Erciyes Med J 2018; 40(4): 188-93 • DOI: 10.5152/etd.2018.18169

INVITED REVIEW

Functions of the Human Intestinal Microbiota in Relation to Functional Foods

Elisavet Stavropoulou[1], Christina Tsigalou[2], Eugenia Bezirtzoglou[3]

ABSTRACT

Interest in functional foods has increased due to their relationship to diet and health. A healthy nutrition preserves the intestinal ecosystem and enhances health. Probiotic *Lactobacillus* appears to be highly sensitive to diet, environmental factors, stress, and antibiotics. Functional foods are known to play an important role in the stability of a human intestinal ecosystem. Moreover, dissemination of antibiotic resistances into consumed dairy and meat products could select some bacterial species. However, awareness of the relationship between food and health must be constant through permanent surveillance systems. The European Union guidelines should be imposed for the safe use of functional foods as foods or either as biotherapeutic agents. Functional foods are foods that surpass classic nutritional habits and have usually beneficial action for their host. They are classified into three main classes: probiotics, prebiotics, and symbiotics. The use of genetically modified probiotics could provide further chances for the industrial and pharmaceutical exploitation of probiotic microorganisms. In contrast, prebiotics are not microorganisms but non-digestible components. They stimulate the growth and/or the activity of several bacteria in a beneficial way. Their action contributes to a healthy and balanced intestinal microbiota. Systematic administration of prebiotics decreases blood lipid counts, as well as blood pressure, but increases the synthesis and absorption of foods and maybe has an anticarcinogenic action. They are also used extensively in the food industry. Last but not the least is the class of symbiotics, which combines a mixture of probiotics and prebiotics with both effects.

Keywords: Functional foods, intestinal microflora, probiotics, prebiotics, symbiotics, microbiota

Cite this article as: Stavropoulou E, Tsigalou C, Bezirtzoglou E. Functions of the Human Intestinal Microbiota in Relation to Functional Foods. Erciyes Med J 2018; 40(4): 188-93.

[1]Centre Hospitalier Universitaire Vaudois(CHUV),Service de Medicine Interne, Rue du Bugnon 21,CH-1011-Lausanne, Vaud, Switzerland
[2]Democritus University of Thrace, Faculty of Medicine, University Hospital, Laboratory of Microbiology, Alexandroupolis, Greece
[3]Department of Food Science and Technology, Democritus University of Thrace, Faculty of Agricultural Development, Laboratory of Microbiology, Biotechnology and Hygiene and Laboratory of Food Processing, Orestiada, Greece

Submitted 04.11.2018

Accepted 06.11.2018

Correspondence Elisavet Stavropoulou, Centre Hospitalier Universitaire Vaudois(CHUV),Service de Medicine Interne, Rue du Bugnon 21,CH-1011-Lausanne, Vaud, Switzerland
Phone: 0030-6946003063
e.mail: elisabeth.stavropoulou@gmail.com

The Concept of Functional Foods

Functional foods are foods that surpass simple nutrition and have usually beneficial action for their host. Fermented products were well-known since thousands of years as formerly the term “acid milk” was mentioned in the Bible.

In 1908, Metchnikoff (1) in his thesis dissertation entitled “The prolongation of life” associated the systematic ingestion of Bulgarian fermented milk and yoghurt to the longevity of the Caucasian people, recognizing the health profits of dairy fermented foods.

Since then, the development and use of many functional foods was introduced in our nutritional habits. Functional foods were developed nowadays in various countries, and they are categorized into three classes as probiotics, prebiotics, and symbiotics.

Differences in national policies and legislation differentiate their features on functional foods. Japan is the only country that highly supports the benefits of functional foods, and in this vein, a plethora of functional foods (>200) are developed and branded under the name FOSHU (Foods for Specialized Health Use). In addition, the US Food and Drug Administration (FDA) implemented a legislation for >15 functional foods.

Origin and Chemical Nature

Since ancient times, fermented foods evolved from empirical cultures with profitable action to synthetic probiotic cultures including selected species of enteric bacteria (2).

Functional foods, such as probiotics, prebiotics, and symbiotics, could modify the activity of the gastrointestinal tract (3).

In 2000, probiotic strains genetically selected with a reinforced profile were used for therapeutic purposes (2).

It is actually more than an axiom that healthful effects are attributed to probiotic lactic acid bacteria (LAB).

The new biotechnological tools were shown to be valuable for the choice of new strains, amendment of several functional properties, nutritional optimization of foods, and launching of sensory and textural qualities of food.

The most important feature of functional foods is associated with the activation of the host immune system that plays a key role in the microbial intestinal balance. This is called the "barrier effect."

Among those foods, dairy functional foods were particularly of interest by showing important health profits, such as reinforced nutritional value, promoting intestinal lactose digestion. Moreover, their clear beneficial action on the urogenital and intestinal microflora is largely discussed as their extensive use aims the prevention of gastrointestinal illness by prohibiting intestinal colonization by enteric pathogens.

Probiotics play a major role in the protection of the integrity of the intestinal ecosystem.

Ways of Action

Various pathways of action are connected with these beneficial bacteria in the intestinal tract and specifically include the following: spatial antagonism (spatial arrangement theory); antagonism for nutrients present in limited quantities; their acid epithelial pH; generation of H_2O_2; generation of antimicrobial features, organic acids, or bacteriocins; production of nutrients providing energy for epithelial cells or other bacteria; and immune system activation (2).

Functions Associated with Functional Foods

It is noteworthy that "therapeutic" roles are associated with their functional ability, as control of the gut peristalsis, reduced occurrence and duration of diarrhea, stabilization of the mucosal integrity, boosting of the immune system, and decrease of the catabolic products excreted by the kidney and liver.

The authors reported their relationship to the prevention of colon cancer as having anticarcinogenic and antimutagenic actions (4), as well as their anti-allergic activities (5).

Anticancer activity remains to be the most controversial. In this purpose, dietary intervention studies were conducted by measuring specific biomarkers, such as colon mucosal markers and immunological markers, as well as fecal water markers (4).

Nevertheless, no experimental data for cancer regression in humans as a result of ingestion of dairy lactic cultures are found.

Meat consumption appears to shift the intestinal microbiota in a non-beneficial profile and correlates the gut microbiota with cancer disease (6). Epidemiological studies report the presence of intestinal cancer to follow an increasing course in developed countries due to the most important consumption of meat (6). In contrast, plant-based diet could reduce cancer risk (7).

Functional foods are stimulating the production of calcium and appear to play a role in the prevention of osteoporosis. Moreover, they have a hypocholesterolemic action, and finally, they compensate us with the feeling of well-being.

Prebiotics and Symbiotics

Prebiotics are non-digestible bioactive functional foods with a beneficial action on the intestinal microbiota of the host (8). They present many properties (8). They are non-hydrolyzed or absorbable substances in the intestine and participate in several metabolic pathways of the beneficial microbiota. They are also able to promote the beneficial microbiota growth, as well as its metabolic potential. Moreover, they develop resistance in stomach acids, bile, and pancreatic secretions and boost the welfare of the host. They are carbohydrates, dietetic fibers non-digestible with a specific action, resulting in the increase of intestinal bacterial volume and mass. Furthermore, they are able to modify the intestinal pH and, finally, to produce volatile fatty acids and gas (2).

Table 1. Microorganisms applied in probiotic products

Yeasts	**LAB**	***Bifidobacterium sp.***	***Lactobacillus sp.***
Saccharomyces cerevisiae	*Enterococcus faecalis*	*B. adolescentis*	*L. rhamnosus*
Saccharomyces boulardii	*Enterococcus faecium*	*B. animalis*	*L. kefir*
	Lactococcus lactis subsp. lactis	*B. bifidum*	*L. delbrueckii subsp.*
bulgaricus			
	Lactococcus lactis subsp. cremoris	*B. breve*	*L. helveticus*
	Leuconostoc mesenteroides subsp. dexiranicus	*B. infantis*	*L. casei GG*
	Pediococcus acidilactici	*B. lactis*	*L. curvatus*
	Sporolactobacillus inulinus		*L. brevis*
	Propionibacterium freudenreichii		*L. acidophilus*
	Streptococcus thermophilus		*L. casei*
			L. crispatus
			L. gallinarum
			L. gasseri
			L. johnsonii
			L. paracasei subsp. paracasei
			L. plantarum
			L. reuteri
			L. cellobiosus

The combination of probiotics and prebiotics as functional foods results in the "symbiotic" approach (from the Greek word to live together), collecting both effects.

The current generation of functional foods is based on the super induction of targeted substances (e.g., conjugated linoleic acids or polyunsaturated fatty acids).

Recently, the role of dairy functional foods as mild therapeutic agents (9) has been examined.

Functional Foods and Intestinal Microbiota

The role of functional foods in the balance of the intestinal ecosystem is largely discussed (8). However, the specific action of prebiotic and probiotic microorganisms in not only regulating the balance of the microbial intestinal flora but also participating actively in the metabolism must be clear.

The human gastrointestinal tract harbors a large variety of microorganisms. First, a human newborn lacks microorganisms before delivery (10). Bacteria colonize newborns from the very first days of life (10). In this way, newborns develop their normal bacterial flora, which originates mainly from the surrounding environment (10, 11), the hospital personnel (12, 13), and the diet (14-16). The profile of the newborn gut microflora is associated definitely with age, race, and mainly on feeding habits (15-19).

Different parts of the gastrointestinal tract harbor different bacterial populations during its downward course. Qualitative and quantitative differences are observed (12). Increasing counts of bacteria are recorded as they move down the digestive tract where the bacterial numbers observed could be as high as >10 million bacteria/mL of fecal fluid (12).

Lactobacillus spp. are normal inhabitants of the human gastrointestinal tract.

Lactobacillus spp. show beneficial effects and improve the human intestinal microbiota (20). Then, they belong to probiotics. Probiotics produce nutrients, bacteriocins, and antimicrobial substances and are capable of removing toxins and preserving food from putrefaction.

Probiotics clearly play a key role in the intestinal microflora by maintaining its balance.

Lactobacillus is a facultative anaerobic or aerobic rod that inhabits the normal human microbiota without showing any pathogenic effect (9, 20). Nevertheless, which particular factors are involved in the evolution of the lactic acid microflora is not yet clear. *Lactobacillus* shows selective adherence to the intestinal ecosystem (21).

It is also noteworthy that some enterobacterial strains possess specific adhesins that facilitate the adhesion and colonization of the gastrointestinal mucosa. This could play a role to their pathogenicity potential (21).

Non-pathogenic anaerobic bacteria species, such as *Lactobacillus* and *Bifidobacterium*, interfere in the adhesion and invasion potential of some enteropathogenic bacterial strains (22). Although there are many studies on probiotics *Lactobacillus* sp., concrete information on their colonization capacity in the gut microbiota is not yet satisfactory.

Dairy Functional Foods and Intestinal Microbiota

Lactic acid Bacteria (LAB) are involved in dairy fermentation since the ancient years. Researchers worldwide identify the microbiota of various "ethnic" products (23-28).

Fermentation could occur through raw milk's microbiota spontaneously or following inoculation of a starter culture. In Greece and specifically in the Epirus area, "pytia" (rennet) is known for centuries as a probiotic starter containing LAB (2).

Dairy preparations, such as yoghurt and kefir, contain probiotics that promote the well-being of the intestinal ecosystem. Various mechanisms are involved as described previously.

In Greece, people in the agrarian sector prepare traditionally unpasteurized dairy foods and containing live cultures of *Lactobacillus*, *Bifidobacterium*, or other probiotic microorganisms.

Knowledge on the nutritional habits of a population is important. Children are ingesting milk and dairy products more commonly than the adult population. In this vein, their intestine is expected to be colonized by probiotics, such as *Lactobacillus paracasei*, *Lactobacillus delbrueckii lactis*, *Lactobacillus lactis lactis*, *Leuconostoc*, and *Bifidobacterium* (10%). These species are sparsely found (5%) in an old person's microflora (29).

It should be noted that old people have particular alimentary and are consuming often fermented traditional foods. Their intestine is colonized by bacterial strains used classically in traditional food preparations (30).

Healthy subjects in all ages are harboring a predominant lactoflora (100%). Qualitative and quantitative differences are observed with increasing age (12, 18). During aging, *Lactobacillus* biotypes and numbers seem to be constant (31).

Environment, Stress, Antibiotics, and Other Factors Altering the Intestinal Microbiota

Furthermore, extended isolation of a person, as in the case of a long space flight or special trainings, modifies the intestinal microbiota (32). It is also extensively discussed that stress influences the gut microbiota. Putrefactive bacteria increase *Clostridium perfringens* in numbers in this last case (33).

Gut diseases, bacterial or viral diarrheas, pseudomembranous colitis, and antibiotic-associated diarrhea have been cured by the use of pharmaceutical probiotics, such as *Saccharomyces boulardii*, *Lactobacillus casei* GG, *Lactobacillus acidophilus*, and *Enterococcus faecium*.

Increased numbers of *Lactobacillus* and/or *Enterococcus* were observed in the intestine of infants with rotavirus diarrhea (34), as well as inhabitants of the Chernobyl nuclear accident (35).

Missing fecal *Lactobacillus* is reported in elderly people by some studies (17,18,21). However, it seems that there is a universal scientific agreement on the preponderance of *Lactobacillus* in all ages (17, 18, 21, 29).

As stated, *Lactobacillus* is very sensitive to environmental factors, diet, antibiotics, and stress (30).

Overuse of antibiotics in animals could spread antibiotic resistances into dairy products and consumer (30). *C. perfringens* strains originating from foods developed resistances in various antibiotics ranging from 8% to 49% (30). Resistant *C. perfringens* strains overwhelm the intestinal flora of an elderly individual (36, 37).

In Greece, multi-resistance in hospitalized patients and outpatients is unregistered (38, 39). It is noteworthy that outpatients had not been treated regularly with antibiotics. In this vein, the observed antibiotic multi-resistance was not expected in outpatients. These acquired resistance patterns may be due to the ingested feed. It is reported that unfortunately in Greece for boosting the quality of animals, antibiotics are placed illegally in their alimentation. In this way, antibiotics could be found at high levels in animal tissues and flesh, as well as in their products consumed by man. Undoubtedly, consumers ingesting such foods will develop antibiotic resistance profiles (30).

Differentiation between autochthonous microorganisms of the gut microflora and transient ones associated with food, environment, and personal habits is not always easy to determine.

Lactobacillus is reported to harbor the normal vaginal flora in high numbers (1). However, excessive antiseptic use during delivery may repress and limit the bacterial species able to colonize the newborn gut (37). *Lactobacillus* is very sensible to antiseptic exposure.

Lactobacillus adheres to the epithelial cells as these species have the ability to ferment monosaccharides of mucin (40). Antibiotics are able to breach the mucosal integrity (40).

Moreover, *Lactobacillus* showed inhibitory action against some pathogenic bacteria, ensuring the safety of many food products (29). Bacteriocins are bactericidal peptides that could suspend the growth of other bacterial species (41). LAB are able to produce bacteriocins.

C. perfringens and *Escherichia coli* were found in high numbers in adult and elderly microflora. *C. perfringens* (25%) was often present in children microflora, followed by *E. coli* (10%) (37). Lower levels of *Bacillus* sp. (2.5%) and *Staphylococcus aureus* (2.5%) were found (37).

C. perfringens was present in both vegetative and spore forms at all ages (19, 37). The occurrence of *C. perfringens* spore forms was higher in children (20%) and aged population (87.5%). Vegetative forms of *C. perfringens* do not appear in children and old people when *Lactobacillus* predominates the microflora. *C. perfringens* vegetative forms were common (70%) in healthy adults (15, 37, 40). Environmental factors and personal habits of hygiene are involved (37).

The presence of *Lactobacillus* is outnumbered by obligate anaerobes in the intestine.

The characterization of the mucosal lactoflora seems to be difficult as methodological limitations of collecting biopsy samples from healthy subjects are not always obvious.

In conclusion, the composition of the human lactoflora remains obscure and speculative despite the many studies undertaken.

Microbial Balance

The plethora of microorganisms inhabiting the human gut is described as the "autochthonous microflora." There is a very complex relationship of bacteria harboring our intestine and our body. Their role is to mediate the gastrointestinal balance between health and disease (37).

When exogenous invaders are introduced in the intestine, the ecosystem fights against these foreign species. In case where the intestinal barrier is damaged, the disease develops (37). However, how the disease occurs is not yet clear as several diseases require an important bacterial bulk in order to initiate illness, and others require much lower bacterial numbers.

Pathogenic *Salmonella* species require large ingested numbers in order to initiate disease. Moreover, not all *Salmonella* species are pathogenic. However, *Salmonella* is susceptible to stomach acidity (42). In contrast, *Shigella* species are pathogenic, and only a few cells of the microorganisms are able to cause the disease (n=200). *Shigella* is able to bear stomach acidity and thereafter resides in the intestine and develops into illness (42).

As already stated, the overall nutritional habits and maintenance of a healthy and functional immune system could protect us from these invading organisms. The type of diet and aging are closely related to the microbial population of our intestine. In a diet rich in starches, the bacterial species that ferment starches will amplify their presence in the intestine. In this vein, the classic example is the excess consumption of sugar. Certain types of microorganisms that live within our intestine thrive on a high sugar diet, most notably *Candida albicans*. A symptom of a swollen abdomen after consuming sugar is an indication of *Candida* blooming as the *Candida* microflora produces poisonous endotoxins.

Metchnikoff believed that premature senescence is the result of bacterial activity (1) and the so-called autointoxication, resulting in chronic infection in the gut. Additionally, when the infection is removed, the symptoms disappeared. These toxemias are generally accepted as due to the absorption of putrefactive substances at the lumen of the intestine as a result of bacterial proteolysis on proteins.

Some of these substances are absorbed and excreted by the kidneys (43).

Although the therapeutic advantages of the lactoflora for the host are previously known, it is obvious that more research must be conducted in this topic in order to provide enough explanations of the involved mechanisms.

Microorganisms Applied in Probiotic Products

Fermented dairy products are considered as complete food providing us with the feeling of fullness by increasing human intestinal bacterial volume and numbers.

Probiotic bacteria introduced by food in the large intestine are participating in the fermentation of alimentary-derived indigestible carbohydrates. This type of fermentation results in the production of short-chain fatty acids (SCFAs) that decrease circulatory cholesterol levels by restricting hepatic cholesterol synthesis or by allocating cholesterol from plasma to the liver (44). Cholesterol, as a precursor of bile acids, participates actively in the de novo bile acid synthesis (44).

Moreover, interesting bacterial activity levels in the intestine appear to enhance bile acid deconjugation. Deconjugated bile acids are known to be non-absorbable at the level of the intestinal mucosa and therein eliminated (44).

Many bacterial strains belong to probiotics (Table 1).

However, *Lactobacillus* and *Bifidobacterium* are more commonly isolated from yoghurts or other fermented dairy products and play an important role in the treatment of gastrointestinal infections by reinforcing the intestinal system against adhesion and invasion of pathogens.

DISCUSSION

The integrity of the intestine seems to be largely dependent on the presence of a healthy microbiota as probiotics are involved in promoting the intestinal defense barrier by regulating the intestinal permeability and microecology (45).

Therefore, probiotic dairy products promote the integrity of the intestinal system by activating the immunological response through the production of immunoglobulin A (46).

Probiotics may reduce the levels of intestinal enzymes, mutagens, and secondary bile salts that are potentially incriminated in colon carcinogenesis. SCFAs, such as acetate, propionate, and butyrate, are known to be produced following the fermentation procedure in the intestine. Elevated levels of SCFA were associated with a low intestinal pH (47) favorable in fighting colon cancer.

In this vein, the relationship between fecal low pH value and total fecal SCFA concentration argues the fact that high concentrations of fecal SCFA could provide protection against chronic bowel diseases.

The human intestine defines a characteristic microflora with specific actions as production of secondary compounds that could lead to health promotion. These secondary compounds include SCFAs, as well as short bioactive peptides originating usually from milk intestinal cleavage.

In contrast, prebiotics play a different role by decomposing the provided substrate in the intestine.

It is somewhat of interest to discuss the damaging effect on the intestinal flora balance of chlorine and sodium fluoride, which are substances that are present in most treated city water systems, and by extension found in most consumed beverages. Additionally, drinking alcoholic beverages contributes to the destruction of the intestinal flora, as well as adding antibiotics in animals or other foods and systematic drug intake.

Particular problems occur when food-ingested bacteria growth remains unchecked (48). Then, probiotics seem to play an important role in keeping in control these pathogenic bacteria that could cause disease. The beneficial probiotic microflora contains live bacteria that inhibit harmful pathogenic microorganisms (49).

Today, healthy eating is promoted shifting toward the potential health benefits of functional foods.

The actual knowledge of innovative technologies, such as nutrigenomics (50), imaging techniques, and converging technologies, is applied currently in nutrition research (51).

Nutrigenomic technology (50, 51) explores the shifts in gene and protein expression and metabolite pathways following the shifts in diet. Where such shifts occur (52), markers could be used to determine the effect of bioactive food components. It is obvious that more time is required to proceed to the identification of the appropriate markers for functional foods.

Glossary

LAB	Lactic Acid Bacteria
FOSHU	Foods for Specialized Health Use
FDA	Food and Drug Administration
Pytia	Rennet

Author Contributions: Conceived and designed the experiments or case: EB, ES. Performed the experiments or case: EB, ES. Analyzed the data: EB, ES, CT. Wrote the paper: EB, ES, CT. All authors have read and approved the final manuscript.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Metchnikoff E. The prolongation of life. Metchnikoff Thesis, New York, Putnam and Sons, 1908.
2. Varzakas T, Arvanitogiannis I, Bezirtzoglou E. Functional dairy foods and flora modulation In: Yildiz F (Editor). Development and Manufacture of Yogurt and Other Functional Dairy Products, 1st Edition, Editor, 2009: 451. [CrossRef]
3. Bezirtzoglou E. Intestinal cytochromes P450 regulating the intestinal microbiota and its probiotic profile. Microb Ecol Health Dis 2012; 23: 18370-5. [CrossRef]
4. Liong M-T. Roles of Probiotics and Prebiotics in Colon Cancer Prevention: Postulated Mechanisms and In-vivo Evidence Int J Mol Sci 2008; 9(5): 854-63.
5. Ouwehand AC. Antiallergic effects of probiotics . J Nutr 2007; 137 (2): 794-7. [CrossRef]
6. Chao A, Thun MJ, Connel CJ, McCullough ML, Jacobs EJ, Flanders WD, et al. Meat consumption and risk of colorectal cancer. JAMA 2005; 293(2): 172-82. [CrossRef]
7. Block G, Patterson B, Subar A. Fruit, vegetables, and cancer prevention: A review of the epidemiological evidence. Nutr Cancer 1992; 18(1): 1-9. [CrossRef]
8. Gibson G, Roberfroid MB. Dietary modulation of the human colonic microbiota: Introducing the concept of prebiotics. J Nutr 1995; 125(6): 1401-12.
9. McFarland LV, Elmer GW. Pharmaceutical probiotics for the treatment of anaerobic and other infections. Anaerobe 1997; 3(2-3): 73-8. [CrossRef]
10. Bezirtzoglou E. Contribution à l'etude de l' implantation de la flore fecale anaerobie du nouveau-ne mis au monde par cesarienne. Doctorat No 13, Paris-Sud, 1985.
11. Lundequist B, Nord CE, Winberg J. The composition of the fecal microflora in breast-fed and bottle-fed infants from birth to eight weeks. Acta Paediatr Scand 1985; 74(1): 45-51. [CrossRef]
12. Bezirtzoglou E, Chavatte P, Romond C. A quantitative study of fecal and other bacteria floras of newborns delivered by cesarian section G. I. Pat Clin 1989; 2: 39-43.
13. Shooter RA, Asheshov EH, Bullimore JF, Morgan GM, Parker MT, Walker KA, et al. Fecal carriage of Ps. aeruginosa in hospital patients. Lancet 1966; 2: 1331-4. [CrossRef]

14. Bezirtzoglou E, Romond C. Occurrence of Bifidobacterium in the faces of newborns delivered by cesarian section. Biol Neonate 1990; 58(5):175-80. [CrossRef]
15. Finegold S, Sutter V, Mathisen G. Human intestinal microflora in health and disease. Academic Press, London, 1983.
16. Bezirtzoglou E, Romond C. Effect of the feeding practices on the establishment of bacterial interactions in the intestine of the newborn delivered by cesarian section. J Perinat Med 1989; 17: 139-43.
17. Mitsuoka T, Kimura TN. Die Fakalflora bei Menschen Zentralbl. Bakteriol. Parasit. Infekt. Hyg 1973; 226(1): 469-78.
18. Ellis-Pegler RB, Crabtree C, Lambert HP. The fecal flora of children in UK. J Hyg 1975; 75: 135-42. [CrossRef]
19. Bezirtzoglou E, Romond MB, Romond C. Modulation of Clostridium perfringens intestinal colonization in infants delivered by caesarean section. Infection 1989; 17(4): 232-6. [CrossRef]
20. Fuller, R. Probiotics in human medicine Gut 1991; 1: 439-49 [CrossRef]
21. Juronen EI, Viikmaa MH, Mikelsaar AV. Rapid, simple and sensitive antigen capture ELISA for the quantitation of myoglobin using monoclonal antibodies. J Immunol Methods 1988; 111(1): 109-15. [CrossRef]
22. Ingrassia I, Leplingard A, Darfeuille-Michaud A. Lactobacillus casei DN-114 001 Inhibits the Ability of Adherent-Invasive Escherichia coli Isolated from Crohn's Disease Patients To Adhere to and To Invade Intestinal Epithelial Cells. Appl Env Microbiol 2005; 71(6):2880-7. [CrossRef]
23. Mata LJ, Mejicanos ML, Jimenez F. Studies on the indigenous flora of Guatemalan children. Am J Clin Nutr 1972; 1380-90. [CrossRef]
24. Psoni L, Tzannetakis N, Litopoulou-Tzannetaki E. Characteristics of Batzos cheese made from raw pasteurized and /or pasteurized standardized goat milk and a native culture. Food Control 2003; 17(7): 533-9. [CrossRef]
25. Mathara JM, Schillinge U, Kutima PM, Mbugua SK, Holzapfel WH. Isolation, identification and characterization of the dominant microorganisms of kule naoto: the Maasai traditional fermented milk in Kenya. Int J Food Microbiol 2004; 94(3): 269-78. [CrossRef]
26. Hossain MA, Ralman S, Chowdhury S, Rashid MA. Bioactivities of extractives. Dhaka Univ J Pharm Sci 2007; 6: 47-50.
27. Kebede A, Viljoen BC, Gadga TH, Narvhus JA, Lourens-Hattingh A. The effect of container type on the growth of yeast and lactic acid bacteria during production of Sethemi, South African spontaneously fermented milk. Food Res Int 2007; 40(1): 33-8. [CrossRef]
28. Mohammed Salih AM, El Sanousi SM, El Zubeir IEM. A Review on the Sudanese Traditional Dairy Products and Technology. Int J Dairy Sci 2011; 6: 227-245. [CrossRef]
29. Vassos D, Maipa V, Voidarou C, Alexopoulos A, Bezirtzoglou E. Development of human lactic acid (LAB) gastrointestinal microbiota in a Greek rural population. Centr Eur J Biol 2008; 3(1): 55-60. [CrossRef]
30. Bezirtzoglou E, Alexopoulos A, Voidarou C. Apparent antibiotic misuse in environmental ecosystems and food. Microb Ecol Health Dis 2008; 20(4): 197-8. [CrossRef]
31. Tiihonen K, Ouwehand AC, Rautonen N. Human intestinal microbiota and healthy ageing. Ageing Res Rev 2010; 9(2): 107-16. [CrossRef]
32. Smirnov KV, Lizko NN. Problems of space gastroenterology and microenvironment. Mol Nutr Res 1987; 31(5-6): 355-644. [CrossRef]
33. Tsiotsias A, Voidarou C, Skoufos J, Simopoulos C, Konstadi M, Kostakis D, et al. Stress-induced alterations in intestinal microflora. Micr Ecol Health Dis 2004; 16: 28-31. [CrossRef]
34. Marteau P, Seksik P, Jian R. Probiotics and intestinal health effects: a clinical perspective. Brit J Nutr 2002; 88(1): 51-7. [CrossRef]
35. Sajjadieh MRS, Kuznetsova LV, Bojenko VB. Dysbiosis in Ukrainian Children with Irritable Bowel Syndrome Affected by Natural Radiation. Iran J Pediatr 2012; 22(3): 364-8.
36. Bezirtzoglou E, Maipa V, Chotoura N, Apazidou E, Tsiotsias A, Voidarou C, et al. Occurrence of Bifidobacterium in the intestine of newborns by fluorescence in situ hybridization Comp Immunol. Microbiol Infect Dis 2006; 29 (5-6): 345-52. [CrossRef]
37. Bezirtzoglou E. The intestinal microflora during the first weeks of life. Anaerobe 1997; 3 (2-3): 173-7. [CrossRef]
38. Hanberger H, Giske CG, Giamarellou H. When and how to cover for resistant gram-negative bacilli in severe sepsis and septic shock. Curr Inf Dis Reports 2011; 13(5): 416-25. [CrossRef]
39. Hatzaki D, Poulakou G, Katsarolis I, Lambri N, Souli M, Deliolanis I, et al. Cefditoren: Comparative efficacy with other antimicrobials and risk factors for resistance in clinical isolates causing UTIs in outpatients. BMC Inf Dis 2012; 228(12): 12-6. [CrossRef]
40. Midtvedt T, Carlstedt-Duke B, Höverstad T, Midtvedt AC, Norin KE, Saxerholt H. Establishment of a biochemically active intestinal ecosystem in ex-germfree rats. Appl Environ Microbiol 1987; 53(12): 2866-71.
41. Green G, Dicks LM, Bruggeman G, Vandamme EJ, Chikindas ML. Pediocin PD-1, a bactericidal antimicrobial peptide from Pediococcus damnosus NCFB 1832. J Appl Microbiol 1997; 83(1): 127-32. [CrossRef]
42. Gorden J, Small PL. Acid resistance in enteric bacteria. Infect Immun 1993; 61(1): 364-7.
43. Cannon PJ, Svahn DS, Demartini FE. The Influence of Hypertonic Saline Infusions Upon the Fractional Reabsorption of Urate and Other Ions in Normal and Hypertensive Man. Circulation 1970; 41(1): 97-108. [CrossRef]
44. Midtvedt T. Microbial bile acid transformation. Am J Clin Nutr 1974; 27(11): 1341-7. [CrossRef]
45. Kleessen B, Bezirtzoglou E ,Matto J. Culture-based knowledge on biodiversity, development and stability of human gastrointestinal microflora Micr Ecol Health Dis 2000; 2: 53-63.
46. Fukushima Y, Kawata Y, Hara H, Terada A, Mitsuoka T. Effect of a probiotic formula on intestinal immunoglobulin A production in healthy children. Int J Food Microbiol 1998; 42(1): 39-44. [CrossRef]
47. Tjellström B, Stenhammar L, Högberg L, Fälth-Magnusson K, Magnusson KE, Midtvedt T, et al. Gut microflora associated characteristics in first-degree relatives of children with celiac disease. Scand J Gastroenterol 2007; 42(10): 1204-8. [CrossRef]
48. Catinean A, Neag MA, Muntean DM, Bocsan IC, Buzoianu AD. An overview of the interplay between nutraceuticals and gut microbiota. PeerJ 2018; 6: e4465. [CrossRef]
49. Valdes AM, Walter J, Segal E, Spector TD. Role of the gut microbiota in nutrition and health. BMJ 2018; 361. [CrossRef]
50. Ferguson JF, Allayee CH, Gerszten RE, Ideraabdullah F, Kris-Etherton P, Ordovas JM, et al. Nutrigenomics, the microbiome, and gene-environment interactions: New directions in cardiovascular disease research, prevention and treatment, Circulation: Cardiovascular Genetics 2016; 9: 291-313. [CrossRef]
51. Rescigno T, Micolucci L, Tecce MF, Capasso A. Bioactive nutrients and nutrigenomics in age-related diseases. Molecules 2017; 22: 105. [CrossRef]
52. Hadrich D. Microbiome research is becoming the key to better understanding health and nutrition. Front Genet 2018. [CrossRef]