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Review Article

ROLE OF PROBIOTICS IN MANAGEMENT OF AILMENT

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ABSTRACT: Probiotic supplements transform the intestinal microbial flora and recommend assure as a sensible means of enhancing gut and immune function. The intestinal microbial flora consists of diverse bacterial species that dwell in the gastrointestinal tract. These bacteria are integral to the ontogeny and regulation of the immune system, protection of the body from infection, and maintenance of intestinal homeostasis. The interaction of the gut microbial flora with intestinal epithelial cells and immune cells exerts beneficial effects on the upper respiratory tract, skin and uro-genital tract. The competence for probiotics to adjust perturbations in immune function after exercise highlight their impending for use in individuals exposed to high degrees of physical and environment stress. Probiotic bacteria have become progressively more popular during the last two decades as an outcome of the constantly expanding scientific substantiation pointing to their advantageous effects on human health. As a consequence they have been applied as various products with the food industry having been very active in studying and promoting them. Within this market the probiotics have been included in an assortment of products, mainly fermented dairy foods. In light of this enduring trend and regardless of the strong scientific substantiation associating these microorganisms to a range of health benefits, advance research is needed in order to establish them and evaluate their safety as well as their nutritional aspects. The purpose of this paper is to review the current credentials on the concept and the probable favorable properties of probiotic and role of probiotics in the disease management.

KEY WORDS: Immunity, gastrointestinal illness, intestinal microbial

INTRODUCTION

The overwhelming use of antibiotics has played a significant role in the outspread/emergence of antibiotic resistance bacteria. Antibiotics added to animal-feed and given to livestock that are used as human food contribute to additional resistance (Ziemer et al, 1998). The reported useful effects of probiotic utilization include improvement of intestinal health, amelioration of symptoms of lactose intolerance, and decline of the risk of an assortment of other diseases, and numerous well-characterized strains of *Lactobacilli* and *bifidobacteria* are available for human use (Granato et al, 2010). The microorganisms constituting the microbiota are unevenly distributed along the digestive tract, as summarized in Table 1. Through their metabolic activities, these organisms play an important role in the use of nutrients ingested with food; (Hooper et al, 2001) they also significantly affect the development and performance of the immune system and other functions (Backhed et al, 2005). **Table 1:** Distribution of the microbiota in the digestive system.

Site of action	Intestinal contents/gram bacterial cells	Discussion
Stomach, duodenum	$<10^3$	Lactobacilli, Streptococci HCl, peristalsis and bile inhibit the adhesion of bacteria and prevent colonization
Fasting, ileus, distal ileum	10^2-10^3	Lack of information: likely activity of fermentation of carbohydrates
Large intestine	1010–1012 (prevalence of anaerobes)	Body location of most microbiota activities

More than a century has passed since Tissier observed that gut microbiota from healthy breast fed infants were dominated by rods with a bifid shape (bifidobacteria) which were absent from formula fed infants suffering from diarrhoea, establishing the concept that they played a role in maintaining health. Since then a series of studies have supported this association but they were originally poorly designed and controlled and faced practical challenges such as strain specificity of properties and the slow growth of probiotics in substrates other than human milk (Toma et al, 2006). By time, they have successfully evolved with the more recent ones accumulating more substantial evidence that probiotic bacteria can contribute to human health (Salminen et al, 2005). Taking into consideration their definition the number of microbial species which may exert probiotic properties is impressive. Some of the most important representatives are listed in Table 2. As far as nutrition is concerned only the strains classified as lactic acid bacteria are of significance and among them the ones with the most important properties in an applied context are those belonging to the genera *Lactococcus* and *Bifidobacterium* (Holzapfel et al, 2001).

Probiotics are viable microbial species, which are ingested for the purpose of altering the gastrointestinal flora in a manner, which confers health benefits. Currently available probiotic products include a wide array of bacterial and fungal species which are consumed in a variety of preparations. The use of microbials originated (unintentionally) centuries ago when people first noted the beneficial health effects of eating fermented foods. Modern probiotic-containing foods and products are the direct derivatives of these early fermented foods. The use of fermented milk and yogurt are the part of human history and their role has been with humanity, to date, between legends and historical data (Hamilton-Miller et al, 2003). The term *probiotic* is derived from Latin (pro) and Greek (bios) meaning literally “for life”. It was first used by Kollath in 1953 to generically describe various organic and inorganic supplements that were believed to have the ability to restore the health of malnourished patients. In 1954, the German researcher Ferdinand Vergin proposed the term *probiotika* to describe active substances that are essential for a healthy development of life. Lily and Stillwell published an article in Science in 1962 wherein they expanded the definition of probiotics to include “the anaerobic bacteria that are able to produce lactic acid and stimulate the growth of other organisms. Parker in 1974 proposed that the term probiotic should include not only microbial organisms but also other substances that contributed to intestinal microbial balance (Parker et al, 1974). Bacteria, unicellular eukaryotes, and other organisms inhabit the human body in large numbers. The human gut is dominated by several bacterial phyla including *Bacteroidetes*, *Firmicutes*, and *Actinobacteria*. The term microbiota, microflora, or normal flora is used to designate this vast host of microbes which coexist with the host Kunz et al, (2009). It is estimated that the human microbiota contains as many as 1014 bacterial cells, a number that is 10 times greater than the number of human cells present in our bodies. Virtually every surface of the human body starting from the skin surface to the genitourinary tract, oral cavity, respiratory tract, ear, and the gastrointestinal tract is colonized heavily by various species of bacteria. By far, the most heavily colonized organ is the gastrointestinal tract (GIT) which houses a huge microbial ecosystem; the colon alone is estimated to contain over 70% of all the microbes in the human body (Whitman et al, 1998).

FUNCTIONS OF GUT MICROBIOTA:

The human microbiome is highly complex and diverse. Its composition and number varies from the nose and mouth to the distal colon and rectum. The composition and complexity of the gut microbiota changes when the baby is weaned to solid foods. Dietary changes in adulthood are also greatly responsible for the composition of gut microbiota. Development of 16S ribosomal RNA (rRNA) gene-sequence-based metagenomic methods has led to major advances in defining the total

microbial population of the gut. This technique has been used to show that 90% of the bacteria belong to two phyla, namely, the Bacteroidetes and Firmicutes (Dominguez-Bello et al, 2010).

PROBIOTICS MICROBES:

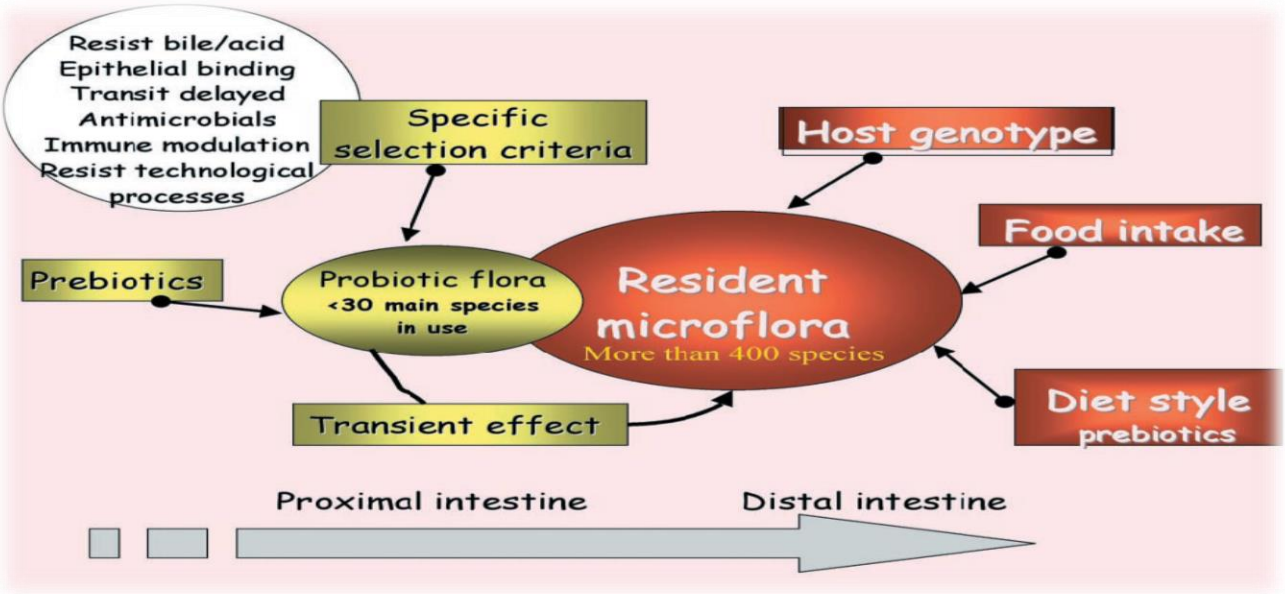
The microbes used as Probiotics represent different types such as bacteria, yeast or mold. However, there are more common species of each such as: 1-Bacteria:

(i) Lactobacillus: acidophilus, sporogenes, plantarum, rhamnosum, delbrueck, reuteri, fermentum, lactus, cellobiosus, brevis, casei, farciminis, paracasei, gasseri, crispatus. (ii) Bifidobacterium: bifidum, infantis, adolescentis, longum, thermophilum, breve, lactis, animalis. (iii) Streptococcus: lactis, cremoris, alivarius, intermedius, thermophilis, diacetylactis. (iv) Leuconostoc mesenteroides. (v) Pediococcus. (vi) Propionibacterium. (vii) Bacillus. (viii) Enterococcus.

(ix) Enterococcus faecium; 2–Yeast and molds: Saccharomyces cerevisiae, Saccharomyces bourlardii, Aspergillus niger, Aspergillus oryzue, Candida pintolopesii, Sacaromyces boulardii.

The type of the microbes used as Probiotics increased due to the increase in the research concerning the subject as well as by the increase of the newly discovered and identified microbes, which could be used as Probiotics.

Figure 1. Relationship between resident and probiotic flora. The resident intestinal microflora is complex and involves more than 400 bacterial species.



CURRENT ROLE OF PROBIOTICS IN VARIOUS DISEASES:

Probiotics seems to have a capable role in either shortening the duration or prevention of infections. Numerous laboratory studies and clinical trials are being conducted to charaterize the safety and efficacy of probiotics in quite a lot of diseases. One of the major challenges we encounter at the present in probiotics is extrapolating the immunomodulatory effects found on laboratory studies with the outcomes in human trials. Multiple factors like genetics, microbial diversity etc play a role in the discrepancies between the laboratory studies and clinical trials. With meta-analysis of strain-specific clinical trials, the role of probiotics has been evolving.

Antibiotic preferred in Diarrhea (AAD):

Antibiotics have shown to alter the intestinal microbiota of the host leading to diminish in amylolytic activity, decline short chain fatty acid production and amplified proteolytic activity. A number of probiotic organisms have been studied in various clinical trials in children and adults to prevent or decrease the AAD (McFarland et al, 2010).

Necrotizing Enterocolitis:

Bacterial colonization patterns are imperative in the pathogenesis of necrotizing enterocolitis since preterm infants of mothers receiving broad-spectrum antibiotics prenatally or preterm infants receiving antibiotics directly postnatally have been found to have elevated menace for Necrotizing enterocolitis sec to a alter in the intestinal microbiota (Cotton et al, 2009).

Acute Pancreatitis:

Infectious complications are the most recurrent and ruthless complications of acute necrotizing pancreatitis (AP) with a mortality rate up to 80%. Bacterial translocation has been verified to be a significant mechanism for the infectious complications in patients with sensitive severe necrotizing pancreatitis (Wu et al, 2009). Several randomized controlled trials have shown that probiotics with or without prebiotics have shown to reduce the infectious complications in patients with acute severe pancreatitis. Besselink et al. conducted a multicenter, double blind, placebo-controlled clinical trial that randomized 296 acute pancreatitis patients to receive 28 days of enteral probiotic therapy or placebo (Besselink et al, 2008).

Obesity and Insulin Resistance:

The composition of the microbiota not only varies from person to person but also varies along the length of the gastrointestinal tract. Genotype, confirmed on studies involving monozygotic twins, also plays an important role on the composition of the intestinal microbiota. The most abundant phyla are *Bacteroidetes*, and *Firmicutes*, together representing 90% of the total microbiota. Despite wide variability in species composition of the intestinal microbiota, functional gene profiles (microbiomes) are similar across healthy individuals (Turnbaugh et al, 2009).

Irritable Bowel Syndrome:

It is one of the most common intestinal disorders in the industrialized and developing nations and incurs significant health care costs. Irritable Bowel Syndrome is defined by symptom criteria of chronic recurring episodes of abdominal pain or discomfort with altered bowel habits in the absence of organic disease. In addition, sensations of bloating with and without visible abdominal distension, increased anxiety and several extra intestinal symptoms commonly occur (Moayyedi et al, 2011).

***Clostridium difficile* (*C. difficile)* infection (CDI):**

Probiotics have been studied in prevention, and treatment of *Clostridium difficile* infections (CDI) and recurrent CDI. In *in vitro* studies, *Saccharomyces boulardii (S. boulardii),* a probiotic yeast has shown to degrade *C. difficile* toxin A and B and increase in anti-toxin secretory IgA levels. *Lactobacillus rhamnosus* GG (LGG) has shown to increase the expression of mucins and decrease the bacterial adherence. With CDI or *C. difficile* toxin acquisition as primary or secondary outcome, several randomized controlled trials have been done (McFarland et al, 1995).

Ventilator Associated Pneumonia:

Ventilator-associated pneumonia is a leading hospital acquired infection in the US. It not only prolongs the duration of mechanical ventilation, length of stay in the intensive care unit and possible recovery of the lung function but also increases the risk of death by 2-10 fold. The pathogenesis of ventilator associated pneumonia is complex but typically involves colonization of the aero digestive tract with pathogenic bacteria, formation of biofilms, and microaspiration of contaminated secretions (Craven et al, 2002).

PROBIOTICS AND IMMUNE FUNCTION:

Interest in the use of probiotics to improve health focuses largely on their potential ability to modulate various factors of the immune system. To function as effective prophylactic agents against common illnesses, probiotics must enhance innate and acquired elements of the mucosal immune system. As the body's first-line-of-defence the mucosal immune system is central to protection

against invading pathogens. The mucosal immune system consists of physical, molecular and cellular components that act synergistically to prevent microbes invading the body.

FACTS REGARDING RELATION OF PROBIOTICS AND OUR HEALTH:

- ✓ Probiotics are valuable and affable microbes.
- ✓ They are able to struggle with the bad microbes and colonize our digestive system.
- ✓ They are competent to ferment our food to simpler byproducts and could endorse our health by many dissimilar mechanisms.
- ✓ Their amount could be deteriorated due to many factors, such as incorrect diet, alcohol, age and so on. This is why they should be taken through our regular diet.
- ✓ In particular cases such as after antibiotic treatments, where they are expected to be affected severely, they should be taken orally in considerable amounts or with food.
- ✓ Probiotics promote health while they:
- Remove the side effect of the pathogens or the harmful microbes.
- Supply the body with useful byproducts.
- Reduce the jobs of our digestive system.
- Reduce the effect of the first attack of harmful compounds, instead of our cells, by their biofilm, which protects our digestive system.
- Reduce the amount of food needed by our bodies due to the correct digestion and metabolism of any amount of food.
- Probiotics in some cases could complement the deficiency in our genetic materials by helping us to borrow the products of their genes.

PROBIOTICS AND FOOD PRODUCTS:

The choice of food products containing probiotic strains is extensive and still growing. The main products existing in the market are dairy-based ones including fermented milks, cheese, ice cream, buttermilk, milk powder, and yogurts, the latter accounting for the largest share of sales. Nondairy food applications include soy based products, nutrition bars, cereals, and a variety of juices as appropriate means of probiotic delivery to the consumer (Rosenthal, 2006), The factors that must be addressed in characterizing the usefulness of the amalgamation of the probiotic strains into such products are, besides safety, the compatibility of the product with the microorganism and the continuance of its viability through food processing, packaging, and storage conditions. The product's pH for instance is a noteworthy factor determining the incorporated probiotic's survival and growth, and this is one of the reasons (Cummings et al, 2004).

Table: 2

Microorganisms considered as probiotics	
Lactobacillus species	*Bifidobacterium* species
L. acidophilus	
L. casei	
L. crispatus	*B. adolescentis*
L. gallinarum	*B. animalis*
L. johnsonii	*B. bifidum*
L. paracasei	*B. breve*
L. plantarum	*B. infantis*
L. reuteri	*B. lactis*
L. rhamnosus	*B. longum*
L. gasseri	

Table 3: Neurochemicals isolated from various microbes.

Genus	Neurochemical
Escherichia, Bacillus, and Saccharomyces	Norepinephrine
Lactobacillus and Bifidobacterium	GABA
Candida, Streptococcus, Escherichia, and Enterococcus	Serotonin
Bacillus and Serratia	Dopamine
Lactobacillus	Acetylcholine

ALLERGY AND PROBIOTICS:

The role of intestinal microbiota in allergy is supported by observations of their quantitative as well as qualitative differences among children and infants suffering from allergies and healthy ones, the former exhibiting colonization by a more adult-like type of microflora. These probiotic effects seem to particularly involve food allergy and atopic dermatitis. The latter is a common chronic relapsing skin disorder of infancy and childhood with hereditary predisposition being an important component of its pathogenesis together with the individual's exposure to environmental allergens. A limited number of strains have been tested for their efficacy in the treatment and prevention of allergy in infants. In a recent study of breast fed infants suffering from atopic eczema *B. lactis* and *L. rhamnosus* GG were found to be effective in decreasing the eczema severity. Furthermore *L. rhamnosus* GG has been found successful in preventing the occurrence of atopic eczema in high risk infants, when supplied prenatally to selected mothers who had at least one first degree relative with atopic eczema, allergic rhinitis, or asthma. Probiotics however have not been very successful in alleviating symptoms of asthma (Ewe et al, 2010).

SAFETY OF ADMINISTRATION OF PROBIOTICS:

Consumers are progressively more using probiotics for there is an assortment of health benefits. In healthy individuals probiotics are secure to be used. Clinical verification for their efficacy is physically powerful in case of antibiotic-associated diarrhea management. However there are areas of ambiguity. Caution has to be exercised with certain patient groups like premature neonates or immune deficiency. Scarcity of information regarding the mechanisms through which probiotics act, appropriate administrative regimes, and probiotic interactions necessitate further investigations in these areas. Properties of probiotics are strain specific. Hence confirmation studies need to be performed, and effects cannot be generalized. A detailed assessment by NIH on the safety aspects has been published. The conclusion which has emerged necessitates the need for systematic reporting of adverse events and better documentation of interventions (Sheehan et al, 2007).

DRUG INTERACTION AND PROBIOTICS:

Since probiotics contain live microorganisms, concurrent administration of antibiotics could kill a large number of the organisms, reducing the efficacy of the *Lactobacillus* and *Bifidobacterium* species. Patients should be instructed to separate the administration of antibiotics from these bacteriaderived probiotics by at least two hours. Similarly, *S. boulardii* might interact with antifungals, reducing the efficacy of this probiotic. According to the manufacturer, Florastor, which contains *S. boulardii*, should not be taken with any oral systemic antifungal products. Probiotics should also be used cautiously in patients taking immunosuppressants, such as cyclosporine, tacrolimus, azathioprine, and chemotherapeutic agents, since probiotics could cause an infection or pathogenic colonisation in immunocompromised patients (Marteau et al, 2002). Warfarin is known as a vitamin K antagonist and acts by blocking the intracellular activation of vitamin K. Intestinal bacteria produce a significant proportion of the vitamin K absorbed in the intestine locally, while antibiotics causing the disruption of the intestinal flora has been associated with symptomatic K vitamin deficiency and severe hemorrhage. It is therefore conceivable that administration of bacteria that alter the local production of vitamin K could affect the sensitivity to warfarin and other vitamin K antagonists (Hilton et al, 1997).

CONCLUSIONS

Symbiotic interactions between the microbial flora inhabiting the GI tract and the mucosal environment are necessary for normal growth and development, host resistance and metabolism. The interactions between the microbial flora and the host immune system have generated curiosity in investigating whether modulating various bacterial populations of the microbial flora can improve

health and reduce susceptibility to illness. The health condition of the mother and the environment where the child is born determines the first species which colonizes his body and which affects his health during his life. Good microbial strain colonies of microflora will guide to good health and will provide us dissimilar types of assistance. In our life, there are numerous factors that perturb our useful microflora, in these circumstances exo-sources should be used. Such exo-sources which contain such constructive microbes or what is named Probiotics could exist in many types of foods, fermented foods, milk and milk products. Also, science, the scientist and the modern companies provide us with different forms of Probiotics for diverse types of illness.

A virtuous circle is therefore formed as the range of new products with enhanced sensory appeal widens, consumer acceptance enhances and the food industry invests more on this growing market by development of new processes and products. On the other hand, the development of probiotics for human consumption is still in its infancy. Further research, in the form of controlled human studies, is needed to determine which probiotics and which dosages are associated with the greatest efficacy and for which patients, as well as to demonstrate their safety and limitations. In addition, the regulatory status of probiotics as food components needs to be recognized on an international level with emphasis on efficacy, security, and validation of health claims on food labels. There is no uncertainty that we will bystander a noteworthy amplify in the role of probiotics in nutrition and medicine over the next decade.

REFERENCES

1. Ziemer, C.J. and Gibson, G.R. (1998). An overview of probiotics, prebiotics and symbiotic in the functional food concept: perspectives and future strategies. International Dairy Journal, 8(5-6), 473–479.
2. Granato, D. Branco, G. F. Nazzaro, F. Cruz, A. G. Faria J. A. (2010). Functional foods and nondairy probiotic food development: trends, concepts, and products. Comprehensive Reviews in Food Science and Food Safety, 9(3)292–302.
3. Hooper, L.V., Gordon, J.I. (2001). Commensal host–bacterial relationships in the gut. Science, 292, 1115–1118.
4. Backhed, F. Ley, R.E. Sonnenburg, J.L. Peterson, D.A. Gordon, J.I. (2005). Host–bacterial mutualism in the human intestine. Science, 307, 1915–1920.
5. Toma, M. M. and Pokrotnieks, J. (2006). Probiotics as functional food: microbiological and medical aspects. Acta Universitatis, 710, 117–129.
6. Salminen, S. J. Gueimonde, M. and Isolauri, E. (2005). Probiotics that modify disease risk. Journal of Nutrition, 135(5) 1294–1298.
7. Holzapfel, W. H. Haberer, P. Geisen, R. Björkroth, J. and Schillinger, U. (2001). Taxonomy and important features of probiotic microorganisms in food and nutrition. American Journal of Clinical Nutrition, vol. 73(2) 365S–373S.
8. Hamilton-Miller, J.M. Gibson, G.R. Bruck, W. (2003). Some insights into the derivation and early uses of the word ‘probiotic’. Br J Nutr, 90,845.
9. Parker, R.B. (1974). The other half of the antibiotic story. Anim Nut Health, 29,4-8.
10. Kunz, C. Kuntz, S. and Rudloff, S. (2009). Intestinal flora. Advances in Experimental Medicine and Biology, 639, 67–79.
11. Whitman, W. B. Coleman, D. C. and Wiebe, W. J. (1998). Prokaryotes: the unseen majority, Proceedings of the National Academy of Sciences of the United States of America, 95(12), 6578–6583.

12. Dominguez-Bello, M. G. Costello, E. K. Contreras M. et al. (2010). Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns, Proceedings of the National Academy of Sciences of the United States of America, vol. 107(26), 11971– 11975.
13. McFarland, L.V. (2010). Systematic review and meta-analysis of Saccharomyces boulardii in adult patients. World J Gastroenterol, 16, 2202–2222.
14. Cotton, C.M. Taylor, S. Stoll, B. Goldberg, R.N. Hasen, N. et al. (2009) Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. Pediatrics, 123, 58-66.
15. Wu, X.G. Zhang, Q.C. (2009). Adjuvant therapy for probiotics in patients with severe acute pancreatitis with hepatic lesion: an analysis of 27 cases. Clin Med, 29, 51-52.
16. Besselink, M.G. Van Santvoort, H.C. Buskens, E. Boermeester, M.A. Van Goor, H. et al. (2008). Probiotic prophylaxis in predicted severe acute pancreatitis: a randomized, double- blind, placebo-controlled trial. Lancet, 371, 651-659.
17. Turnbaugh, P.J. Hamady, M. Yatsunenko, T. Cantarel, B.L. Duncan, A. et al. (2009). A core gut microbiome in obese and lean twins. Nature, 457, 480-484.
18. Moayyedi, P. Ford, A.C. (2011). Symptom-based diagnostic criteria for irritable bowel syndrome: the more things change, the more they stay the same. Gastroenterol Clin North Am, 40, 87-103.
19. McFarland, L.V. Surawicz, C.M. Greenberg, R.N. Elmer, G.W. Moyer, K.A. et al. (1995). Prevention of beta-lactam-associated diarrhea by Saccharomyces boulardii compared with placebo. Am J Gastroenterol, 90, 439-448.
20. Craven, D.E. De Rosa F.G. Thornton, D. (2002). Nosocomial pneumonia: emerging concepts in diagnosis, management, and prophylaxis. Curr Opin Crit Care, 8, 421-429.
21. Rosenthal, K.L. (2006). Tweaking Innate Immunity: the Promise of Innate Immunologicals As Anti-infectives. Can J Infect Dis Med Microbiol, 17, 307-314.
22. Cummings, J.H. Antoine, J.M. Azpiroz, F. Bourdet-Sicard, R. Brandtzaeg, P. Calder, P.C. Gibson, G.R. Guarner, F. Isolauri, E. Pannemans, D. Shortt, C. Tuijtelaars, S. and Watzl, B. (2004). PASSCLAIM--gut health and immunity. Eur J Nutr 43 Suppl, 2, II118-II173.
23. Ewe, J. A. Wan Nadiah, W. A. and Liong, M. T. (2010). Viability and growth characteristics of Lactobacillus in soymilk supplemented with B-vitamins. International Journal of Food Sciences and Nutrition, 61(1), 87–107.
24. Sheehan, V. M. Ross, P. and Fitzgerald, G. F. (2007). Assessing the acid tolerance and the technological robustness of probiotic cultures for fortification in fruit juices. Innovative Food Science and Emerging Technologies, 8(2), 79–284, 2007.
25. Marteau, P. Seksik, P.and Jian R. (2002). Probiotics and intestinal health effects: a clinical perspective, British Journal of Nutrition, 88 (1), S51–S57.
26. Hilton, E. Kolakowski, P. Singer, C. and Smith, M. (1997). Efficacy of Lactobacillus GG as a diarrheal preventive in travelers, Journal of Travel Medicine, 4(1), 41–43, 1997.