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The New Perspectives on the Microbiome and Probiotics

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The human body is a cocktail of human and bacteria cells. Recent studies have revealed that being healthy is not about the absence of bacteria in the body, but rather a balance in the ratios of 'good' and 'bad' bacteria in the gut. In fact, not even the placenta of a mother is sterile since bacteria have been isolated from umbilical cordblood and amniotic fluids of healthy mothers [1]. Therefore, it is possible to suggest that humans probably require certain bacteria for proper development during gestation. This is evident in the meconium microbiome of full term and preterm babies. The relatively higher abundance of *Lactobacillus* genus in the meconium of preterm babies than their full term counterparts have been suggested to be involved in events that trigger preterm labor [2]. The human microbiome acts to enhance homeostasis [3] by communicating with each other through quorum sensing and with the host cells through hormonal response and immune regulation. However, factors such as diet, drug usage, the immune system, and emotions (stress, chronic anxiety, etc) may alter the composition of bacteria in the gut resulting in dysbiosis. Recent advances in metagenomics and metabolomics have made it possible to identify changes in the microbiome and in metabolic profiles during dysbiosis, thus helping to identify biomarkers of diseases. For instance, in obesity, the levels of Firmicutes increase but Bacteriodetes decrease (Lecomte) relative to lean controls. These alterations result in significant increase in the urine 2-hydroxyisobutyrate levels (indicating improper digestion of dietary proteins) and decreased levels of urinary xanthine levels (indicating high serum uric acid levels) in obese people [4]. Also, the microbiota profiles of children with celiac disease (CD) differ significantly from healthy controls. CD childrens have higher levels of Bacteroides particularly *B. vulgatus* and *B. fragilis* which have proinflammatory effects [5]. Using metabolomics, Tjellström., *et al*. [6] observed higher levels of acetic, *iso*-butyric, and *iso*-valeric acids in the feces of CD children compared to healthy controls, indicating a change in gut metabolic activity during the disease. Other diseases associated with dysbiosis include autism spectrum disorder, type 2 diabetes (T2D), inflammatory bowel disease (IBD), *Clostridium difficile* infection (CDI), etc [7]. The therapies available for treating these diseases include abstinence from foods that trigger the disease (as in CD and T2D), the use of anti-inflammatory drugs or surgery (as in IBD) or antibiotic treatment (as seen in CDI) which do not completely treat the disease. However, a number of studies have shown the possibility of restoring the gut microbiota through the consumption of probiotics and symbiotics (probiotics plus prebiotics) and also by fecal microbiota transplantation [8]. These strategies promise cheaper therapies with no adverse effects. Simrén., *et al*. [9] have extensively reviewed studies showing the effects of probiotics such as *Bifidobacterium bifidum* MIMBb75 in treating functional bowel disorders. Other probiotics (*Bifidobacterium animalis* subsp *lactis*, *Streptococcus thermophiles, Lactobacillus bulgaricus,* and *Lactococcus lactis* subsp *lactis*) have psychoactive effect as they alter emotions and cognitive functions in humans when consumed [10]. They do this probably by producing neuroactive substances; GABA (gamma-aminobutyric acid) that affects the brain [11]. GABA has mostly been produced in lactic acid bacteria by L-glutamate decarboxylase when L-glutamate is added to the culture medium. GABA also has other application as a major building block for the synthesis of 2-pyrrolidone and biodegradable polyamide nylon 4, which opens its application area in the industrial biotechnology. Therefore, many recombinant *Corynebacterium glutamicum* (the major L-glutamate producing microorganism), have been successfully used to achieve direct fermentative production of GABA from glucose [12]. Fecal microbiota transplant has also been applied successfully to treat *Clostridium difficile* infection, Chron's disease and many others [13]. However, its low acceptability and the tendency of pathogen transfer through stool

administration; new stool substitute transplants are being developed. This synthetic stool approach proved promising as it treated two patients with *C. difficile* following 2-3 days of administration and they remained symptom free even after 6 months [14]. The University of Guelph researchers in Canada have developed a more sanitary way of synthetic poop, named Re POO Pulate by careful examination of bacterial colonies grown from the stool of healthy volunteers, and 33 different bacteria were grown in a robotic intestine simulator affectionately called Robo-gut to create a 'super-probiotic' stool substitute. Since Open Biome, Boston (USA) based first human stool bank in pill form was opened, several companies are under development for other diseases. Indeed, probiotic bacteria ingested into the body may not remain in the gut forever to produce their health effects, but they may stimulate the growth of indigenous bacteria to recolonize the gut and perform their natural functions to ensure homeostasis.

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