



What could probiotic do for us?

Yuan Kun Lee*

Department of Microbiology, Yong Loo Lin School of Medicine, National University of Singapore, 5 Science Drive 2, Singapore 117597, Singapore

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Abstract

Gastrointestinal microbes play important roles in the health and disease of the host. There are many documented evidences which demonstrated that disturbance of intestinal microbiota is linked to the risk of developing infectious, inflammatory and allergic diseases. Human intestine is home for a complex consortium of 10^{13} – 10^{14} microbial cells. Interactions between the intestinal microbes, pathogens and the host lead to exclusion of toxins (mycotoxins) and pathogens (colonization resistance), interference in disease progression as demonstrated in the prevention of oral infection, dental caries, diarrhoeas (Antibiotic Associated Diarrhoea, Travellers' Diarrhoea and Rotavirus Diarrhoea), postoperative infection, respiratory infection and certain cancers. The group of beneficial intestinal microbes termed probiotics alter intestinal epithelial cell tight junction and immunological functions. Lately, laboratory and clinical studies demonstrated gut-brain axis communication and intestinal microbial (both pathogens and probiotics) modulation of host psycho-neuroimmunological functions, in relation to depression, anxiety and memory dysfunction. These open up many possibilities of probiotics supplementation for moderating intestinal microbiota as an approach in disease prevention and treatment.

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1. Introduction

The intestinal tract of adult carries 1–2 kg of microbes. It is a common knowledge that pathogenic microbes could cause infectious diseases such as diarrheal, while others are associated with inflammatory and allergic diseases [1–3].

On the other hand, the majority of the gut microbes do protect us from pathogens via colonization resistance, modulation of immunity, and benefit us through digestion of foods and production of vitamins. Thus it is logical to assume that the supplementation of selected microbes could impart beneficial effect to us and they are termed probiotics. The FAO/WHO have defined probiotics living microorganisms which when administered in adequate amounts confer a health benefit on the host [4].

2. Factors determining the microbial colonization of human intestinal tract

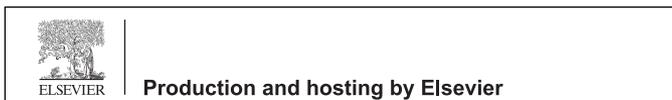
We are born with a sterile gastrointestinal tract (GI), its colonization begin at birth. The GI microbiota profile is determined by a number of factors:

- (i) *Exposure after birth and during infancy.* The window for colonization of GI tract is within the first two years after birth. Once established, it is difficult for a new comer to replace the commensal microbes, such is termed colonization resistant [5], unless the long term diet habit and physiology changed with life style and age. As expected the GI microbiota profile of infant born by natural birth and those by caesarean birth are different [6,7]. Caesarean birth infants and infants who are not frequently exposed to microbes in the environment are prone to develop allergic diseases, such as atopic eczema and asthma [8,9].
- (ii) *Survival in GI environments and adhesion on GI surface.* The microbes that reach our GI tract need to survive through the passage and adhere on GI mucosal surface to colonize, and to establish interaction with the host. The stomach and large intestine are acidic while the small intestine is alkaline. The incoming microbes also need to tolerate the action of digestive enzymes, such as the proteases, amylases and lipases. The adhesion–receptor interaction on the surface of the GI tract often involves specific carbohydrate moieties on the surface of the microbes and the GI surface [10], thus

* Corresponding author at: Tel.: +65 65163284.

E-mail address: micleeyk@nus.edu.sg (Y.K. Lee).

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the carbohydrate diet may interfere with the colonization of microbial types.

- (iii) *Colonization of GI surface.* The ability of the incoming microbes to colonize and reproduce in specific segment of our GI tract is determined by the microenvironment, which in turn is largely determined by the physiology stage of the host and the dietary habit [11,12].

3. Scientific and clinically demonstrated probiotic effects

The following summarizes scientific and clinically demonstrated beneficial effects of selected probiotics.

- (i) *Diarrhoeas.* It is reasonable to assume that a newly arriving diarrheic microbes would find it difficult to establish in a GI tract that is clouded with commensal microbes. It is therefore not surprising that one of the earlier clinical demonstration of probiotic effect is the prophylactic prevention of antibiotic-associated diarrhoeas with lactobacilli preparation [13]. In the placebo group of elderly patients (median age 65) taking ampicillin, 14% suffered from diarrhoea, while none of the subject (median age 64) taking a lactobacillus preparation Lactinex went down with diarrhoea. The anti-diarrhoeic mechanism of probiotics appear to be both competition for adhesion on mucosal surface [14] and their immunogenicity for recovery [15].
- (ii) *Allergic diseases.* The immunomodulating effect of probiotics is best demonstrated in their prevention of atopic eczema in infants [16–18]. A dosage of 2×10^{10} CFU/day was delivered for 2–4 weeks to the mothers before expected delivery, and to the infants for 6 months. Such preventive effect was evidence from birth to at least 7 years old. To date, more than 10 clinical trials using various probiotics had been conducted to demonstrate the anti-allergic effect of probiotics. Most of them showed positive effect but three trials using same probiotics and protocol showed negative effect. This suggested that host factors could be involved in the disease preventing probiotic effects.
- (iii) *Chronic idiopathic inflammatory bowel diseases.* Therapeutic approaches that correct the aberrancies in microbiota and eliminate the inflammation inducing bacteria and adjuvants for the treatment of IBD, in conjunction with anti-inflammatory and immunosuppressant agents, showed best results in pouchitis [19] and to a lesser extent ulcerative colitis [20].

It should be mentioned that probiotic effect in relieving IBS symptoms is strain specific. *Lactobacillus casei* Shirota strain showed positive (89% probiotic vs 56% placebo) on constipation and stool consistency but no change in degree of flatulence and bloating sensation in chronic idiopathic constipation patients (either sex, age 18–70) in 4 weeks [21]. *L. plantarum* 299v reduced flatulence significantly (6.5–3.1 per day in test group vs 7.4–5.6 per day in placebo), however no significant difference between test and placebo in abdominal pain and

defecation function was observed in 4 weeks [22]. On the other hand, a study on the *L. rhamnosus*, even at a large dosage (1×10^{10} CFU/d) showed no significant reduction in flatulence, abdominal pain and defecation function in test group compared to the placebo [23].

- (iv) *Mucosal immunity.* The continued consumption of probiotics *Lactobacillus gasseri* PA16/8, *Bifidobacterium longum* SP07/03 and *B. bifidum* MF20/5 for two Winters and Springs did not show difference in incidence of common cold among non-vaccinated healthy adults (18–67 years) [24,25]. The duration of episode was nevertheless shortened by almost 2 d (Placebo 8.9 ± 1.0 vs probiotic 7.0 ± 0.5 d), with accompanied increase in cytotoxic T cells and T suppressor cells.

Orally consumed probiotics ascend to the vaginal tract after they are excreted from the rectum; vaginal administration allows for direct replacement of the probiotics for unhealthy vaginal microbiota and consequently results in maintenance of a low pH and production of antimicrobial substances like acids and hydrogen peroxide. Data from 127 patients in two studies showed a statistically significant decrease in recurrence of bacterial vaginosis in patients given *Lactobacillus* [26,27].

In a different study, oral intake of probiotic VSL#3 during the last trimester of pregnancy countered the decrease of *Bifidobacterium* and the increase of *Atopobium*, that occurred in control women during late pregnancy. The modulation of the vaginal microbiota was associated with the maintenance of anti-inflammatory cytokines IL-4 and IL-10, and the decrease of the pro-inflammatory chemokine Eotaxin, suggesting a potential anti-inflammatory effect on the vaginal immunity, with potential implications in preventing preterm birth [28].

- (v) *Cancers.* Nasopharyngeal carcinoma, rectal cancer, breast cancer and bladder cancer have been associated with diets high in nitrate, fat and protein [29–31]. The presence of certain GI bacteria such as *Escherichia coli*, *Clostridium* sp. and *Peptostraptococcus* sp. could transform dietary components into carcinogens [32–34]. Competitive replacement of carcinogen-producing bacteria by *L. casei* Shirota (oral 1×10^{10} CFU three times daily) prolonged recurrence-free period of superficial bladder cancer after transurethral resection [35,36]. Habitual consumption of the same probiotic bacterium (*L. casei* Shirota) by patients with multiple colorectal adenomas or early cancers (age 40–65) showed adjusted odds ratio of developing at least one tumour of 0.76 after 2 years and 0.85 after 4 years. The relative risk of developing adenomas with moderate or severe atypia decreased from 0.80 after 2 years to 0.65 after 4 years, while measurement of short-chain fatty acids in faeces showed an increase in butyric acid content during lactobacilli treatment [37].
- (vi) *Metabolic disorders.* High-fat diet may change intestinal microbiota profile result in reduced epithelia barrier function, increased endotoxemia, chronic low-grade systemic inflammation and ultimately metabolic disorders [38,39]. Supplementation of probiotics could be a route

in reverting the microbiome imbalance and metabolic disorder [40,41].

- (vii) *Mental state*. Forced Swimming Test (FST) is a model for predicting the extent of depression in rodents; the increased immobility in this test is considered a reflection on the state of behavioural despair. It was observed that young rodents separated from mothers showed double the count of immobility as compared to the control in the FST. Depressed rodents treated with the anti-depressant drug citalopram reduced the immobility count, so did the supplementation of the probiotic *Bifidobacterium infantis* to the level of the control [42]. In a rodent model chronic fatigue (28 d exposure to FST), administration of *L. acidophilus* (vs placebo) reduced immobility and post-swim fatigue, in tandem with reduction in brain measurements of oxidative stress inflammatory cytokine (TNF alpha) [43]. Such observations in the animal studies are in accordance with human intervention study, where *L. casei* fermented beverage was found to improve mood scores of healthy adults with mild depression symptoms, and improvement in anxiety by Beck Anxiety Inventory after eight weeks of consumption of the fermented beverage [44,45].
- (viii) *Memory*. It was an unexpected observation that the memory of germ-free mice was impaired as compared to normal mice as shown in Novel Object Test [46]. Memory lost could be prevented by dietary probiotic supplementation, and was due to restoration of hippocampal Brain-derived Neurotrophic Factor (BDNF) and expression of c-Fos in the hippocampus. There appears to be multiple lines of communication between the gut and our brain [47,48]: (1) gut microbes lower oxidative stress and systemic inflammatory cytokines; (2) gut microbes influence neurotransmitter precursor levels via amino acids and neuronal membrane structure via fatty acids (the vagus nerve conduit); (3) gut microbes attenuate intestinal permeability through attenuation of hypothalamic-pituitary-adrenal (HPA) axis response and reduce central neuroinflammation; (4) gut microbes lower uraemic toxin burden.

4. Conclusion

Human gut home for a complex consortium of 10^{13} to 10^{14} bacterial cells, outnumber the body cells of the host by a factor of 10. Gut microbiota and its microbiome should be considered a fluidized genetic and metabolic component of us. Thus harnessing functionality of probiotics as ingredient of functional foods is a desirable approach in the promotion of health and disease prevention.

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