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Review Article

Probiotics Nowadays

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Abstract

"Probiotics will be to medicine in the 21st century as antibiotics and microbiology were in the 20th century"

The consumption of probiotics has increased in the past few years. The most commonly used probiotics are lactobacilli and bifidobacteria. Probiotics have shown to exhibit several benefits such as improve intestinal tract health, enhance the immune system, synthesize and enhance the bioavailability of nutrients and vitamins, reduce symptoms of lactose intolerance, decrease the prevalence of allergy in susceptible individuals and reduce the risk of certain cancers.

Keywords: *Gut microflora; Probiotic strains; Prebiotics; Gastrointestinal disorders*

"Probiotics will be to medicine in the 21st century as antibiotics and microbiology were in the 20th century" [1].

The prevalence of atopic diseases such as asthma, eczema and allergic rhinitis has increased dramatically in the second half of the 20th century. They have a significant impact on quality of life. The social and emotional impact of childhood eczema on the family is higher than that of diabetes. They also place a substantial economic burden on the community. As allergic diseases are usually not curable, their rising prevalence poses a major public health problem [2,3].

The newborn shows many special characteristics after delivery. It comes out sterile, needs half an hour to establish bacterial colonization in its various mucosal membranes, and it has a more or less complete, but tiny immune system. Waiting for its own immune system to take over its host defense, it needs help from the mother and environment [4, 5]. Early exposure to germs will cause the immune system to steer towards infection-fighting mode, and away from over-reacting to normally benign substances [6].

There was evidence that supported an inverse relationship between atopic disease [AD] and end toxins in day care and animal exposure. Two cohort studies have found a positive association between infections in early life and AD, and measles vaccination and AD. Antibiotic use was correlated with an increase in AD risk even into the antenatal period, though few studies did not reach statistical significance. Some small-randomized controlled trials have suggested that probiotics can reduce AD severity and may be able to prevent it to some extent [7].

Brief history of probiotics

In 1899, Tissier was the first to isolate and describe bifid bacteria [8]. During 1908, Metchnikoff first introduced the concept of probiotics [9]. Then, Fuller in 1989 redefined probiotics [10]. The latest definition was given by Roberfroidin 2000 [11]. What are the biotic components? [12,13].

Probiotics-the actual microbes that grow in the gut (G.I. tract). They are 'Friendly Microbes'. The term Pro Biotic means "For Life" in the Greek language.

Prebiotics-are nutrients for the microbes (but NOT for the host). They are mainly carbohydrates. Symbiotic-as in symbiosis, where both pro- and Prebiotics are mixed together and function normally.

Synbiotics-as in synergism, where pro- and Prebiotics function together to give an enhanced effect.

Probiotics

By definition, probiotics are "living microorganisms used as food additives having a beneficial effect on the host by improving digestion and intestinal hygiene". A probiotic is a viable microbial dietary supplement that beneficially affects the host through its effects in the intestinal tract [14]. FAO/WHO 2001 defined probiotics as "live microorganisms that when administered produced some therapeutic or preventive health benefit to the host" [15].

The most commonly used probiotics are lactobacilli and bifid bacteria. Lactobacillus rhamnosus GG (LGG) is the best characterized probiotic and has been extensively studied in humans [16,17]. Probiotics are numerous such as: *Lactobacilli species*, bifid bacteria species, some gram positive cocci species *Lacto coccslactis, Streptococcus salivarious, Enterococcus faceium, S. diaacetylactis, S.intermedius, Bifid bacterium Lactis, Streptococcus thermophilus, and Saccharomyce Boulardii*.

Not all probiotics have the same effect; rather, they are strain specific (i.e. with specific mechanism). Lactobacillus bacteria are mainly found in the small intestine, while bifid bacteria reside in the large intestine [18].

A viable probiotic must survive passage through the gut, resist the secretions of the upper gut (hydrochloric and bile acids), colonize in the human intestinal tract, adhere to intestinal epithelium cells, produce antimicrobial substances and antagonize both carcinogenic and pathogenic flora [19].

Probiotic consumption may improve intestinal tract health, enhance the immune system, synthesize and enhance the bioavailability of nutrients and vitamins, reduce symptoms of lactose intolerance, decrease the prevalence of allergy in susceptible individuals and reduce the risk of certain cancers [20].

They are basically bacteria that tend to decrease inflammation and have competitive metabolic interactions with some of the pro inflammatory organisms. They influence intracellular signaling when they come in contact with the mucosa and inhibit the adherence and translocation of pathogenic bacteria.

They down regulate the mucosal epithelial cell stimulus to keep inflammation going [21]. Their effects may involve modifying gut PH, antagonizing pathogens through production of antimicrobial and antibacterial compounds within acidic medium [22]. They compete for pathogen binding and receptor sites as well as for available nutrients and growth factors, thereby stimulating immunomodulatory cells (Th1-Th2) and producing lactase [9].

The strain specificity of the probiotic action varies and the mechanisms of action differ. For instance, *L. reuteri* and *L. rhamnosus* GG produce pathogen- inhibitory substances while *S. boulardii* and *L. acidophilus* inhibit pathogen attachment. *S. boulardii* inhibit the action of microbial toxins. *S. boulardii* and *L. rhamnosus* GG stimulates immunoglobulin A while *S. boulardii* has tropic effects on intestinal mucosa [23].

There are various immunological mechanisms of action of probiotics. Live *Streptococcus thermophilus* and *Lactobacillus acidophilus* could enhance barrier function by inhibiting the adhesion and invasion of entero invasive *Escherichia coli* into human intestinal cell and act on epithelial cells by enhancing phosphorylation of actinin and occludin in the tight junction region [24].

Lactobacillus rhamnosus GG was able to prevent cytokine-induced apoptosis in intestinal epithelial cell models through the inhibition of a tumor necrosis factor (TNF). It induced activation of the pro apoptotic p38/mitogen-activated protein kinase [25].

Moreover, probiotics interact with epithelial and immune cells and alter signal transduction pathways in the presence or absence of pathogenic bacteria and cytokines through the effect of the toll receptors. Epithelial cells release interleukin-8 in response to pathogenic bacteria which respond to whole or part of bacterial components (such as *E. coli*) but not to probiotic strains [26].

Bacterial DNA is also recognized in a differential manner by epithelial cells, with pathogenic strains evoking a phosphorylation of the extra-cellular signal-regulated kinase pathway and activation of activator protein-1. Some probiotic strains can modulate the nuclear factor-κB pathway in response to TNF-α [27].

Probiotics promote anti-allergic processes by degradation and modification of macromolecules; hence, preventing a leaky gut. Enhancement of Th1 immunity such as by *L. plant arum & L. casei,* produce IL-12 & IFN-alpha and by IgA production. B. Longumenhance the transforming growth factor-Beta (TGF-Beta), suppress Th2 and induce oral tolerance [6].

Probiotics stimulate the gut-associated lymph tissues (IgA) which in turn stimulate the production of mucus to form a protective barrier by up- regulating mucin encoding genes and exerting immunosuppressive effect on intestinal epithelial cells via inhibiting the transcription factor NF-κ B pathway.

It promotes differentiation of lymphocytes into Th1 and Th3 type and modulates immune development indirectly by influencing the composition of intestinal micro biota and creates an environment that promotes bifido bacterial growth which is associated with a reduced risk for allergic disease [28, 29].

So, if we look now at the fields where probiotics are used or experimented we find that they are present in nearly all fields of medicine.

The potential applications of probiotics for prevention and/or treatment of a large number of gastrointestinal disorders include:

Rota associated diarrhea [30,31] -Antibiotic-associated diarrhea [32]
Infantile diarrhea [33]
Inflammatory bowel disease [34, 35] -Irritable bowel syndrome [36,37]
Neonatal necrotizing enter colitis (NEC) [38]
Enteropathy in HIV infection [39]
Other diseases that have been reportedly treated with probiotics include:
Allergy and atopic Eczema [40]
Infections in the urogenital tract [41]
Infection of the respiratory system [42]-Obesity [43]
Encephalopathy [44]
Intestinal pain [45]
Gluten intolerance and gastroenteritis [46] -Helicobacter pylori infection [47]
Colon cancer [48]
Proposed use of probiotics for Dental caries [49]
Radiation induced diarrhea [50]
Cardiovascular risk reduction [51]
Constipation [52]
Rheumatoid arthritis [53]
Probiotics & PAIN in Brain gut axis [54]

Prebiotics

Prebiotics are non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and activity of one or a limited number of bacterial species that already reside in the colon and participate in intestinal flora modulation for better equilibrium [55].

Prebiotics with probiotics form Synbiotics which act on the gut micro flora and modulate intestinal mucosa which affect the glycosylation of the intestinal cell layer to improve vectorial transports and defend against microbes in immunological processes [56]. It is also a part of the enterocyte nutrition [57].

Are probiotics safe?

There are several studies on malnourished and healthy infants receiving probiotics. They found no adverse effects with adequate growth. Infants receiving formula supplemented with probiotics are well tolerated [58,59].

However, there are some disadvantages: [60]

Infection: When probiotics are given to persons with severe underlying disease, they may cause systematic infection.

Metabolic and enzymatic effect: Theoretically they may have some effect on metabolism of bile salts and mucous (not reported yet).

Immunological effects: Immune deficient patient ingesting large amount of certain probiotics can cause relapse of autoimmune reactions.

Gene transfer: Genetically modified probiotics may harbor antibiotic resistant genes.

Some issues regarding the safe use of probiotics were raised by the outcomes of several clinical trials for example [61]:

1. A mixture of six probiotic bacteria (*L. acidophilus, L. casei, L. salivarious, L. Lactis, B. bifidum, and B. infantis*) used to treat patients with severe acute pancreatitis had increased their risk of mortality, although this bacterial mixture inhibited the growth of most pathogens that caused pancreatitis complications in the preclinical animal studies [62]
2. The occurrence of bacteremia and fungemia in ill patients and immune deficient individuals has also been reported.
3. Another possible risk is transferring of antibiotic resistance genes to the host, as *L. reuteri* and *L. plant arum* have been found to carry such genes [63]
4. Thus, future clinical trials using probiotics should be accompanied by safety monitoring.
5. *Lactobacillus GG* has been proven safe both *in vitro* and *in vivo* (in animal models), as well as in a number of human studies. Although there have been rare cases of bacteremia and liver abscess in patients with short gut syndrome, there is no other probiotic that has undergone extensive safety evaluation to a degree comparable to that undergone by *Lactobacillus GG* [62]
6. The use of probiotics during pregnancy, in neonates, and in children has not been associated with any adverse immunologic effects [64]

Conclusion

As a result, probiotics are beneficial to health, improve the intestinal microbial balance, promote and stimulate immune responses, enhance macrophage activity and phagocytosis, and regulate Th1/Th2 reaction. They also decrease allergy, increase immunity and reduce inflammation with improving and strengthening the intestinal mucosa.

Functional food (Prebiotics and probiotics) is important for the intestinal mucosa under two years of age. Using infant formula with probiotics protects and modulates defensive mechanism of the growing infant and may prevent some forms of atopy and infection with no serious side effects which may be better than other treatments.

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