Importance of gut microbiota in health and diseases of new born infants (Review)

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Abstract. The multifarious assortment of microorganisms present in gut of humans is termed as gut microbiota. These include 1,000 species accompanied by approximately 2 million genes in an individual adult. The gut microbiota has multifactorial protective roles against allergic reactions, inflammation, cardiac pathological states and even in the state of malignant carcinogenesis existing in humans. By contrast, adverse alterations in the microbiota result in chronic pathological states, including autoimmune diseases, cancer and circulatory system obstructions. Gut bacteria also maintain sensitivity towards nutritional changes as well as antibiotics. The present review article focused on the importance of gut bacteria in newborn infants with special reference to their protective role in various pediatric pathological states linked with gut bacteria. In addition, the importance of probiotics in relation to gut microbiota are to be discussed.

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1. Introduction

The community of microorganism species residing in the digestive tracts of mammals including humans, forms gut microbiota (Fig 1). The growing advancements in molecular as well as metabolic research fields allowed us to study in depth interdependent relationships existing among microbiota and its host (1). The prospective impacts of gut microbiota have been documented in literature and are of an immune, metabolic, anti-cancerous, pro-carcinogenic and pro-inflammatory nature. Evidence suggested that the composition of microbiota may be affected by enduring treatment with microbes in the form of probiotics or by an influential high-fiber diet or by antibiotics (2). These studies have raised the possibility of playing with the varied microbiota species in the gut in order to have a futuristic control over upcoming adult pathological states (3,4).

The present review has also focused on the idea of utilization of probiotics to influence gut microbiota (2). Randomized controlled trials utilizing probiotic supplements in preterm infants for the prevention of various pediatric diseases such as sepsis and necrotizing enterocolitis are being carried out by the scientists worldwide regardless of current evidence. There are increasing calls for observational studies to establish baseline data in these infants. Thus, it is clear that substantial research is being focused on the gut microbiota owing to its multi-factorial contribution in maintaining normal physiological homeostasis. We reviewed these developments pertaining to the importance of gut microbiota in pediatrics.

2. Various influences of gut microbiota

The observed important influxes triggered by microbiota (Fig. 2) are the result of competitive binding effect of harmful microorganisms, which do not allow beneficial bacteria adherence to gut mucosa (5,6). *Bifidobacteria* and *Lactobacillus* species of microorganisms have been observed to show supremacy in infant gut to promote local and systemic immune influences for the future prevention of adult pathological states such as eczema, allergic and inflammatory disorders (7). Moreover, the macrophage function in intestinal mucosa as well as in blood-brain barrier is affected by gut microbiota as it is observed to be associated with maturation of immune cells and signaling molecules (8). The important influences of gut microbiota is also warranted based on earlier pre-clinical studies which included germ-free mice showing lack of mature lymphatic system in the absence of beneficial bacteria (9). On the other hand, beneficial gut microbiota have also been observed to fortify the colonic defense barrier against various patho-

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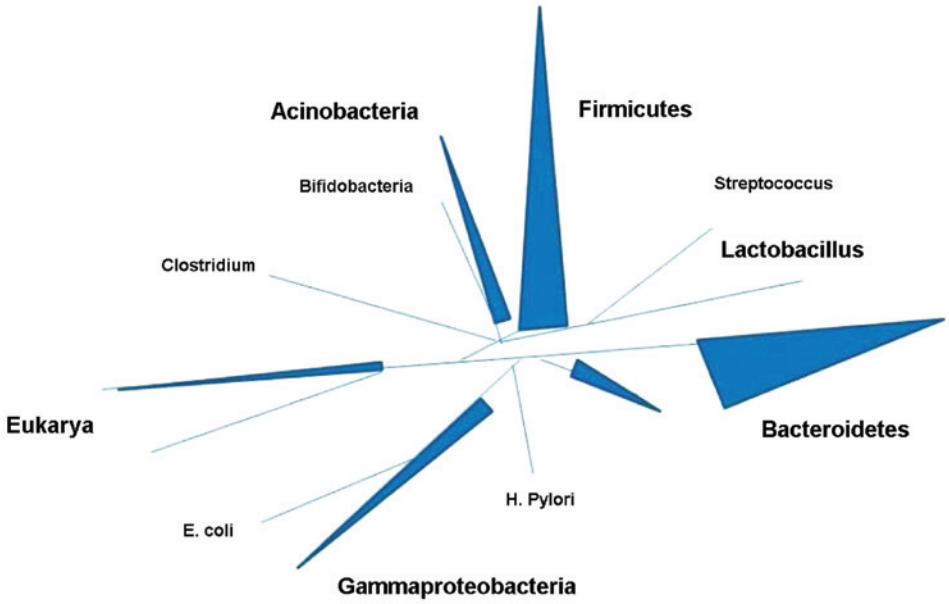

Figure 1. Major unrooted phylogenetic tree showing gut microbiota components in healthy adults. The size of the triangle indicates relative abundance, and the orientation of limbs denotes similar morphology.

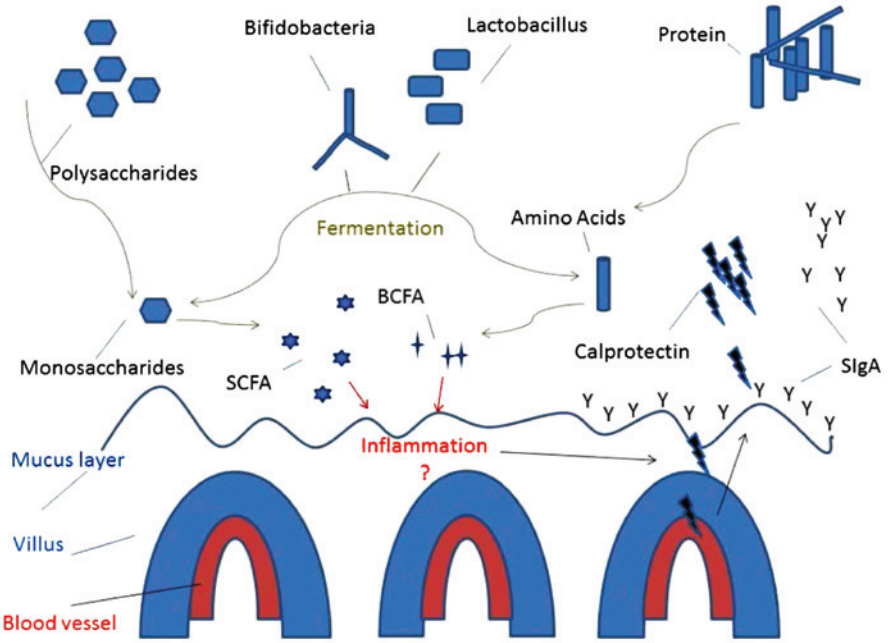

Figure 2. Interaction between gut microbiota, metabolites, inflammation and immunity at the gut mucosa. SCFA, short chain fatty acids; BCFA, branched chain fatty acids; SIgA, secretory immunoglobulin A.

logical states (10). Furthermore, in humans, the pathological state of viral gastroenteritis has been found to be significantly less in the infants with proper gut microbiota because of breast feeding as compared to infants who lack proper gut microbiota due to formula feeding. The above observation occurs due to the protective properties of gut bacteria, i.e., *Bifidobacteria* and *Lactobacillus* species that act by maintenance of acidic hostile environment for enteric viruses (11). Furthermore, gut microbiota offers protection via the production of bacteriocins that are known for their anti-enteropathogenic proteins (12). Scientific research is also being focused on these gut bacteria for the future use in medicinal applications (13).

3. Anti-carcinogenic effects of gut microbiota

The anti-carcinogenic properties of gut microbiota have been observed in an earlier study on *Lactobaclli* and *Bifidobacteria* strains (14). The study confirmed the unique abilities of these microbiota species as potential factors resulting in the inhibition of tumor cell proliferation, and carcinogen degradation. In addition, these microorganisms have been shown to produce antioxidants that directly help in the prevention of carcinogenesis. The above observation was confirmed by later studies confirming the anti-carcinogenic properties of *F. prausnitzii* (a butyrate producer) and *E. rectale* against colon cancer in

young patients (15-17). The mechanism of action is mainly the lowering of colonic pH that resulted in anti-carcinogenic effect. Furthermore, the efficacy of chemotherapeutic drugs has been noted to be affected by the colonic pH (18-20). Previously, it was confirmed that lack of complete gut bacteria, the capability mostly observed in preterm infants make them more vulnerable to deadly pathological state of cancer (21).

4. Influence of pribiotics, probiotics and symbiotics on gut microbiota

The term pribiotics involves specific ingredients that directly or indirectly affect beneficial gastrointestinal microflora in terms of composition as well as function. For instance, many carbohydrate-based ingredients are being utilized worldwide as pribiotics. The influential role of pribiotic Lactulose, is well documented for its medicinal effect to treat chronic condition of constipation in young infant and adults by stimulating the growth of *Bifidobacteria* and *lactobacillus* (1). Furthermore, prebiotics such as human milk oligosaccharides found in breast milk offer a progressive environment for the growth of beneficial bacteria, which in turn are useful in the fermentation of carbohydrates for energy purpose (1).

A class of microorganisms that are administered live in tolerable volumes into the human system and provide health benefits to host are collectively termed as probiotics (2). Studies currently in progress aim to utilize bacteria strains of breast milk as probiotics for medicinal purpose. The latest advanced techniques such as microencapsulation are being exploited for the utilization of bacterial strain in breast milk as probiotics (22). The nature of probiotic bacteria whether it is alive or dead did not affect its benefical probiotic effects, as confirmed in an earlier *in vitro* study (23). In addition, the change of nature of a probiotic enhances its efficacy, for example, heat-treated *lactobacillus* strains have been observed to be more stable with better probiotic effects (24,25). These probiotic mircrogainisms such as *lactobacillus* have been reported to offer protection against various infections on mucosal layers of vagina, oral mucosa and nasal mucosal surface (26). Previous experimental findings have confirmed that these properties differ in *in vitro* and *in vivo* environments (27). Additionally, the same probiotic microorganisms may show different properties in an infant or adult confirming the influence of age on probiotic effect (28). A previous study has also confirmed the role of the surrounding environment and cross contamination on the probiotic effect of certain microorganisms (29). Furthermore, when prebiotics and probiotics are combined, they are termed synbiotics. The most beneficial advantage of synbiotics in medicine is that they work simultaneously at two separate locations for example in human gut the pribiotic part of synbiotic was observed to be concentrated in the colon region while the probiotic part was seen more in the small intestine (30).

5. Therapeutic potential of probiotics and its influence on microbiota

Probiotics. The utilization of probiotics has proved its beneficial effects worldwide. The application of probiotics along with the diet has been observed to reduce necrotising enterocolitis in infants (31). Few pre-clinical studies have confirmed the protective potential of *Bifidobacterium* supplementation (32,33). To enhance the efficacy and applicability of probiotics different combinations of probiotics, such as *Lactobacillus* and *Bifidobacterium*, have been utilized in preterm neonatal infants. In addition, a study on young infants undergoing antibiotics treatment evidenced a prominent increase in body weight gain following the administration of probiotics (34). New endeavors are being planned worldwide aiming towards the use of probiotics in the form of personalized medicine which currently consitutes the future of medical treatment (35).

Gut bacteria, cholesterol and morbid obesity. The gut bacteria *Firmicutes* has been observed to affect the concentration of serum cholesterol in infants that ultimately results in leanness in adulthood (36). The influence of gut bacteria on cholesterol synthesis has been studied in various animal studies (37,38). The major mechanisms responsible for the influence of gut bacteria on cholesterol synthesis include inhibition of a rate-limiting enzyme responsible for endogenous cholesterol biosynthesis, elevation in cholesterol excretion, reduction in cholesterol absorption by small intestine and stimulation of faecal bile acid loss (39). By contrast, a decrease in the gut bacteria has been observed to be associated with a rapid increase in cholesterol levels confirming the inverse relationship (40).

Gut microbiota and hormonal influences. The gut bacteria have been reported to influence hormone secretion as well as hormone interactions. Gut bacteria affect the release of hormones as well as certain signaling molecules, biologically active peptides that are specifically involved in the appetite regulation and control (41). Furthermore, a recent study showed the existence of a correlation among insulin resistance and intestinal microflora during a metabolic syndrome (42). In addition, a study has proven the inflicting role of microbiota on fat accumulation. The findings demonstrated that faecal transplantation of microbiota from obese mice caused elevation in body fat as compared to microflora from lean mice (43).

6. Gut microbiota and neurological development

The observed correlation of immunology and gut bacteria automatically links the latter with neurology (44). The gut bacteria indirectly influence the neurological system by affecting immune responses that in turn directly influence development of glial cells, cerebral vasculature and some neuronal pathways (45). The confirmatory studies in this regard in animals have proven the indirect effects of gut microbiota on neurological system by using mouse models of the relapsing-remitting inflammatory disease (46).

7. Safety aspects

The beneficial part of probiotics therapy was discussed above, but it is also associated with certain adverse effects. The adverse effects have short- and long-term implications (47). The observation of probiotic-related sepsis is one

of the adverse effects reported in immunologically immature infants (48). In another study, *Lactobacillus acidophilus* sepsis was confirmed in a premature infant (49). However, in adults, *Bifidobacterial* strains resulted in wound abscesses following obstetric and gynecological procedures. Cerebral palsy is the result of adverse effects of the administration of high volumes of probiotics in premature infants (50). In view of the above literature, not a single probiotic study in preterm infants provided firm inference with regard to best combination of probiotics, appropriate dose of probiotics and effective timing and duration of probiotic treatment. Therefore, at present the results obtained in animal model studies are useful for understanding the influential world of probiotics.

In conclusion, the above citations demonstrate that gut microbiota play influential roles in safeguarding of normal homeostasis right from birth. Moreover, evidence requiring therapeutic potential indicate the importance of gut microbiota in the form of prebiotics, probiotics and synbiotics. However, more focused investigations are necessary in the area to manage safety aspects of probiotic therapeutics.

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