.1.3 Patulin and the Harm on Human Health 278
10.1.4 Ochratoxin and the Harm on Human Health 279
10.1.5 Microcystin-LR and the Harm on Human Health 280
10.1.6 Other Biotoxins 281

10.2 The Methods of Removing Biotoxins 282
10.2.1 Introduction 282
10.2.2 Traditional Methods of Removing Biotoxins 282
10.2.3 New Methods of Removing Biotoxins 284
10.3 Potential of LAB to Reduce Biotoxins 287
10.3.1 Introduction 287
10.3.2 The Application of Lactic Acid Bacteria in Reducing Effects of Biotoxins 288
10.3.3 The Mechanism of Biotoxins Adsorption Using Lactic Acid Bacteria 294
10.3.4 The Degradation of Biotoxins by Lactic Acid Bacteria 298
References 300

Chapter 1
Introduction

Wei Chen and Linlin Wang

Contents

1.1 Background 2
1.2 The Habitats of Lactic Acid Bacteria 4
1.3 The Current Taxonomy of Lactic Acid Bacteria 5
1.4 The Safety of Lactic Acid Bacteria 7
1.5 The Role and Importance of Lactic Acid Bacteria 10
1.6 Lactic Acid Bacteria, to the Future and Beyond 14
References 15

Abstract Food microbiology is the science which studies microorganisms that inhabit, create, or contaminate foods, which normally are of plant and animal origins. Among food-related microorganisms studies so far, probiotic lactic acid bacteria draw extensive attention for their unquestionable importance in food, industry, and health-related fields. This chapter gives a brief introduction to the historical background, habitats, taxonomy, role, and significance of lactic acid bacteria and ends with some thoughts about future development in this field. Taken together, this general introduction hopefully helps the reader to familiarize with the subject and makes the digestion of the more specific aspects easier.

Keywords Lactic acid bacteria · Habitats · Taxonomy · Safety

Food microbiology is the science which studies microorganisms that inhabit, create, or contaminate foods, which normally are of plant and animal origins. Among food-related microorganisms studies so far, probiotic lactic acid bacteria draw extensive attention for their unquestionable importance in food, industry, and health-related fields (Gaspar et al. 2013; Hugenholtz et al. 2002; Lee and Hase 2014; Matthews et al. 2004; Sanders et al. 2013; Turnbaugh 2012). This chapter gives a brief introduction to

W. Chen (✉) · L. Wang
School of Food Science and Technology, Jiangnan University, Wuxi, Jiangsu, China
e-mail: weichen@jiangnan.edu.cn

W. Chen, A. Narbad, *Lactic Acid Bacteria in Foodborne Hazards Reduction*,
https://doi.org/10.1007/978-981-13-1559-6_1

the historical background, habitats, taxonomy, role, and significance of lactic acid bacteria and ends with some thoughts about future development in this field.

1.1 Background

The first and most important question is what lactic acid bacteria are. Lactic acid bacteria are normally defined as a group of Gram-positive, catalase-negative, and nonsporulating, aero-tolerant, acid-tolerant, and strictly fermentative cocci or rods bacteria which primarily ferment carbohydrates to lactic acid as one of the main fermentation products (Hugenholtz et al. 2002). Lactic acid bacteria lack cytochromes and are unable to synthesize porphyrins. Its features can vary under certain conditions. Catalase and cytochromes may be formed in the presence of hemes, and lactic acid can be further metabolized, resulting in lower lactic acid concentrations.

Lactic acid bacteria, which are widely distributed in nature, and very rich in biodiversity, are closely related to human production and life. Lactic acid bacteria are valuable biological resources of human and have important social and economic values. Based on reliable archaeological evidence, the history of human use of lactic acid bacteria can be traced back to more than 10,000 years ago. In the long history, the utilization of lactic acid bacteria has made outstanding contributions to the development and practice of human society. For example, thousands of years ago, lactic acid bacteria were widely used in cheese, pickles, yogurt, and other foods and drinks. Among them, yogurt is regarded as "God's gift" by the ancient nomadic people. Although the ancients did not know the principle of yogurt fermentation, they know that yogurt had the magical function of preventing diseases and ensuring health. The scientific research and real application of lactic acid bacteria began in the 1850s. After that, scientists from all over the world made unremitting efforts; therefore, the research on lactic acid bacteria had attracted more and more attention. Russian scientist Metchnikoff who is the Nobel Prize winner put forward clearly in the "longevity theory" that there were a lot of lactic acid bacteria in yogurt. These large number of lactic acid bacteria inhibit the growth of harmful bacteria, reduce the production of bacterial toxins, and play an important role in maintaining health and prolonging life of the residents in the Balkan island. China, which has rich food fermentation resources, is one of the earliest countries to utilize lactic acid bacteria to ferment food. At present, almost every nation has its own lactic acid bacteria fermented food. For example, Mongolian, Kazakh, and Tibetan in Xinjiang, Inner Mongolia, and Tibet have their own traditional fermented koumiss, yogurt sour milk, sour camel milk, and cheese. Milk cake in Yunnan and fermented sour meat and fish (Pradeep et al. 2014) in Hunan, Guizhou, Guangxi, and other regions. Nowadays, people have clearly realized the probiotic function of lactic acid bacteria, and the resources of lactic acid bacteria are being widely applied. Although they are widely present in nature ever in our digestive systems and man had early learned to live together with them for thousands of years, it remains difficult to pinpoint the precise beginnings of human being's awareness of the roles of lactic acid bacteria in our foods. Several significant dates and events in the history of lactic acid bacteria are listed below (Table 1.1).

Table 1.1 Significant events in the history of the lactic acid bacteria

Decade	Event
1000 B.C.E	Start making pickles in China (pickled vegetables)
1780	Scheele identified lactic acid as the principal acid in sour milk (Scheele 1780)
1847	C. Blondeau determined that lactic acid is the product of certain microbial fermentation (Blondeau 1847)
1857	Louis Pasteur showed that microorganisms cause the souring of milk (Pasteur 1857)
1873	Lister isolated *Lactococcus lactis* from sour milk (Lister 1873)
1884	Hueppe first named “yogurt bacteria” as “lactic acid bacteria” (Milth 1884)
1899	Henri Tissier isolated *Bifidobacterium bifidum* from the feces of infants (Tissier 1906)
1900	Ernst Moro discovered *Lactobacillus acidophilus* (Moro 1900)
1905	Stamen Grigoroff isolated *Lactobacillus bulgaricus* from yogurt, that is, *Lactobacillus Bulgaria* (Grigoroff 1905)
1907	Elie Metchnikoff predicted the benefit of LAB in human being (Minot 1908)
1930	Minoru Shirota isolated *Lactobacillus casei*
1935	Minoru Shirota started manufacturing and selling Yakult
1983	Isolated *Lactobacillus rhamnosus* from healthy human
2001	FAO/WHO proposed a definition of “probiotics”
2002	The joint experts of the FAO/WHO in London drafted the guidelines for the evaluation of probiotic in food
2003	People’s Republic of China’s Ministry of Health No. 84 approved *Lactobacillus reuteri* as a probiotic strain that can be used as a healthy food
2008	The world gastroenterology organization has identified the potential functions of lactic acid bacteria

The prehistorical period is normally divided into the food-gathering period and the food-producing period. Human might remain ignorant of lactic acid bacteria until there was a shift from “hunter-gathering” to “food-producing” agricultural societies in which food storage and preservation became a real big issue. Around one-third of the food supply is lost due to microbe-related spoilage. All food raw materials are contaminated by microorganisms, and the microbial reactions mostly resulted in spoilage of the food, which actually take part in the mineralization of organic materials in nature. To extend the shelf life of foods, the progress of such natural degradation paths must be prevented or delayed, which is mainly by drying or fermenting. Man had early learned to live with microbial-infected food and noticed that lactic acid bacteria might serve as excellent ambassadors for an often maligned microbial world. By serendipity, early humans might find that “spoiled” foods sometimes were still edible or even desired than its original ones. A case in point is food fermentation. Accordingly, food fermentation became an organized activity before 4000 B.C.E. In this connection, lactic acid bacteria are often employed for production of fermented foods including sour milk, yogurt, cheese, fermented sausages, and fermented vegetables such as sauerkraut, pickles, and olives. It is widely accepted that Louis Pasteur was the first person who appreciated and understood the presence and the critical role of food microbes (LAB). He revealed and isolated the microorganisms (*Lactococcus lactis*) which afforded the souring of milk in 1857 and in 1878. The Nobel laureate Elie Metchnikoff, in one of his books *Prolongation of life*, hypothesized that the longevity of people in the Balkans might due to the bacteria in yogurt in 1907. Minoru Shirota manufactured Yakult by using a special strain of the bacterium *Lactobacillus casei Shirota* in 1935. The term "probiotic bacteria" was proposed in the 1970s and redefined as "Live microorganisms which when administered in adequate amounts confer a health benefit to the host" by the FAO/WHO in 2001. In general speaking, *Lactococcus lactis* is widely accepted as the most important industrial dairy starter microorganism and has been used for hundreds of years. Moreover, interest in probiotic lactic acid bacteria has been rekindled dramatically over the last two decades for their potential health benefits against bacterial infection, diarrhea, IBD, and even tumorigenesis (Wu et al. 2011; Schieber et al. 2015; Sanders et al. 2013; Lee and Hase 2014). In addition, probiotic interventions with disorders (such as diabetes, obesity and metabolic syndrome, nonalcoholic fatty liver disease, etc.) outside the gastrointestinal tract are increasingly recognized (Backhed et al. 2004; Forslund et al. 2015; Llopis et al. 2016).

1.2 The Habitats of Lactic Acid Bacteria

The growth range of lactic acid bacteria is relatively wide. Some species can grow below 15 °C or above 45 °C and also can grow in pH 3~11. This phenomenon shows that lactic acid bacteria have strong adaptability to the environment. Thus it can be seen that lactic acid bacteria are widely distributed in nature, such as in plant materials and their products, different types of fermented foods, fruits, soil, water, cavities (mouth, genital, intestinal, and respiratory tract) of human and animals, and other natural habitats.

Lactic acid bacteria in fermented dairy products mainly include the genera of *Lactobacillus*, *Lactococcus*, *Leuconostoc*, *Pediococcus*, and *Enterococcus*. Generally, the genus *Lactobacillus* is the dominant bacteria. Lactic acid bacteria in sourdough mainly include the genera of *Lactobacillus brevis*, *Lactobacillus plantarum*, *Lactobacillus sanfranciscensis*, *Lactobacillus crustorum*, *Lactobacillus paralimentarius*, *Lactobacillus mindensis*, *Staphylococcus pentose*, and *Enterococcus faecium*. Lactic acid bacteria in sauerkraut mainly include the genera of *Leuconostoc*, *Pediococcus*, *Lactococcus*, and *Lactobacillus*. Lactic acid bacteria in fermented meat products mainly include the genera of *Lactobacillus*, *Enterococcus faecium*, *Leuconostoc mesenteroides*, *Lactobacillus brevis*, and *Streptococcus*.

The genera of *Lactobacillus* and *Enterococcus* are the main lactic acid bacteria in the oral cavity. The genus of *Streptococcus* is the dominant bacteria, leading to the dominant position. The main lactic acid bacteria in the stomach are *Lactobacillus*, *Streptococcus*, and *Bifidobacterium*. Lactic acid bacteria in small intestine mainly include *Streptococcus equinus*, *Streptococcus sanguinis*, *Enterococcus casseliflavus*, *Enterococcus faecalis*, *Enterococcus faecium*, *Enterococcus gallinarum*, *Lactobacillus ruminis*, *Pediococcus acidilactici*, and *Bifidobacterium pseudocatenulatum*. Lactic acid bacteria in large intestine mainly include the genera of *Lactobacillus*, *Streptococcus*, *Enterococcus*, and *Bifidobacterium. Lactobacillus* and *Enterococcus* are the main lactic acid bacteria in female genital tract. The genera of *Propionibacterium* and *Streptococcus* on the human skin surface are the predominant bacteria. In addition to digestive tract, urogenital tract, and body surface, there are also a number of lactic acid bacteria in other organs of human. The lung is an important respiratory organ of human. For a long time, the lung is considered sterile. With the development of molecular biology technology and sequencing technology, more and more evidences show that there are a certain number of microbes in the lungs, mainly *Prevotella*, *Sphingomonas*, *Pseudomonas*, *Acinetobacter*, *Fusobacterium*, *Megasphaera*, *Veillonella*, *Staphylococcus*, and *Streptococcus.*

Mice are the most detailed mammalian animals. Through high-throughput sequencing technology, it is shown that there are significant differences in microbial community structure in different segments of the intestinal tract of mice. For example, the Lactobacillaceae is the dominant flora in the stomach and small intestine, and the Bacteroidaceae, Prevotellaceae, Rikenellaceae, Lachnospiraceae, and Ruminococcaceae are the dominant flora in the large intestine and feces. *Enterococcus* and *Streptococcus* were initially colonized in the intestinal tract of pigs, and *Lactobacillus* and *Bacteroides* were also colonized in the intestine. *Lactobacillus, Bifidobacterium*, and *Enterococcus* are the dominant bacteria in the gut of pigs, cow, and other animals. Soil and water are also the habitats of lactic acid bacteria, especially in sewage. At present, a variety of lactic acid bacteria are isolated from sewage, including *Lactobacillus ruminis*, *Lactobacillus coryniformis*, *Lactobacillus sharpeae*, *Lactobacillus fermentum*, *Lactobacillus agilis*, *Lactobacillus casei, Bifidobacterium angulatum*, *Bifidobacterium catenulatum*, *Bifidobacterium choerinum*, *Bifidobacterium longum*, *Bifidobacterium breve*, *and Bifidobacterium adolescentis*.

1.3 The Current Taxonomy of Lactic Acid Bacteria

In the last 30 years of the nineteenth century and the first 10 years of the twentieth century, more and more lactic acid bacteria were separated and discovered. At that time, lactic acid bacteria mainly refer to some microorganisms that can acidify milk. Because of the similarity in physiological characteristics and cell morphology, it is very necessary to classify them scientifically and rationally.

It should be pointed out that the term of lactic acid bacteria has no strict taxonomic significance, and thus their members might be heterogeneous from a taxonomic viewpoint. Based on phylogenetic relationship analysis, lactic acid bacteria can be classified into the *Firmicutes* and *Actinobacteria*, including 41 genera as follows: *Bacillus*, *Halolactibacillus*, *Saccharococcus*, *Brochothrix*, *Listeria*, *Sporolactobacillus*, *Gemella*, *Abiotrophia*, *Aerococcus*, *Alkalibacterium*, *Carnobacterium*, *Desemzia*, *Isobaculum*, *Marinilactibacillus*, *Trichococcus*, *Enterococcus*, *Melissococcus*, *Tetragenococcus*, *Vagococcus*, *Lactobacillus*, *Paralactobacillus*, *Pediococcus*, *Leuconostoc*, *Oenococcus*, *Weissella*, *Lactococcus*, *Lactovum*, *Streptococcus*, *Lachnobacterium*, *Aeriscardovia*, *Alloscardovia*, *Bifidobacterium*, *Metascardovia*, *Parascardovia*, *Scardovia*, *Atopobium*, and *Olsenella.* Other genera that are currently included in the lactic acid bacteria are *Fructobacillus*, *Lacticigenium*, *Pilibacter*, and *Sharpea* which are the new genera of lactic acid bacteria and have not been included in the handbook of *Bergey*'*s Manual of Systematics of Archaea and Bacteria* published in 2015. Notably, *Bifidobacterium* is quite different from other LAB based on 16S ribosomal ribonucleic acid (16S rRNA) sequence-associated phylogenetic relationship analysis (Stefanovic et al. 2017). And the principal genera of lactic acid bacteria are listed below (Table 1.2).

In 1901, Martinus Willem Beijerinck who is the microbiologist and botanist of Holland named *Lactobacillus* as the genera name of lactic acid bacteria (Beijerinck 1901). Then, Orla-Jensen who is a Danish microbiologist published “The main lines of the natural bacterial system” in the *Microbiological Research* magazine in 1909, which is an important progress in the history of bacterial taxonomy (Orla-Jensen 1909). Orla-Jensen wrote a book about lactic acid bacteria in 1919–1943 named *The Lactic Acid Bacteria*. In this book, lactic acid bacteria were systematically classified and described for the first time, which established the foundation of modern lactic acid bacteria taxonomy (Orla-Jensen 1919). It can be said that the publication of Orla-Jensen’s book indicated the formation of the science and technology system of lactic acid bacteria and has a great influence on the development of the whole bacterial taxonomy (Orlajensen and Snogkjaer 1940). Based on the idea and method of taxonomy of lactic acid bacteria proposed by Orla-Jensen, Rogosa (Rogosa et al. 1947), Sharpe (Sharpe 1979), Kandler, and Weiss (Barrangou et al. 2011) made a more reasonable and accurate exploration about the classification of lactic acid bacteria according to the characteristic marker enzymes, growth temperature, oxygen demand, environmental physiological preferences, and metabolite types in lactic acid fermentation pathway. In 1971, Lechevalier submitted a classification system based on cytochemical characteristics, which established the foundation of microbial chemical taxonomy. In 1957, PHA Sneath, a British bacteriologist, created a numerical taxonomy method for microbial classification by using the computer

Table 1.2 Principal genera of the lactic acid bacteria

Genus	Cell morphology	Fermentation	Lactate isomer	DNA (mole % GC)
Lactobacillus	Rods	Homo/hetero	DL, D, L	32–53
Lactococcus	Cocci in chains	Homo	L	33–37
Leuconostoc	Cocci	Hetero	D	38–41
Pediococcus	Cocci	Homo	DL	34–42
Streptococcus	Cocci in chains	Homo	L	40
Bifidobacterium	Rods	Hetero		46–67

technology in the classification of bacteria. The relationship between bacterial species was quantified by calculating the similarity coefficient between bacteria. This method enables bacterial classification to go from qualitative description to quantitative analysis (Sneath 1957). In 1969, Mandel reviewed the use of G + C content for bacterial classification. The content of G + C is an indicator of the classification of bacteria. Using nucleic acid hybridization to analyze the homology of DNA, DNA-rRNA molecular hybridization technology is also used for the classification of bacteria, and the application of these techniques and more classification indexes have greatly improved the scientific and accurate classification of bacteria including lactic acid bacteria (Gasser and Mandel 1968; Mandel 1969). Different taxonomic indexes have certain limitations. For this reason, Colwell put forward the concept of polyphasic taxonomy in 1970. Polyphasic taxonomy mainly refers to a taxonomy of microbial classification and phylogenetic evolution by comprehensively utilizing all kinds of different microbial information available. It includes phenotypic information, genotypic information, and phylogenetic information. Polyphasic taxonomy, which covers all the contents of modern microbiological taxonomy, is considered as the most effective means to study the classification of microorganisms and can describe and define all levels of taxonomy.

1.4 The Safety of Lactic Acid Bacteria

Most probiotics are not used safely for a long time. The longest application period is *Lactobacillus acidophilus* and some strains of *Lactobacillus casei*, which have been in the market for 60 years. However, the application time, which many lactic acid bacteria used for producing fermented milk, such as *Lactobacillus delbrueckii, Streptococcus thermophilus*, and *Lactococcus lactis*, is still very short. *Lactobacillus* and *Bifidobacterium*, the most common lactic acid bacteria used in food fermentation for centuries with the aim of increasing the shelf life of foods and improving food safety, do not possess any pathogenic characteristics. Because they are isolated from fermented foods or the human gut microbiota and usually regarded as safe, *Lactobacillus* and *Bifidobacterium* are not involved in the infection process, except for a small number of enterococci. However, there are also rare cases of infection, which are mainly preclinical assessments of new strains or mixed strains, usually as opportunistic infections in people with predisposing conditions (Ouwehand et al. 2003; Lahtinen et al. 2009). For healthy people, there does not seem to be any risk of lactic acid bacteria use; rather, there may be benefits. Therefore, the safety of lactic acid bacteria is very important for high-risk patients and immunodeficiency patients.

It is difficult to identify potential toxic factors of common nonpathogenic microorganisms such as *Lactobacillus* and *Bifidobacterium*. Therefore, potential risk factors have been proposed as an important indicator for evaluating probiotics. Potential risk factors which can partially determine the safety of probiotics are based on the knowledge of potential virulence factors of pathogens. Specific potential toxicity factors are shown in Table 1.3.

Table 1.3 Potential risk factors for some lactic acid bacteria

Relation	Properties	Notes
Metabolism of microbes	Hyaluronidase activity	Important in *Enterococcus*
	Gelatinase activity	
	DNAse activity	
	Mucus degeneration	Mucosal barrier with autoimmune abnormalities
	Formation of D-lactic acid	D-lacto-toxicity
	Amino acid decarboxylase activity	Formation of biogenic amines
Adhesion characteristics	Adhesion to intestinal mucosa	Transfer
	Adhesion of extracellular free proteins	
	The adhesion of essential nutrients and treatment mixtures	
Blood	Resistance to bacteria	Bacteremia
	Erythrocyte dissolution	Anemia
	Hemagglutination reaction	Thrombotic syndrome, endocarditis
Immunology	The composition of cell wall	Arthritis
	Modulate the immune response to inflammation	Inflammation, immunosuppression
The property of microbe	Capsule formation	Resistance to bacteriophore
	Transfer of genetic material	The acquisition of toxic genes

Ouwehand et al. (2003)

The first step in the safety evaluation of lactic acid bacteria is to unequivocally identify the strains correctly. Taxonomy is required to describe a strain, including DNA–DNA hybridization and rRNA sequence determination. In this respect, relevant regulations have been formulated by various countries and organizations. For example, the qualified presumption of safety approach established by the European Food Safety Authority supports the safety of commonly used *Lactobacillus* and *Bifidobacterium*. It provides a basis for genera, species, and strains to be identified as safe. The QPS approach establishes the safety aspects that should be determined and fulfilled for a certain taxonomic unit.

The safety evaluation of probiotics is usually based on pathogen, toxicity, metabolic activity, and intrinsic characteristics of bacteria. Then the safety of the strain was evaluated through in vitro, animal, and human clinical studies. SPF mice or germ-free mice are now used to study the pathogenicity and toxicity of strains.

To ensure the safety of the probiotic strains used, the following experiments should be carried out at least to verify its safety: (1) determine the patterns of antibiotic resistance; (2) assess the metabolic activities (e.g., d-lactate production, bile salt deconjugation) and the side effects during human studies; (3) supervise the post-market epidemiological studies of adverse incidents in consumers; (4) test the toxin, if the strain under evaluation belongs to a species that is a known mammalian toxin producer; and (5) determine the hemolytic activity, if the strain under evaluation belongs to a species with a known hemolytic potential.

In the United States, the Food and Drug Administration (FDA) controls the safety of food and complementary diets. Probiotics, as a regular food and dietary supplement, have been sold in the United States. However, before supplying to consumers, the new microbial strains had to be carefully evaluated for potential health hazards. Lactic acid bacteria have been accepted as safe without any real scientific criteria, partly because they exist as normal commensal microbiota and because of their presence for generations presumably without adverse effect. Currently, harmless probiotics include *L. acidophilus*, *S. thermophilus*, *Lc. lactis* subsp. *cremoris*, *Lc. lactis* subsp. *lactis*, *L. delbrueckii* subsp. *bulgaricus*, *L. delbrueckii* subsp. *lactis*, and *L. fermentum.* They can be used as additives in specific foods such as fermented milk (including yogurt and buttermilk), sour ice cream, and soft cheese.

Most European Union Member States believed that foods that were not considered edible until 1998, such as probiotics, are now considered to be a new type of food. The purpose of the EC new food regulation (258/97) is to ensure the free circulation of new foods and to protect the interests of consumers, especially those who wish to provide information on safety and health. , nutritional value, metabolism, application prospects of new probiotic strains and their prospects, and the level of unqualified substances contained in it is equivalent to the evaluation of the existing ordinary microorganism. These assessments can not be used as criteria for evaluating new foods. However, other aspects of the strain need to be evaluated according to the principles and procedures of the new type of food.

The FAO and WHO convened a joint FAO-WHO Working Group to draft guidelines for evaluating lactic acid bacteria used in food. The working group proposed a framework of strain identification and functional characterization, followed by safety assessment and phase 1, 2, and 3 human trials. It recommended that probiotic foods be properly labeled with the strain designation, minimum numbers of viable bacteria at the end of shelf life, storage conditions, and manufacturer's contact details. The working group further considered that assessment of lack of infectivity by a probiotic strain in immunocompromised animals would increase confidence in the safety of the probiotic.

In summary, the safety testing of lactic acid bacteria mainly includes the following aspects:

1. Lactic acid bacteria strain must be unequivocally identified and defined with correct taxonomy and deposited in a recognized international culture collection for access by manufacturers, scientists, and regulators to ensure organisms can be monitored for genetic drift and comparison with clinical isolates.
2. Novel strains from species with pathogenic, toxigenic, or other adverse properties need to be evaluated with scientific rigor and to be systematically screened for antibiotic resistance and its transference.
3. Immunomodulatory effects of lactic acid bacteria need to be assessed in defined target populations.
4. Clinical studies should comply with the gold standard of randomized, double-blind placebo-controlled design.

5. Lactic acid bacteria in animal feed additives or veterinary products should be evaluated for their safety in the human food chain.
6. Labeling of lactic acid bacteria products should accurately reflect content, shelf life, claimed attributes, and dose.
7. Following the introduction of novel lactic acid bacteria, intake data should be gathered, especially for long-term consumption.
8. Epidemiological surveillance for any associated adverse effects, particularly infection, should be instituted.
9. Characterization of clinical isolates for comparison with endogenous and probiotic strains as integral to confirming its safety.

1.5 The Role and Importance of Lactic Acid Bacteria

Food is an essential part for human life. Food safety is a matter of national economy and people's livelihood. According to the strategy of global food safety established by World Health Organization, chemical harmful substances which include two major categories are the main hazard factors of food safety, such as microbial toxins and heavy metal environmental pollution (Zhai et al. 2014). Microbial toxins can be classified into bacterial toxins and mycotoxins. However, cereals, peanuts, other crops, and animal products are susceptible to mycotoxins, such as aflatoxin, ochratoxin, and other mycotoxins, and foods that have been contaminated by these mycotoxins may induce malignant cancers such as gastric cancer and liver cancer (Duarte et al. 2010; Monbaliu et al. 2010; Delmulle et al. 2005; Ngundi et al. 2005). In addition, microcystins have a strong carcinogenic effect on the liver, and even a very low dose of long-term exposure can cause permanent damage to the liver (Aguete et al. 2001). Toxic heavy metals mainly include lead, cadmium, arsenic, mercury, chromium, zinc, and copper (Yoon et al. 2008). The most toxic to human is lead; it is difficult to discharge from the body, which will cause irreversible loss of children's mental retardation, Alzheimer's disease, and carcinogenesis (Jing et al. 2009).

In developing and developed countries, foodborne diseases which have the most serious impact on children, pregnant women, and the elderly are widely spread and pose a serious threat to health. In addition to its direct health effects, foodborne diseases can cause considerable stress on the health-care system and significantly weaken the capacity for economic production. Diarrhea is the most common symptom of foodborne diseases. Millions of children die from diarrhea every year, and hundreds of millions of children suffer from recurrent diarrhea. Recently, food safety problem has happened frequently in China. The food safety problems do not affect the public health seriously but the development of food industry and even the social stability. Therefore, it is urgent to ensure the safety of food.

In recent years, the function of probiotics has been further developed and analyzed with the in-depth exploration of the physiological characteristics and mechanism of the strains. At present, a considerable number of studies showed that probiotics have the potential ability to antagonize and reduce the risk factors of food safety. Therefore, we will summarize the research of probiotics in reducing microbial toxins and alleviating the toxicity of heavy metals, so as to provide some reference for the application of probiotics to food safety.

Lead can cause toxicity to multiple organs or systems at the same time. There is a certain relationship between the toxicity and the solubility and form of the compound. Acute lead poisoning can cause abdominal pain, diarrhea, vomiting, headache, dizziness, coma, vasospasm, and liver and kidney damage and can even be life-threatening. Chronic lead poisoning can cause symptoms such as vertigo, anemia, joint pain, and heart failure. So far, there are few articles about lactic acid bacteria to alleviate lead toxicity. However, a large number of studies have shown that some properties of lactic acid bacteria may lead to the ability of lactic acid bacteria to prevent or alleviate the toxicity of lead. The specific research can be summed up in the following four aspects:(1) Lactic acid bacteria can absorb heavy mental ions in vitro, and this ability to absorb heavy mental ions is strain specific. (2) Lead can cause the inactivation of antioxidant enzymes and produce reactive oxygen species (ROS), resulting in oxidative damage to the body. A large number of studies showed that lactic acid bacteria have excellent antioxidant properties and can alleviate oxidative damage caused by various diseases. (3) The bivalent cation such as zinc, calcium, and magnesium can compete with lead and reduce the absorption of lead, while lactic acid bacteria have the function of promoting the absorption of these microelements. (4) Studies have suggested that gut microbes may be the target of toxic of lead. Meanwhile, a large number of animal experiments showed that lactic acid bacteria have the function of regulating intestinal flora, which can also alleviate the lead poisoning by adjusting the intestinal flora.

Cadmium is a kind of heavy metal with strong toxicity, and its incubation period is very long. Acute cadmium poisoning can lead to symptoms such as cough, chest tightness, dyspnea, nausea, vomiting, and abdominal pain. Large doses of cadmium cause acute liver injury and lead to death. Chronic cadmium poisoning involves renal injury (proteinuria, nephrolithiasis, chronic renal failure), bone injury (bone pain, osteoporosis, osteomalacia, spontaneous fracture), reproductive organ injury (testicular and ovarian injury), and cancer (lung, prostate cancer). A large number of studies have shown that lactic acid bacteria may prevent or alleviate the toxicity of cadmium. Its mechanism may be that lactic acid bacteria could combine with cadmium before they are absorbed by the intestine and excreted through feces in order to reduce the absorption of cadmium by human. On the other hand, lactic acid bacteria by enhancing the expression of tight junction, to protect the integrity of the intestinal barrier, maintain intestinal permeability, thereby reducing the absorption of cadmium in intestine.

The existence form of copper is closely related to its toxicity. Under normal conditions, when the intake of copper is 100–150 times greater than that of the human need, it can easily cause toxic reactions and lead to great harm to the human body. The content of copper in liver was the largest, followed by the kidney and brain. When copper enters the brain with blood circulation, it will cause brain damage and affect human's ability to learn and remember. Symptoms of copper poisoning include a metallic taste in the mouth, accompanied by salivation, nausea, vomiting, hematemesis, and pain in the upper abdomen. Sometimes the excretion is black and the nerve is weak, memory declines, attention is not concentrated, and the temper is irritable and easy to be excited. In addition, copper poisoning can also cause symptoms such as liver swelling or abnormal liver function and induce cancer and even death. Lactic acid bacteria can effectively adsorb heavy metal ions, and it is an excellent antioxidant. It can remove free radicals and alleviate oxidative stress and oxidative damage in the body. Moreover, lactic acid bacteria can be used as a new dietary therapy to treat injury induced by copper. In addition to the three heavy metals mentioned above, the effect of lactic acid bacteria on the reduction of other heavy metals has also been reported, as shown in Table 1.4.

Nitrite is the general name of a type of inorganic compounds. It is usually used as an additive for processing meat products and can inhibit the growth of pathogenic bacteria and spoilage microorganisms. Excessive intake of nitrite will seriously damage human health. At present, the degradation of nitrite is divided into three main categories: physical method, chemical method, and biological method. The mechanism of biodegradation of nitrite is mainly related to the ability of probiotic metabolites to remove nitrite. Probiotics can produce acidic or nitrite reductase during the growth process to degrade nitrite. The mechanism of biodegradation of nitrite is that probiotics can produce acidic substance or nitrite reductase during the growth process to degrade nitrite. It has been proved that *Lactobacillus*, *Leuconostoc mesenteroides*, *Pseudomonas*, *Pediococcus*, *Acinetobacter*, and other probiotics have the ability to degrade nitrite.

Biogenic amine, which is widely used in food, especially fermented food, is the general name of a type of small molecule nitrogenous compounds with biological activity (Cvetković et al. 2015; Guarcello et al. 2015; Li et al. 2014). Excessive intake of biogenic amines can cause damage to the cardiovascular system and nervous system of the human body; it can lead to a rise in blood pressure, faster heartbeat, blood sugar increase, overproduction of adrenaline, and headache (Maintz and Novak 2007). Biogenic amines have good thermal stability, and ordinary cooking

Table 1.4 Lactic acid bacteria with the function of adsorbing other heavy metals

Heavy metals	Lactic acid bacteria	References
Arsenic	*Lactobacillus casein* DSM20011	Halttunen et al. (2007)
Nickel	*Lactobacillus caucasicus* CIDCA8348 and *Lactobacillus caucasicus* JCM5818	Gerbino et al. (2012)
Silver	*Lactobacillus* A09	Lin et al. (2005)
Aluminum	*Lactobacillus plantarum* CCFM 639 and *Lactobacillus rhamnosus* E/N	Yu et al. (2016) and Polakberecka et al. (2014)
Iron	*Lactobacillus plantarum* 299 V, *Lactobacillus delbruecki* Lb-12, and *Streptococcus thermophiles* STM-7	Hoppe et al. (2015) and Sofu et al. (2015)
Zinc	*Lactobacillus delbruecki* Lb-12, *Streptococcus thermophiles* STM-7, and *Lactobacillus*	Sofu et al. (2015) and Mrvčić et al. (2009)

cannot eliminate biogenic amines in food. The main methods for controlling the content of biogenic amines in food are as follows: (1) optimization of production technology and storage conditions, (2) chemical methods, (3) physical methods, and (4) biological technology (Zhang et al. 2015; Fan et al. 2014). At present, the best way to control biogenic amines in food is to inoculate specific microorganisms that can degrade biogenic amines. Bacteria mainly degrade biogenic amines by synthesizing amine oxidase or amine dehydrogenase. For example, *Lactobacillus plantarum* 2142, *Lactobacillus casei* 2763, and *Lactobacillus curvatus* 2771 all have the function of degrading biogenic amines (Rabie et al. 2011).

Nitrosamine is a strong carcinogen, which is widely distributed in many daily consumer goods. Among them, the level of nitrosamine is the highest in tobacco and salted products. It is found that most of the nitrosamines can be degraded by microorganisms. The method of microbial degradation of nitrosamines is simple and inexpensive and will not cause pollution to the products. Lactic acid bacteria can produce some special enzyme which can reduce the content of nitrosamines and nitrite in the fermentation process of pickled products, such as enzyme system that decomposes nitrosamines and nitrite.

Microcystins which have good water solubility and high thermal stability are consumed by drinking water contaminated by microcystins and consuming foods containing microcystins or health products made from blue-green algae. Therefore, microcystins can depend on the food chain to pose a potential threat to human beings. Microcystins have high selectivity and specificity to human liver cells mainly through the blood transfer to the liver, and the liver is the major toxic organ of microcystins. At present, there are three kinds of methods to reduce the pollution of microcystin: physical, chemical, and biological methods. Compared with the physical and chemical reduction methods, the biological reduction method has the advantages of low cost and easy operation. It can be used in algal cells and microcystins at the same time. In other words, it has great potential for the degradation and adsorption of microcystins (Zamyadi et al. 2012; Antoniou et al. 2005). At present, the related research on the eliminating of microcystins by lactic acid bacteria is only in the initial stage. The study found that *Bifidobacterium* (Bb12) and *Lactobacillus rhamnosu*s GG (LGG) have the ability to eliminate microcystins (Meriluoto et al. 2005).

Aflatoxins are secondary metabolites produced by strains of *Aspergillus* parasitized and *Aspergillus flavus* (Zhang et al. 2012). *Aspergillus flavus* and *Aspergillus parasiticus* are common in food, especially in peanuts and corn products. Among the mycotoxins have been found, AFB1 is the most toxic one. Therefore, the research on the mechanism of aflatoxin carcinogenesis is mainly focused on the exploration of the mechanism of AFB1 carcinogenesis. Many studies have shown that many microorganisms have the ability to adsorb or degrade aflatoxins, including lactic acid bacteria, yeasts, and *Bacillus* (Sezer et al. 2013; Oluwafemi et al. 2010). Compared with the traditional physical and chemical methods, biological methods have the advantages of high safety, mild treatment conditions and less damage to the products. Lactic acid bacteria can alleviate aflatoxin mainly through its metabolites to reduce the content and toxicity of aflatoxin, such as bacteriocin and short-chain fatty acids (Lavermicocca et al. 2003; Ström et al. 2002). On the other hand, lactic acid bacteria can alleviate aflatoxin through inhibition of the growth of Aspergillus flavus and the production of Aspergillus flavus.

Patulin which was first discovered by Glister in 1941 and isolated patulin at University of Oxford were the secondary metabolites produced by fungi (Geiger and Conn 1945). The contamination of fruits, dairy products and feed with patulin is very serious, which poses a great threat to human health. Therefore, many countries have set up a limited standard for patulin in food. Patulin mainly damages the body by reacting with thiol-containing compounds such as glutathione and cysteine. Symptoms of acute poisoning include spasms, convulsions, dyspnea, pulmonary hemorrhage, edema, gastrointestinal ulcers, and congestion, while subacute toxicity is mainly manifested by intestinal dysfunction, including gastrointestinal ulcers, swelling, and bleeding (Appell et al. 2009). At present, researches on the removal of patulin by lactic acid bacteria are at an early stage. In 2007, the Austrian scholar Fuchs first screened out a strain of *Bifidobacterium* VM 12 from 30 strains of lactic acid bacteria, which could better remove patulin in the solution (Fuchs et al. 2008). It was guessed that the adsorption of *Lactobacillus* on patulin may be related to the polysaccharide and protein on the surface of lactic acid bacteria (Hatab et al. 2012).

To explore the effect of lactic acid bacteria in alleviating toxins, we can further develop the probiotic function of lactic acid bacteria and related functional products in order to provide a novel solution for alleviating the toxin effect by dietary strategy.

1.6 Lactic Acid Bacteria, to the Future and Beyond

Life is not sterile, and we live in a microbial world. The microbes were here first and cohabit the planet with us now. Man learned to handle foods in ways that extended their shelf life, and lactic acid fermentation is among the oldest forms of food preservation. Although it sometimes appears that LAB protects our foods, this is by no means their primary role in nature. In the present view of life on this planet, the primary function of all species in nature is self-perpetuation. Therefore, advancements in the application of LAB remains largely lie in exploring their genetics and metabolic studies. LAB fermentations are still used to produce the so-called fermented food today, but preservation is no longer to be the main objective of LAB fermentation. To this end, it is rather the specific taste and texture, maintaining the human health, and promoting benefits that will be the goal of the fermentation in the future (Wu et al. 2011; Turnbaugh 2012; Tian et al. 2015; Cani et al. 2013). Moreover, tomorrow's probiotic LAB might probably move beyond the microorganisms commonly used as probiotic LAB today. For example, LAB is normally nonpathogenic and noninvasive and non-colonizing bacterium. Therefore, recombinant probiotic LAB may represent an interesting direction in the future, especially to deliver oral vaccine, improve natural immune responses, and restore antigen-specific tolerance. Taken together, dietary supplement of probiotic LAB might have a potential in clinical. Thus, the most exciting era of LAB may lie in its future. Working together, we might create the next epoch in this field. To prepare for this, it is the time for us to gain a foundational understanding of the fields today and learn to love these little creatures that are so small but so smart.

Indeed, fermentation not only improves preservation properties but also confers some special flavors and textures which are quite different from the original ones (Zhao et al. 2011, 2016; Costello and Henschke 2002). In addition, LAB fermentation might also rank as one of the effective biological methods which naturally enhanced food safety such as by destroying naturally occurring toxins, suppressing foodborne illness and allergic reactions, or removing heavy metal ions (Zhai et al. 2013, 2014, 2016; Wang et al. 2011, 2014a, b; Tian et al. 2015; Liu et al. 2013; Guo et al. 2010; Chen et al. 2012a, b; Cheikhyoussef et al. 2008, 2009, 2010). Taken together, LAB is not only of economic significance, flavor preference, and health benefit but is also of value in reducing the toxicity or pathogenicity of foods.

References

Aguete, E.C., A. Gago-Martínez, J.A. Rodríguez-Vázquez, S. O'Connell, C. Moroney, and K.J. James. 2001. Application of HPLC and HPCE to the analysis of cyanobacterial toxins. *Chromatographia* 53 (1): S254–S259.

Antoniou, Maria G., Armah A. De La Cruz, and Dionysios D. Dionysiou. 2005. Cyanotoxins: New generation of water contaminants. *Journal of Environmental Engineering* 131 (9): 1239–1243.

Appell, Michael, Mary Ann Dombrink-Kurtzman, and David F. Kendra. 2009. Comparative study of patulin, ascladiol, and neopatulin by density functional theory. *Journal of Molecular Structure Theochem* 894 (1): 23–31.

Backhed, F., H. Ding, T. Wang, L.V. Hooper, G.Y. Koh, A. Nagy, C.F. Semenkovich, and J.I. Gordon. 2004. The gut microbiota as an environmental factor that regulates fat storage. *Proceedings of the National Academy of Sciences of the United States of America* 101 (44): 15718–15723. https://doi.org/10.1073/pnas.0407076101.

Barrangou, Rodolphe, Sampo Lahtinen, Fandi Ibrahim, and Arthur Ouwehand. 2011. Genus lactobacillus [M]. In *Lactic Acid Bacteria*, 77–91.

Beijerinck, M. 1901. Sur les ferments lactiques de l'industrie. Archives Néerlandaises des. *Sciences Exactes et Naturelles* 6: 212–243.

Blondeau, C. 1847. Des fermentations. *Journal de Pharmacie* 312: 244–261.

Cani, P.D., A. Everard, and T. Duparc. 2013. Gut microbiota, enteroendocrine functions and metabolism. *Current Opinion in Pharmacology* 13 (6): 935–940. https://doi.org/10.1016/j.coph.2013.09.008.

Cheikhyoussef, A., N. Pogori, W. Chen, and H. Zhang. 2008. Antimicrobial proteinaceous compounds obtained from bifidobacteria: From production to their application. *International Journal of Food Microbiology* 125 (3): 215–222. https://doi.org/10.1016/j.ijfoodmicro.2008.03.012.

Cheikhyoussef, A., N. Pogori, H.Q. Chen, F.W. Tian, W. Chen, J. Tang, and H. Zhang. 2009. Antimicrobial activity and partial characterization of bacteriocin-like inhibitory substances (BLIS) produced by Bifidobacterium infantis BCRC 14602. *Food Control* 20 (6): 553–559. https://doi.org/10.1016/j.foodcont.2008.08.003.

Cheikhyoussef, A., N. Cheikhyoussef, H.Q. Chen, J.X. Zhao, J. Tang, H. Zhang, and W. Chen. 2010. Bifidin I – A new bacteriocin produced by Bifidobacterium infantis BCRC 14602: Purification and partial amino acid sequence. *Food Control* 21 (5): 746–753. https://doi.org/10.1016/j.foodcont.2009.11.003.

Chen, X.H., X.M. Liu, F.W. Tian, Q.X. Zhang, H.P. Zhang, H. Zhang, and W. Chen. 2012a. Antagonistic activities of Lactobacilli against helicobacter pylori growth and infection in human gastric epithelial cells. *Journal of Food Science* 77 (1): M9–M14. https://doi.org/10.1111/j.1750-3841.2011.02498.x.

Chen, H.Q., F.W. Tian, S. Li, Y. Xie, H. Zhang, and W. Chen. 2012b. Cloning and heterologous expression of a bacteriocin sakacin P from Lactobacillus sakei in Escherichia coli. *Applied Microbiology and Biotechnology* 94 (4): 1061–1068. https://doi.org/10.1007/s00253-012-3872-z.

Costello, P.J., and P.A. Henschke. 2002. Mousy off-flavor of wine: Precursors and biosynthesis of the causative N-heterocycles 2-ethyltetrahydropyridine, 2-acetyltetrahydropyridine, and 2-acetyl-1-pyrroline by Lactobacillus hilgardii DSM 20176. *Journal of Agricultural and Food Chemistry* 50 (24): 7079–7087. https://doi.org/10.1021/jf020341r.

Cvetković, Biljana R., Lato L. Pezo, Tatjana Tasić, Ljubiša Šarić, Žarko Kevrešan, and Jasna Mastilović. 2015. The optimisation of traditional fermentation process of white cabbage (in relation to biogenic amines and polyamines content and microbiological profile). *Food Chemistry* 168: 471.

Delmulle, Barbara S., Sarahg De Saeger, Liberty Sibanda, Ildiko Barna-Vetro, and Carlos H. Van Peteghem. 2005. Development of an immunoassay-based lateral flow dipstick for the rapid detection of aflatoxin B_1 in pig feed. *Journal of Agricultural and Food Chemistry* 53 (9): 3364–3368.

Duarte, S.C., A. Pena, and C.M. Lino. 2010. A review on ochratoxin A occurrence and effects of processing of cereal and cereal derived food products. *Food Microbiology* 27 (2): 187–198.

Fan, H., Y. Luo, X. Yin, Y. Bao, and L. Feng. 2014. Biogenic amine and quality changes in lightly salt- and sugar-salted black carp (*Mylopharyngodon piceus*) fillets stored at 4°C. *Food Chemistry* 159: 20–28.

Forslund, K., F. Hildebrand, T. Nielsen, G. Falony, E. Le Chatelier, S. Sunagawa, E. Prifti, S. Vieira-Silva, V. Gudmundsdottir, H.K. Pedersen, M. Arumugam, K. Kristiansen, A.Y. Voigt, H. Vestergaard, R. Hercog, P.I. Costea, J.R. Kultima, J.H. Li, T. Jorgensen, F. Levenez, J. Dore, H.B. Nielsen, S. Brunak, J. Raes, T. Hansen, J. Wang, S.D. Ehrlich, P. Bork, O. Pedersen, and MetaHIT Consortium. 2015. Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. *Nature* 528 (7581): 262–266. https://doi.org/10.1038/nature15766.

Fuchs, S., G. Sontag, R. Stidl, V. Ehrlich, M. Kundi, and S. Knasmüller. 2008. Detoxification of patulin and ochratoxin A, two abundant mycotoxins, by lactic acid bacteria. *Food and Chemical Toxicology* 46 (4): 1398–1407.

Gaspar, P., A.L. Carvalho, S. Vinga, H. Santos, and A.R. Neves. 2013. From physiology to systems metabolic engineering for the production of biochemicals by lactic acid bacteria. *Biotechnology Advances* 31 (6): 764–788. https://doi.org/10.1016/j.biotechadv.2013.03.011.

Gasser, F., and M. Mandel. 1968. Deoxyribonucleic acid base composition of the genus Lactobacillus. *Journal of Bacteriology* 96 (3): 580.

Geiger, Walton B., and Jean E. Conn. 1945. The mechanism of the antibiotic action of clavacin and penicillic acid 1, 2. *Journal of the American Chemical Society* 67 (1): 112–116.

Gerbino, E., P. Mobili, E.E. Tymczyszyn, C. Frausto-Reyes, C. Araujo-Andrade, and A. Gómez-Zavaglia. 2012. Use of Raman spectroscopy and chemometrics for the quantification of metal ions attached to Lactobacillus kefir. *Journal of Applied Microbiology* 112 (2): 363–371.

Grigoroff, S. 1905. Etude sur un lait fermente comestible. Le 'Kisselo-Mleko' de Bulgarie. *Revue médicale de la Suisse romande* 35: 714–720

Guarcello, Rosa, Annamaria Diviccaro, Marcella Barbera, Elena Giancippoli, Luca Settanni, Fabio Minervini, Giancarlo Moschetti, and Marco Gobbetti. 2015. A survey of the main