Clinical Nutrition 29 (2010) 701–725

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Review

Therapeutical use of probiotic formulations in clinical practice

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ARTICLE INFO

Article history:
Received 16 October 2009
Accepted 5 May 2010

Keywords:
Probiotic
Microbiota
Dysbiosis
Disease

SUMMARY

Background & Aims: The spreading of gastrointestinal diseases is growing all over the world. Although for some of them an effective therapeutic approach has been found, palliation rather than cure is very frequent due to a partial knowledge of their aethiology and pathogenesis. This review, analyzing the main clinical studies, aims at being a state of the art update of the use of probiotic formulations in daily practice.
Methods: In this review we include all the most significant clinical trials involving the use of probiotic formulations for the treatment of several pathologies.
Results: Dysbiosis has been observed in irritable bowel syndrome patients. Probiotics may exert a beneficial effect on Crohn's disease affected patients who have shown gut microbiota antigens and altered wall permeability. Moreover some probiotic formulations seem to enhance the therapy for Helycobacter Pylori reducing its pathogenic potential. Intestinal ecology imbalance has been also linked to cancer induction, allergy, skin and urogenital diseases. In addition probiotics administration seems to be particularly useful to ease post-operative complications.
Conclusion: Further future clinical trials, involving large numbers of patients, will be mandatory to achieve definite evidence of the preventive and curative role of probiotics in medical practice.

1. Introduction

The gastrointestinal (GI) tract starts from the mouth, involves the oesophagus, the stomach, the small and large intestine and ends at the anus (Fig. 1). The GI tract has four main functions: ingestion, digestion, absorption, and defecation. In a normal human adult male, the GI tract is approximately 6.5 m long and can be divided into the upper tract which is made up of mouth, pharynx, oesophagus and stomach and the lower tract which is made up of the small intestine (duodenum, jejunum and ileum), the large intestine (cecum, colon and rectum) and anus.

1.1. Normal bacterial flora of the GI tract

Aerobic and anaerobic bacteria, yeast and fungi live into the GI tract which has more than 400 m^2 of surface area. All these organisms in a healthy intestinal tract live in a natural balance called symbiosis. There are more than 2000 species of commensal bacterial organisms within our bodies, the vast majority in the gut.[1] In fact the mammalian gut is considered one of the most densely populated ecosystems on Earth with a bacterial load in the region of 10^{12} organisms/g of fecal material in the large intestine.[2] The several species of microorganisms in the adult human gut are known as the microbiota which may contain nearly 100 times the number of genes contained within the human genome. The genome of these collective organisms is called the microbiome. The longitudinal distribution of intestinal microorganisms increases in density progressing from the small bowel to colon (Fig. 2). Anaerobic bacteria benefit the host by performing metabolic functions including fermentation, providing short-chain fatty acids (SCFAs), producing vitamins, adding to the trophic action of the epithelium and aiding in the development of the immune system.[3]

The stomach harbours only very few bacteria (mainly acid-tolerant lactobacilli) because of the acidity due to the gastric juice. In the colon there are about a million times more bacteria than in the stomach due to a higher exposure to nutrients, slow transit, and low-redox potential.

About 50% of feces are made up of bacteria. While new bacteria are produced, the old ones are flushed out of the intestine and they will be finally present in the feces. The different strains of bacteria living in the GI tract are summarized in Table 1.

The normal flora which colonizes the GI tract exert several functions: 1) synthesizing and excreting vitamins in excess of their

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doi:10.1016/j.clnu.2010.05.004

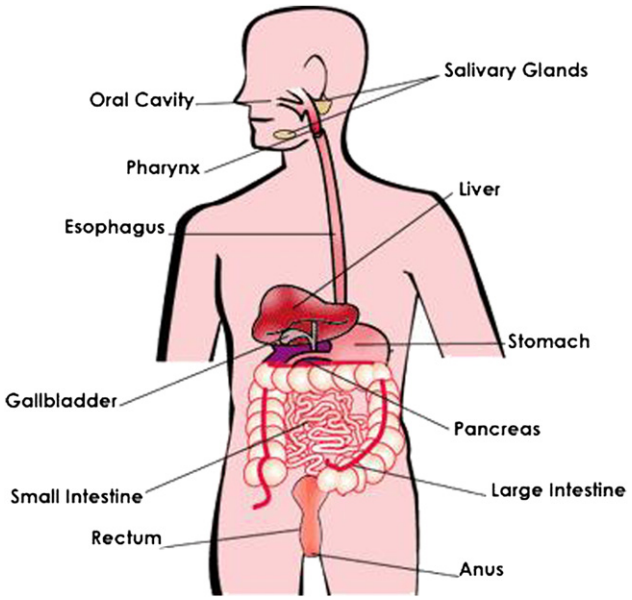

Fig. 1. Anatomy of the gastrointestinal tract.

own needs, which can be absorbed as nutrients by their hosts (enteric bacteria secrete Vitamin K and Vitamin B12, and lactic acid bacteria produce certain B-vitamins); 2) preventing the pathogens colonization by competing for attachment sites or essential nutrients; 3) being likely to produce substances which inhibit or kill non indigenous species; 4) stimulating the development of certain tissues, i.e., the caecum and certain lymphatic tissues (Peyer's patches) in the GI tract; 5) stimulating the production of natural antibodies; 6) producing a variety of substances ranging from relatively non-specific fatty acids and peroxides to highly specific bacteriocins which inhibit or kill other bacteria.[5,6] Gut microbiota are also known to influence energy balance and in turn, emerging evidence demonstrates the importance of gut microbiota in the pathophysiology of obesity.[7]

The initial acquisition of intestinal microbiota plays a key role in the development of immune processes and protection against pathogens. The human fetus is sterile in utero and microbes

Table 1
GI flora components.[9]

Oral cavity (saliva)	Streptococcus, Veillonella, Lactobacillus, Bifidobacterium, Fusobacterium, Staphylococcus, Bacteroides, Corynebacterium, Neisseria, Yeasts
Stomach	Streprococcus, Lactobacillus, Bifidobacterium, Bacteroides, Enterobacteriaceae, Yeasts
Duodenum	Streptococcus, Lactobacillus, Veillonella, Bacteroides, Bifidobacterium, Enterobacteriaceae, Yeasts
Ileum	Streptococcus, Lactobacillus, Bifidobacterium, Bacteroides, Clostridium, Enterobacteriaceae, Yeasts
Colon	Bacteroides, Eubacterium, Ruminococcus, Coprococcus, Peptostreptococcus, Bifidobacterium, Streptococcus, Enterobacteriaceae, Lactobacillus, Clostridium
Feces	Bacteroides, Eubacterium, Ruminococcus, Coprococcus, Peptostreptococcus, Bifidobacterium, Streptococcus, Enterobacteriaceae, Clostridium, Lactobacillus, Veillonella, Yeasts

colonize it during its passage through the birth canal. The host genotype is important in determining the populations of intestinal organisms which, after birth, are influenced by the baby exposure to numerous bacteria from the environment (e.g., skin, mouth, mother's milk). This initial microbiota is relatively unstable and changes during the initial period of life.

Reinhardt et al.[8] report that infants are initially colonized by facultative anaerobes such as enterobacteria and gram-positive cocci, which are thought to create a reduced environment favorable for the establishment of obligate anaerobes, including *Bacteroides*, *Bifidobacterium*, and *Clostridium*.

Tennison et al.[3] report that the type of birth delivery has a significant impact on the development of the gut microbiota in fact vaginal delivery allows infant exposure to maternal bacteria, i.e. the longer the birth process is the greater exposure you have, while infants born by cesarean delivery acquire bacteria by exposure to the mother as well as isolates transferred by nursing staff, other infants, air and equipment. Following birth, oral and cutaneous bacteria from the mother will be mechanically transferred to the infant by suckling, kissing and caressing. Moreover the Authors observed that breast feeding exposes the infant to bacteria, especially bifidobacteria, from milk ducts, nipple, and surrounding skin. Breast milk contains antimicrobial components and growth factors that stimulate the development and maturation of the intestinal mucosa. The

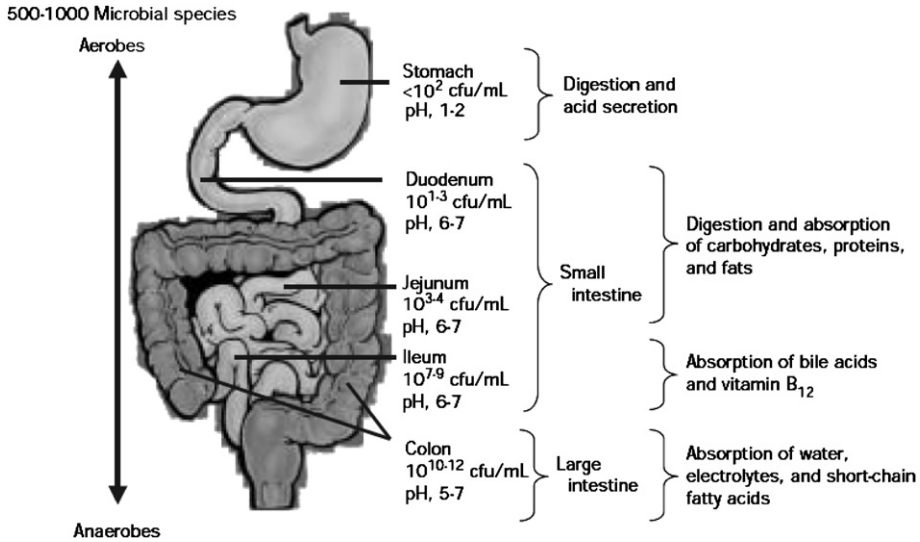

Fig. 2. Picture reported from "Dibaise et al.[4] Gut Microbiota and Its Possible Relationship With Obesity". Key physiologic and microbiological features of the gut, relative concentrations of bacteria and the pH at various locations within the adult gut are shown (cfu = colony-forming unit).