

PROBIOTICS AND FUNCTIONAL FOODS

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Contents

1. Introduction
 2. Functional Nutrition: Concept and objectives
 3. Main categories of functional food ingredients
 4. Gut Microbiota: composition, main functions, and the host-microbe cross-talk
 5. Probiotic bacteria and prebiotics are crucially important categories of functional food ingredients
 6. Mechanisms and sites of probiotic health-promoting action
 7. Personalized Nutrition: State-of the art
 8. Prospective scientific and applied researches in the functional foods and probiotics
 9. Concluding Remarks
- Glossary
Bibliography
Biographical Sketches

Summary

Current nutrition research is aiming at health promotion, disease prevention and performance improvement. The provision of human being with required nutritional ingredients depends on both how well the host is provided with balanced foods and what state of intestinal microecology host has. Many food, endogenous and probiotic low molecular weight biologically active ingredients have structural and functional resemblance and are the universal regulators of genetic, epigenetic, physiological and metabolic processes. Food quality, safety, and understanding of interplay among such active substances are central requirements for development of modern health benefit products. Recently received knowledge in genomics, epigenomics, metabolomics, and microbial ecology convincingly showed each individual human being is unique on the genetic level; his intestinal microbiota is also unique on the strain level. Various biogenic and abiogenic factors, ageing, deficiency or excess of nutrients can induce deep changes in host microbiota, cell metabolism, epigenetic gene regulation, and damages to vital cell components. Genome damage, epigenetic changes of gene expression and information communication disorders levels connected with moderate diet disorders and/or microecological disturbance may be of the same order of magnitude as the damages caused by environmental genotoxins. Personalized diet rations with using of nutrient balanced spectrum of traditional, organic, functional foods as well as special foods for intestinal microbiota will improve genome stability, epigenetic regulation and promote compensation of negative consequences of

phenotypic expression of polymorph genes unfavorable for health and longevity and on the contrary will optimize the realization of gene alleles that ensure the best adaptation of individual human being and its harmonious work in the ordinary conditions, in the hard load and in the extreme conditions. The important step of applied realization of personalized diet conception is the creation of an anthropology passport of ethnics and certain individuals allowing to determine nutrient preferences of ancestors, evolutionary connections of human and microbiota genes and their epigenetic regulation with determined micronutrients, to reveal gene alleles involving in nutritional status, tendency or resistance to alimentary connected pathology. This review discusses how functional foods and probiotics are currently defined, health claims and safety considerations in using these products, factors, including molecular, driving the functional food phenomenon, and finally, what the future may hold for these and personal food categories.

1. Introduction

According to modern scientific doctrine the human being is a “superorganism”, the consortium of numerous *Eukarya*, *Bacteria*, *Archaea*, and *Viruses*. The total number of superorganism somatic and germ cells is about 1 trillion, and microbe cells - about 100 trillions. From chemical point of view adult man contains at least 25 millions of different molecules that include 300000 different lipid compounds, about 1 millions various proteins, and thousands of other simple and complex substances. All human functional and metabolic systems are working in concordance profitably for whole organism and for its separated components, supporting human homeostasis and health in the specific environment conditions. Disorders coursed by biotic or abiotic stress factors can result in tissue, organ and regulatory systems disturbances which are usually accompanied by development of various diseases including so-called “civilization diseases”. The developed countries spend plenty money for maintenance of own citizens’ health using traditional medical remedies and tools: USA-about 15%, Germany-11%, Canada-10%, Great Britain- 8% of their Gross Domestic Product. But a vast majority of other countries have no economic facilities for such expenditures. In 1985, S.B. Eaton and M. Konnor were the first who had supposed the enlargement of the quantity of “civilization diseases” cases could be connected with sharp changes of human being life style and diet at the second part of XX century. Hypodynamia, multiple extreme stresses, imbalance diet critically decreased the people ability to adapt adequately to modern life and resulted in increase of disease incidences. The imbalance of nutrition is the most important component of human lifestyle actively influencing the people health and diseases. According to the USA Ministry of Health about 70% of all human mortality cases are due by imbalance nutrition. On the other hand, correctly organized nutrition rations are practically the only mean prolonging human life (for 25% and more). Recent anthropology investigations of foods, nutrition rations and nutrition behavior of people for the last 200 hundreds years have shown the most intensive nutrition structure changes have been connected with accelerated industrialization of agriculture and animal husbandry and novel food processing technologies. For example, 80% of present people use only 18-20 raw material types of plant and animal origin for preparation of their meals. On the other hand, the present food ration is characterized by increased number of saturated lipids, light-utilized carbohydrates; such diet contains a plenty different artificial compounds of human

origin (antibiotics, hormones, pesticides, chemical manures, trans-isomers of fatty acids and so on) and lack important nutrients. Every day human being has got about 15-20 grams of only technical functional ingredients (food dye-stuffs, sweetening, thickening, loosen agents, foam catchers, etc) with meals. Physical and chemical treatment of raw materials and food products destroy or completely eliminate many extremely important health benefit nutrients (vitamins, plant anti mutagenic substances, fatty and amino-acids and so on). Some natural food nutrients that in small quantity could be useful for organism, in consumption in higher concentration might be responsible for toxic effects. For example, bean lectin phytohemagglutinin in large quantity possess expressed toxic action to live organism. Even milk products used in increased quantity can produce negative effect to humans because milk contains some hormones and peptides enable to cause inflammation reactions in different tissues and organs. During evolution additional very important nutrient provision system has appeared in mammalian; symbiotic gut microbiota plays one of the key role in provision of human being by energy, numerous micronutrients, signal molecules, in metabolizing some exogenous and vast majority of endogenous nutrient substances. The various hurt agents producing disturbance in the host microbial ecology can result in disorders of host provision with a lot of nutrients of microbial origin. Thus, the provision of human being with required nutritional ingredients depends on both how well the host is provided with balanced foods and what state of intestinal microecology host has. Chronic imbalance in hundred biologically active functional ingredients (“nutrition imbalance”) should regard as a lead starting mechanism of many ecological and medical disorders and negative consequences. It means to decrease the risk of alimentary associated diseases the human nutrition ration and intestinal microbial ecology must be maintained in balanced condition.

2. Functional Nutrition: Concept and Objectives

2.1. Economic and Marketing Aspects of Functional Food Manufacture and Application.

Now increasing scientific evidences appear that food-stuffs not only satisfy appetite sensation, taste/aroma and the nutritional requirements of people but also provide beneficial physiological, metabolic and psychological effects over and above the provision of the basic nutrients. It is necessary to remember that more than 2000 years ago ancient Greek physician Hippocrates, considered as the father of Western medicine, said, “Let food be thy medicine and medicine be thy food”. The use of foods for their medical value as for their nutritional benefits is an ancient tradition in China, India, Egypt and Japan. At present, most people in the developed countries actively welcome everything that contributes to improving the quality of life and longevity. The food products became to be regarded as effective means of supporting physical and mental health and/or reduce the risk of many human diseases beyond basic nutritional functions. In the 1960s L.C. Pauling was the pioneer, who again offered an idea that the foods and nutrients might be considered as drugs. The great authority of this twice Nobel Prize laureate scientist quickly drew the attention of the international scientific world and socially active members and stimulated searching for foods and nutrients which were conducive to human health. Soon it had been found the link between obesity, type 2 diabetes and simple carbohydrates; osteoporosis and calcium;

hypertension and sodium; constipation and dietary fibre-containing products; atherogenic dislipoproteinemia and saturated fatty acids consumption (Sweden, USA); constipation, allergy, other pathological conditions and gut microflora disorders (Sweden, Japan, USSR, France, China), and so on. As a result at the beginning of XXI century thousands of various physiologically active food supplements (additives) were worked out and introduced international food market for correction of specific nutrition disturbances and health disorders associated with them. Marketing investigations showed that the people desire more to consume health foods reminiscent of natural products in form, taste and aroma. Such foods soon were named “functional foods. At present, the scope of functional food sale in the world is between about US\$75billion and US\$167 billion a year, depending on how strictly the sector is defined. USA and Japan have the largest markets of functional foods. Collectively, the US, EU and Japan market account for approximately 90% of global consumption of functional foods and beverages. Now 60% citizens of North America and about 32% - of West Europe use functional foods for supporting their health. The functional food industry is projected to grow 56 percent between 2008 and 2011. It is contemplated during the nearest 15-20 years the market of such health benefit functional foods will reach 30% of all food market and will come to US\$250-300 billion per year. In 2003 among functional foods (vitamin – containing and medical foods, sport foods, food for pregnant women, kid’s foods, etc), serving European market, were various milk products (65%), pastes, soft cheeses, jams (23%), bread-making products (9%), different soft drinks (3%). Over 10,000 functional products had launched globally between 2004 and 2007. For example, in China functional foods marked with the logo, sky blue stained, are used for body weight reduction, blood lipid and glucose regulation, improvement of sexual potency, vision, sleep, memory, gastrointestinal function, radiation protection and so on. Among the objective economic reasons why the peoples need food with additional health benefits: the increase in the number of the elderly, the people’s desire to improve their quality of life, the rise in cost of health care, etc. Participants of the International Symposium on “Functional Foods: Scientific and Global Perspectives (Paris, 2001)” came to a unanimous conclusion that functional foods ensure “unprecedented facilities for extended use of food products for health improvement, disease risk reduction and productivity increase”.

2.2. Concept of “Functional Food” and Terminology

The concept of “Functional Food” as an independent science, applied to Health and Nutrition, has been first formed in Japan at the end of the 1980s. The Japanese government and health authorities came to the conclusion that improvement of life quality in elderly peoples might be reached if health care costs were to be controlled by using a special group of food products. Later this concept was extended to other age groups. At about the same time corresponding terminology appeared. Today, in the world scientific literature the products and substances used in ordinary life and medicine for human health support, prophylaxis and treatment of diseases are designated as “functional foods”, “nutraceuticals”, “medical foods”, and rarely “health food”, “super foods”, “pharmafoods” and so on. It means that a universally accepted definition of functional foods has not as yet been established by legislation in the world. According to the initial Japanese definition, the concept of “Functional Food” had meant that the employment of foods of natural origin that are systematically applied could produce

positive regulatory effects to specific host physiological systems and organs or their functions improving the human physical and mental health. Primarily (1991), this group of foods was named “Foods for specified health use” (FOSHU). In the USA and Russia the term “Functional foods” was introduced in the scientific literature in 1994. The Scientific Concepts of Functional Food in Europe have been formulated in 1995-1998. According to the European approach, an obligatory condition for a functional food product (its acting functional ingredient) is to demonstrate the ability of such a product in safe quantity to provide health benefit influencing specific key host function(s). While the functional food category is not officially recognized by FDA (USA), Expert Report of Institute of Food Technologists (USA, 2004) and American Dietetic Association (2009) defined “functional foods” as “food and food components that provide a health benefit beyond basic nutrition (for the intended population)”. Examples may include conventional foods; fortified, enriched or enhanced foods; and dietary supplements. Bioactive food components (nutrients), are defined “as traditional vitamins, minerals, essential fatty acids for which recommended intakes have been established and other components that include phyto-chemicals or other bio-actives presented in foods for which a physical or physiological effect has been scientifically documented or for which a substantial body of evidence exists for a plausible mechanism, but for which a recommended intake and function have not been definitively established”. The last Russian National Standard (Functional food products; terms and definitions. GOST 52349-2005) defines functional foods “as foods for systematic (regular) use in nutrition ration composition by all groups of healthy inhabitants maintaining and improving state of health and reducing risk of nutrition-associated diseases via functional nutrition ingredients that are present in such products”. Functional nutrition ingredients are determined “as substances or their complexes of animal, plant, microbial or mineral origin or identical to natural ones, and live microorganisms included in functional food composition, that can produce benefit effect(s) to one or several physiological functions and metabolic processes”. In 1991, the Foundation for Innovation in Medicine (USA) proposed the term “nutraceuticals” that refers to nearly any bioactive substance that delivers a health benefit. Later, the nutraceuticals were defined as any “diet supplements that deliver a concentrated form of a presumed bioactive agent presented in a nonfood matrix, and used to enhance health in dosages that exceed those that could be obtained from normal food”. From a practical point of view, the functional foods tend to be broken down into several groups. Depending on outward appearance, the functional foods can have form resembling medicines for oral use (a tablet, capsule, powder, soft gel, gel cap, liquids etc.) or present in their naturally-occurring form (milk products, soup, pastes, jams, bread-making products, sweets, soft drinks, etc.). The first group of functional foods, usually named nutraceuticals (food additives, dietary or food supplements), may contain corresponding functional ingredient(s) in quantity up to or more 10 Reference Daily Intakes (RDI); that is why the food supplements recommend to assign only for short periods of time (from 18 to 45 days). The second group are functional foods, resembling the traditional article of foods, contain functional nutrient(s) in the number of about 10-50% from the RDI; they use systematically for an indefinitely long period in the composition of traditional diet rations. Depending on the origin or activity of functional ingredient(s) the second category of functional foods could be distinguished as: a) Unmodified functional foods, naturally containing the required quantity of functional ingredient (s) (e.g., consumption of 150.0 g persimmon covers practically completely

RDI of iodine ions in adult man; 400.0 g water-melon – of magnesium ions and folic acid); b) Processed functional foods with added or enhanced functional ingredients are the food-stuffs additionally enriched (fortified) with required quantity of functional component (s) (e.g., juices or milk enriched with vitamins or prebiotics); c) Processed functional foods with eliminated negative compounds are some natural food-stuffs containing chemicals or ingredients that can produce harmful effect on the human organism; removing this chemical component from food product makes it functional (e.g., macaroni without gluten; lactose eliminated milk; low (zero) fat spreads); d) Processed functional foods with modified structure. These natural articles of food may be manipulated such way that they begin to display greater activity (e.g., functional probiotic foods containing fructo-oligosaccharides improving growth and activity of probiotic bifidobacteria); in this group may be also included food-stuffs in which the bioavailability and activity of one or more functional ingredients has been improved (e.g., porridge containing ground flax seeds). Thus, the functional foods may include those to which desirable components are added or changed, as well as those from which undesirable components are removed or changed.

At the beginning, the main aim and tasks of foods for specified health use were only to optimize the human nutrition rations. It was supposed that such products increase human internal nutrient reserves resulting in improving its adaptation facilities (especially in stress situations) and health, and in this way decrease the risk of diseases. Their purpose is to support well-being and to reduce the risk of diseases rather than prevention or especially their treatment. On the other hand, every day experimental and clinical data are accumulated showing that certain macro- and micronutrients entering host organism via food in adequate quantity can produce positive health effects to specific tissues, organs, physiological functions and biochemical reactions. This and similar information had allowed functional food manufacturers and distributors to organize the active market advertisement positioning food-stuffs containing certain health benefit nutrients as effective health protectors. In this connection to eliminate a disinformation for the consumers a number of international and national Nutrition Guidance and Control Organizations (e.g. European Food Safety Authority-EFSA and US Food and Drug Administration-FDA) were forced to work out the recommendations in conformity with which an article of food can be applied to the functional food if a manufacturer (distributor) furnishes convincing proof that his product produces a beneficial action to one or several key functions or metabolic reactions in a human being. In the last 10 years or so, the health claims situation connected with functional foods undergoes considerable difficulties because the vast majority of regulator organizations in the Europe and North America controlling the market with functional food suppliers began to require for estimation of health claims of these foods using assessment methods closely related to those utilized for pharmaceutical preparations.

2.3. Functional Foods Health Claims.

In the USA, EU, Japan, Russia and other developed and some developing countries there are strict regulations governing food labeling, product formulation, food processing, packaging, marketing, registration and licensing details. Because distinguishing between foods and traditional medicines is not an easy task, many international and national academic, scientific and regulatory organizations are trying to

establish a scientific basis for functional food health claims to protect consumers from false and misleading claims and simultaneously to stimulate manufacturers of such foods for innovation in the product development, marketing and promotion. Now in the world there is no harmonized legislation on health claims. In the majority of countries labeling legislation prohibits to use the words “preventing, treating or curing a human disease” to any articles of food. The main aim of health claims is to impress upon the consumers so that food-stuffs recommended as functional foods, really can help reduce the risk of diseases and support well-being. At present, two types of functional foods have been approved by the Japanese government: those with approved health claims (FOSHU) and foods that may provide health benefits without any health claims. Some European Guidance Organizations (the European Commission Concerted Action of Functional Food Science in Europe-FUFOSE, the EFSA, the European Health Claims Alliance-EHCA) and similar organizations in some other countries have developed several science-based approaches for estimation of beneficial effects of the food products to human health. Any foods can be regarded as functional foods if they produce a beneficial effect on the next identified physiological functions, metabolic and behavioral reactions: health claims relating to the role of a nutrient or other substance in growth, development and the functions of the body; relating to psychological and behavioral functions; relating to substrate metabolism, defense against reactive oxidative species; relating to gastrointestinal physiology and function; relating to slimming, weight-control, a reduction in the sense of hunger, an increase in the sense of satiety or a reduction of the available energy from the diet; relating to immune system condition and colonization resistance; relating to indigenous microbial ecology condition; relating to cardiovascular system condition and etc. The FUFOSE also offers two types of health claims relevant to functional foods: “enhanced function” claims that are connected with food interfering into specific normal physiological, metabolic and psychological activities and “reduction of disease-risk” claims that related to the consumption of a food that might help reduce the risk of a specific diseases or condition. According to the recommendations, all groups of health claims must be based on the well designed investigations with the use of correspondingly identified, characterized and validated biomarkers. Besides, the functional food-stuffs with health claims should consider the amount and frequency of consumption, any possible interplays with other dietary compounds, impact on metabolic pathways, and potential for adverse effects (food safety aspects). According to the USA FDA, the claims used on food and dietary labels should be divided into three categories: Health Claims, Nutrient Content Claims, and Structure/Functional Claims. Health Claims describe an interaction between functional foods (nutraceuticals) or their bioactive ingredient(s) and reducing risk of a diseases or health-related condition. It means that Health Claims include two essential components: substances (whether a food or food component) and a diseases or health-related condition. Nutrient Content Claims characterize the level of a nutrient in the food. These claims describe the level of a nutrient or bioactive compound in the food product, using terms such as *free*, *high*, and *low*. Most Nutrient Content Claim regulations apply only to those nutrients or dietary substances that have an established daily value. Structure/Function Claims describe the role of a nutrient bioactive intended to affect normal structure or function in humans or acts to maintain such structure or function (e.g., improves microbial balance; enhances natural immune function). In addition, they may describe a general well-being from the consumption of nutrient or dietary compounds. Structure/Function claims may also depict a benefit

connected with a nutrient deficiency disease. Even Structure/Function claims must be based on evidence derived from the human studies. According to Russian GOST 52349-2005, any articles of food may be related to functional foods if the content of health benefit macro- and micronutrients in the product is within 10-50% of established RDI for healthy inhabitants. In such concentration this nutrient/bioactive dietary ingredient has to maintain or improve the state of health or reduce risk nutrition-associated diseases. Ordinary diet can include various conventional foods containing different quantity and spectrum of potentially physiological active similar substances. To exclude side effects, the total number of functional nutrients eaten must not be more RDI for healthy individuals. The sense of Russian functional food claims is very close to U.S. Nutrient Content and Structure/Function claims used on food and dietary labels.

In Japan, the foods, identified as FOSHU, must be approved by Ministry of Health and Welfare after the submission of comprehensive science-based evidences supporting the corresponding claims for such foods. In USA, unlike health claims, dietary guidance statements (Nutrient Content claims) and Structure/Functional claims are not subject to FDA review and authorization but they must be truthful and not misleading. The manufacturers of foods that make Structural/Function claims on labels must submit a notification to the FDA no later than 30 days after marketing the dietary supplement that includes the information concerning the Structure/Function claim.

In Russia, all nutraceuticals should be approved by corresponding State Regulator Agency before these food supplements will be introduced to the market. Regulation Guidance concerning functional foods is open question up to now. In the Spanish speaking countries of Latin America, also there is no a harmonized legislation on functional foods. The major health benefits are always difficult to substantiate. Large scale clinical trials are expensive to commission and complicated to manage. The costs for a clinical study can range from \$2 to \$4 million and a functional food product development can take up to ten years. Nevertheless, according to the last regulation rules in a majority of developed countries, specific health claims have been made and approved.

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Biographical Sketch

Boris A. Shenderov is a physician, a Doctor of Medical Science (1976), Professor of Microbiology, Immunology and Virology (1979), an Active Member of New-York Academy of Science (1996). Nowadays, he lives and works as a main researcher and head of Research Group “Probiotic and Functional Foods” at the Moscow Research Institute of Epidemiology and Microbiology after G.N. Gabrichevsky. His main research interest is Medical Microbial Ecology; Genetics of Microorganisms; Probiotics; Functional Foods; Biotechnology. He is an author of more 400 scientific papers, including 10 books, 30 inventions. He is a Honorary President of Russian Association “EPIDBIOMED”, Project Director of a Program “Health through Nutrition” in All Russian Association of Specialists in the Restoration Medicine, a Scientific Expert of Russian Humanities Fund, councilor of Executive Board of International Society of Microbial Ecology and Disease (SOMED); a Member of Executive Board of International Society of Gnotobiology (IAG), a Member of Russian Society of Microbiology and Epidemiology after I. Mechnikov. He is also a Deputy Head of Editorial Committee of Journal “Clinical Nutrition”(St. Petersburg); member of Editorial Committee of Journal “Bulletin of Restoration Medicine”, member of Editorial Boards of Journals “Antibiotics and Chemotherapy”, “Microbiology, Epidemiology and Immunobiology”, “Professional Nutrition” (Russian Journals).