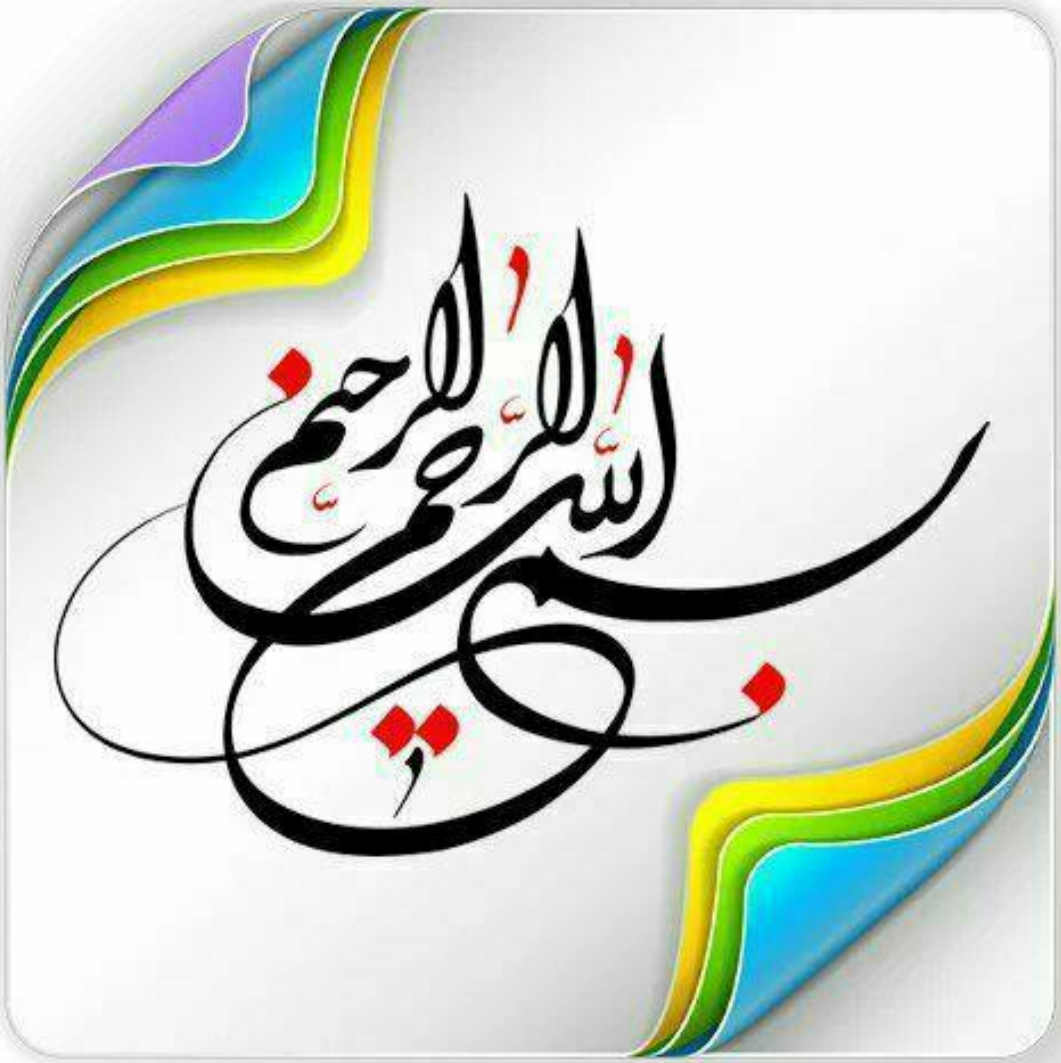
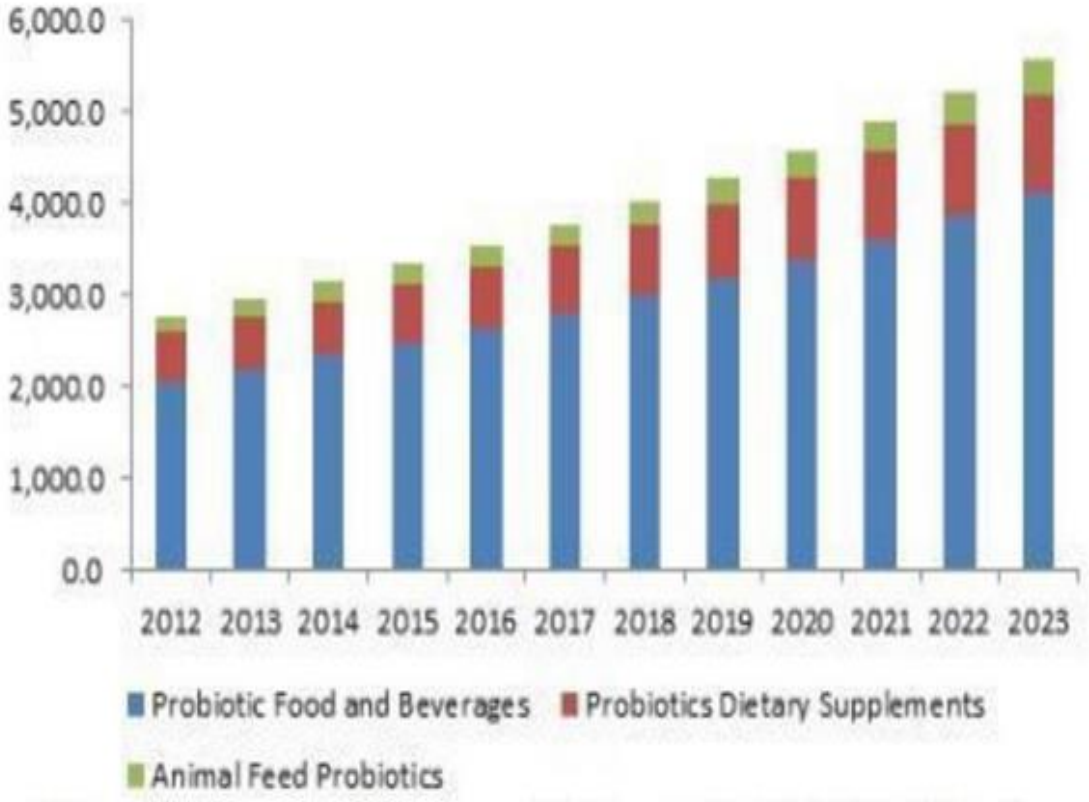

بسم الله الرحمن الرحيم

PROBIOTICS

Metchnikoff in the early 1900s suggested that beneficial bacteria could be administered to replace harmful microbes with useful ones.



U.S. probiotics market size, by application, 2012 - 2023 (USD Million)

Probiotics are live bacteria and yeasts that have been found to help promote better digestive health and support your immune system. These microorganisms exist in your intestines and help to break down food, absorb nutrients, and minimize harmful bacteria that may otherwise cause disease. You can get more probiotics by incorporating probiotic-rich foods or supplements into your diet. Foods containing probiotics include yogurt, kimchi, sauerkraut, and kefir.

The word "Probiotic" means
Pro (for) + biotic (life) = For Life

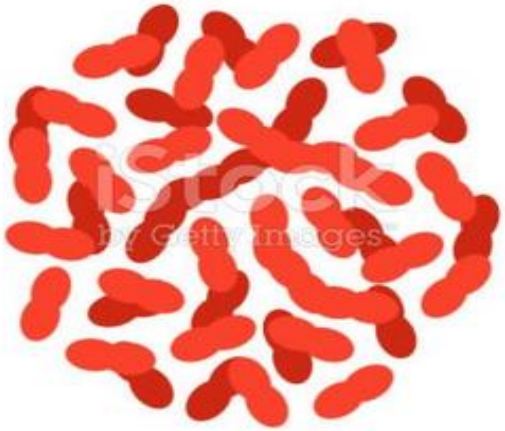
Probiotics are beneficial micro-organisms which are good for your health, especially for your **digestive system** and **immunity** .
According to the joint FAO/World Health Organization, Probiotics are defined as, **"Live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host".**

You may think of bacteria as being harmful, however, there are both beneficial and harmful bacteria in your digestive system.
Since beneficial bacteria can help digest food, absorb nutrients, make vitamins and stimulate immunity,
it is very important to maintain their number.

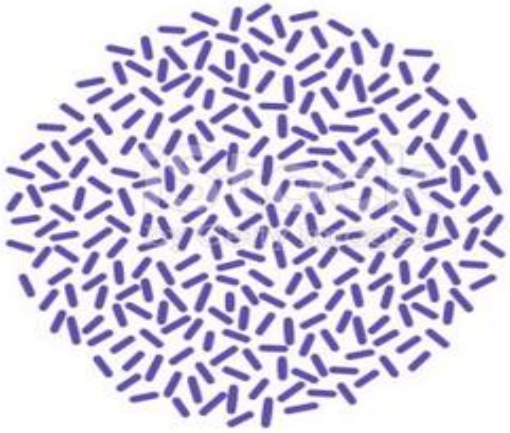
Probiotics help to increase the number of beneficial bacteria and decrease the number of harmful bacteria in your body,
thus help you enjoy your life.

PROBIOTICS

LACTOBACILLUS

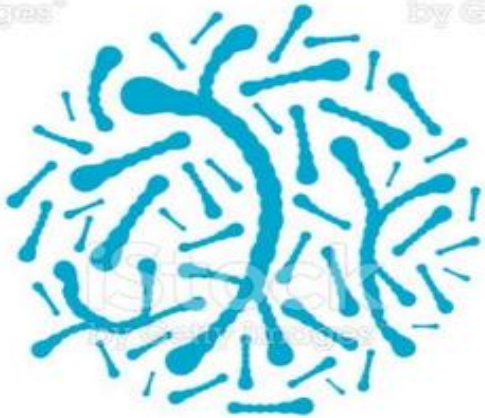


LACTOCOCCUS



PROPIONIBACTERIUM

STREPTOCOCCUS THERMOPHILUS

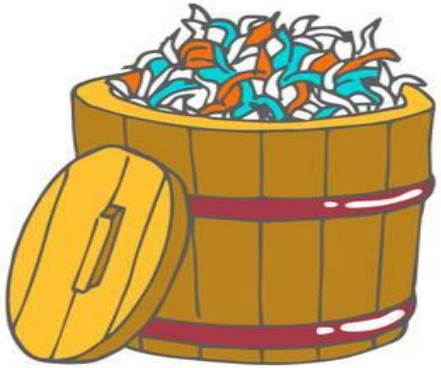


BIFIDOBACTERIUM

BULGARICUS

PROBIOTIC FOOD

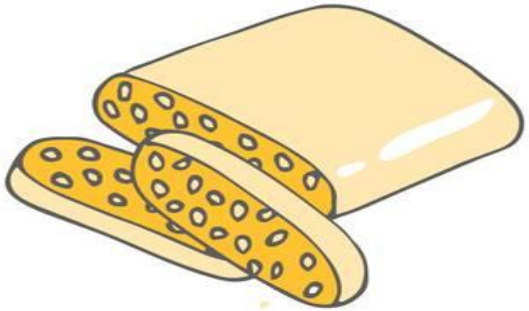
kombucha



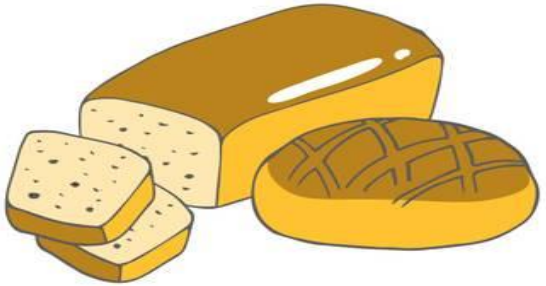
sauerkraut

dairy products

miso soup



soy tempe



sourdough bread

ProBioticS

Aids digestion

They reach the Intestine alive.

It improves bowel movement

They can be ingested as food.

They produce beneficial effect on health.

Prevent harmful bacteria from multiplying in the intestine.

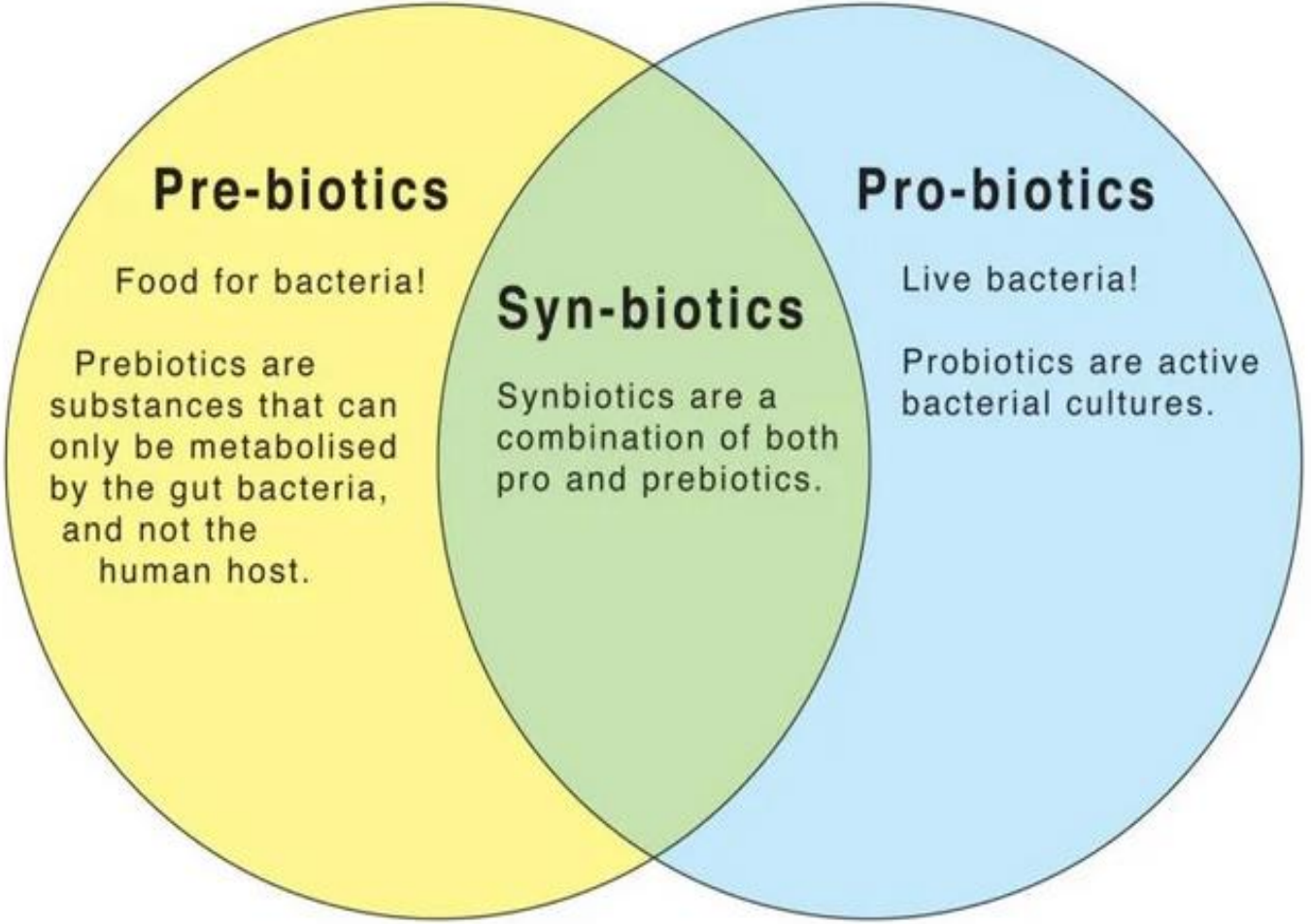
World Health Organization (WHO) defines "probiotics" as "**live microorganisms** that, when administered in **adequate amounts**, confer a perceived **health benefit** on the host". These intentionally ingested microorganisms consist **mainly of bacteria but also include yeasts.** Products containing dead microorganisms and those made by microorganisms are, by definition, not probiotics.

Probiotics (Greek *pro*, for, and *bios*, life) confer various benefits especially to individuals who experience major changes in their normal microflora due to disease, surgery, or other medical treatments, or whose normal microflora changes for other reasons, such as poor diet. Oral administration of probiotic organisms reestablish the natural balance of gastrointestinal flora and return the host to normal health and nutrition.

Probiotic microorganisms are host-specific; thus a strain selected as a probiotic in one animal may not be suitable in another species. Probiotics are subcategorized into probiotic drugs, probiotic foods (e.g., foods, food ingredients, and dietary supplements), direct-fed microbials (probiotics for animal use), and designer probiotics (genetically modified probiotics).

Prebiotics

Probiotics should **not be confused with prebiotics** which are food ingredients, typically complex carbohydrates (mostly consisting of nonstarch polysaccharides and oligosaccharides) that escape digestion in the upper gastrointestinal tract and are available for microorganisms living in the colon.



Most prebiotics are used as food ingredients in chocolates, biscuits, cereals, spreads, and dairy products. Commonly known prebiotics are:

1. Oligofructose
2. Inulin
3. Galacto-oligosaccharides
4. Lactulose
5. Breast milk oligosaccharides

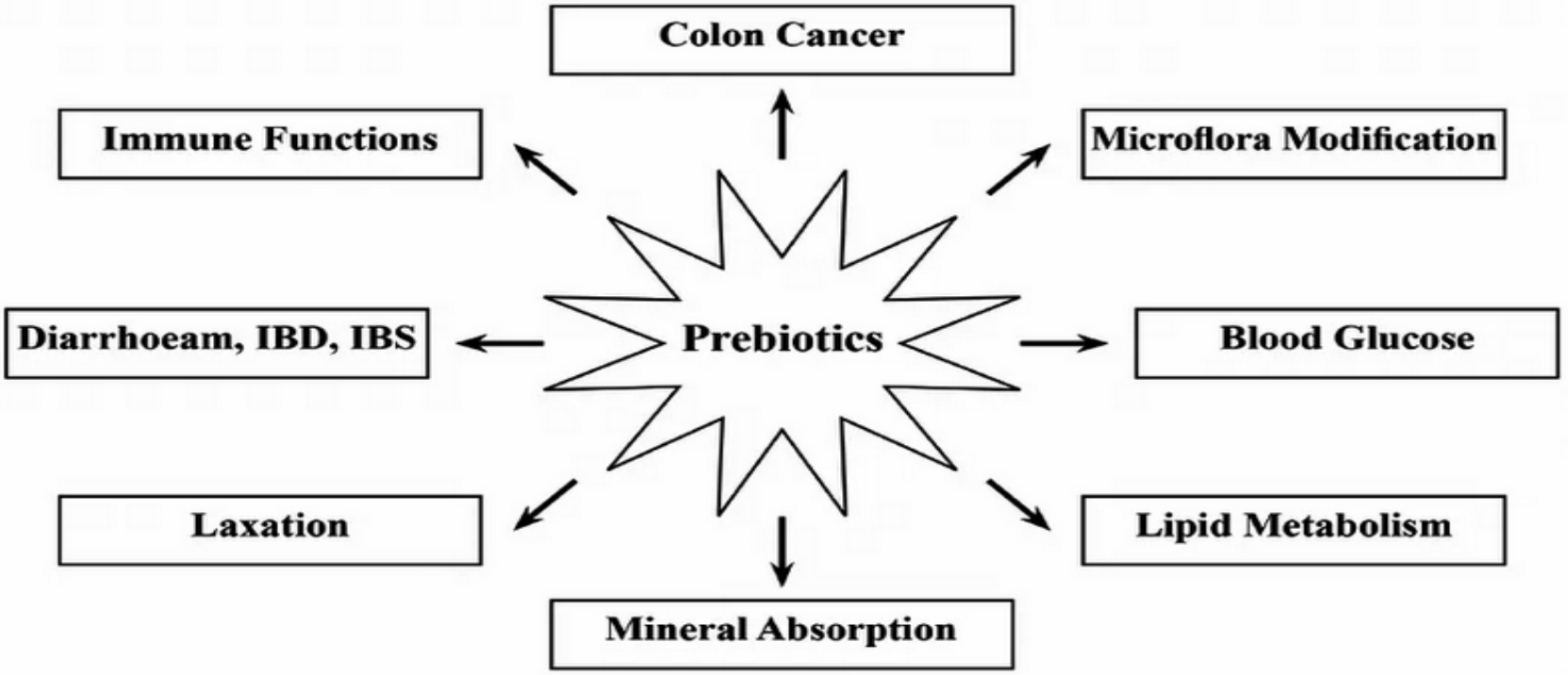
The prebiotic **oligofructose** is found naturally in many foods, such as wheat, onions, bananas, honey, garlic, and leeks. Oligofructose can also be isolated from chicory root or synthesized enzymatically from sucrose. **Inulin** is a prebiotic fiber that occurs naturally in asparagus, garlic, onions, wheat, garlic, leeks, chicory, oats, soybeans, and Jerusalem artichokes.

Galacto-oligosaccharides which are mainly used in infant milk formula are made up of plant sugars linked in chains. They are found naturally in dairy products, beans, and certain root vegetables. **Lactulose** is a man-made sugar that contains two naturally occurring sugars, galactose, and fructose. Lactulose is produced industrially by isomerization of lactose via a 1,2-enediol intermediate.

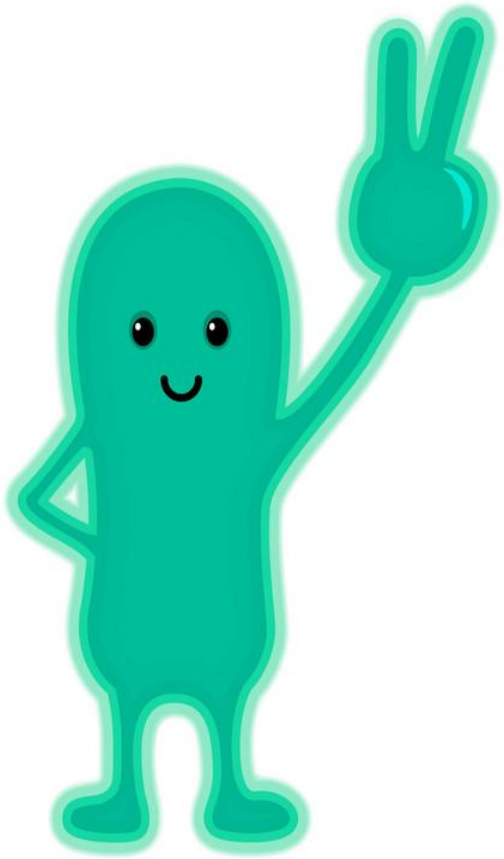
Health Benefits of Prebiotics

The use of both prebiotics and/or probiotics is intended to influence the gut environment for the benefit of human health and their beneficial effects extend beyond the gut. Fermentation of oligofructose in the colon results in a large number of physiologic effects, including:

- Increasing the number of bifidobacteria in the colon
- Increasing calcium absorption
- Increasing fecal weight
- Shortening gastrointestinal transit time
- Possibly lowering blood lipid levels

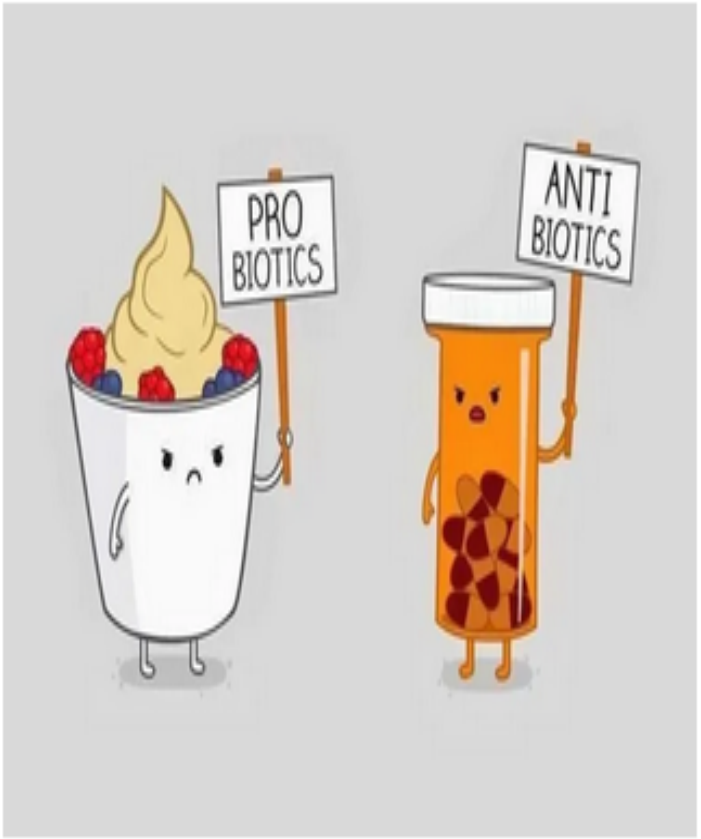


Possible health benefits of prebiotics (image source)



PROBIOTIC

Probiotics vs. Antibiotics



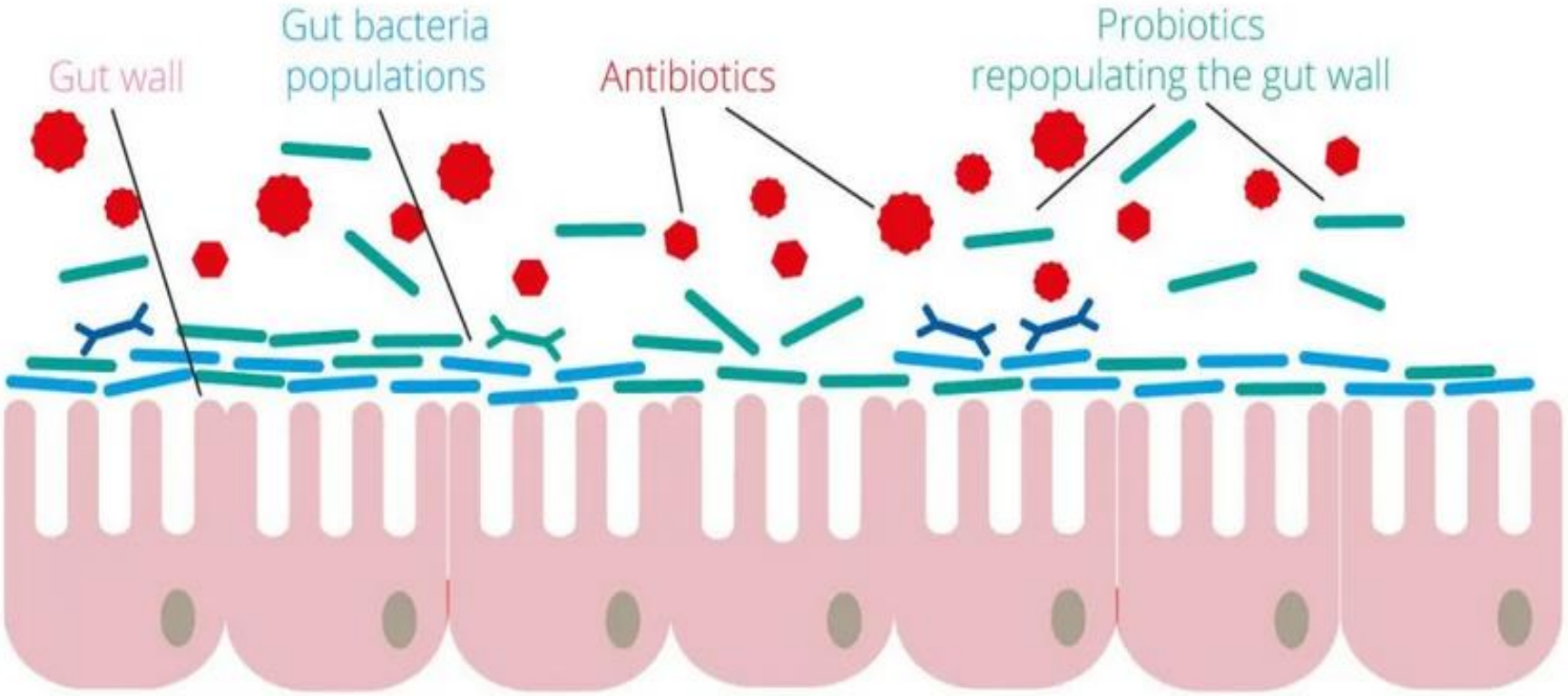
The term "**probiotic**" literally means "**for life**" and "**antibiotic**" literally means "**opposing life**" are two opposing categories of supplements or drugs. **Antibiotics** (Greek *anti*, against, and *bios*, life) are used to prevent and treat infections caused by pathogenic bacteria whereas **probiotics** (Greek pro, for, and bios, life) are used to replenish good bacteria.

For example, during the course of antibiotics treatment, good bacteria of the gut are also wiped out, taking probiotics helps to restore the gut microbiome, thus restoring the healthy state of the gut.

Prebiotics s**electively stimulate the growth of selective bacterial genera** such as bifidobacteria and lactobacilli in the colon. The increase in colonic bifidobacteria benefits human health by producing digestive enzymes, vitamins, reducing blood ammonia levels, and inhibiting potential pathogens. Lactulose is a synthetic disaccharide used as a drug for the treatment of constipation and hepatic encephalopathy

Antibiotics along the gut cell wall

Antibiotics kill both good and bad bacteria. Probiotics help to replenish the good bacteria populations.



Probiotic Microorganisms

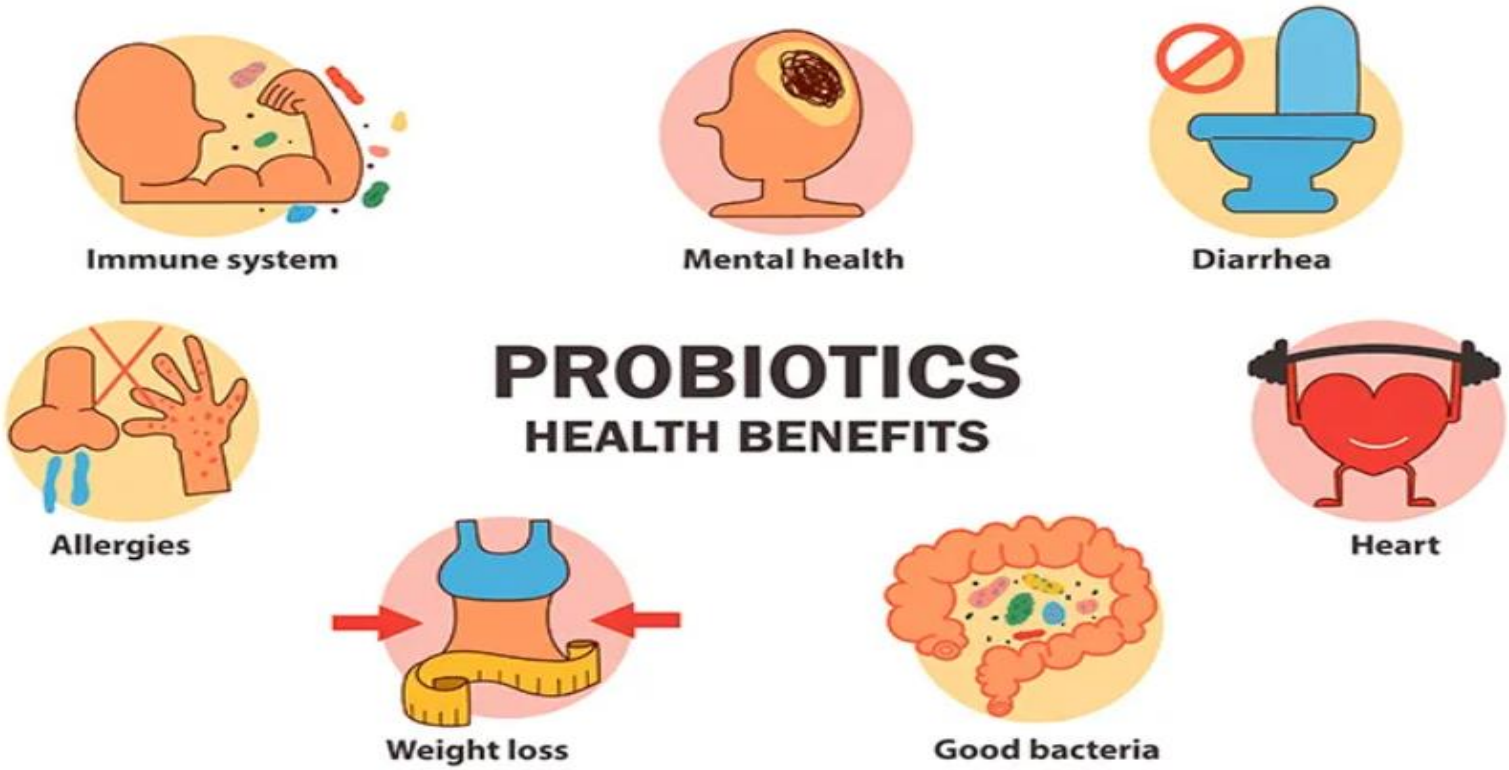
- A probiotic should contain a number of viable cells greater than 10^6 to 10^8 per dose to be efficacious. Seven microorganisms most often used in probiotic products are ***Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus, Escherichia,*** and ***Bacillus.***
- These beneficial microorganisms are **naturally present in fermented foods** (such as yogurt, kefir, etc), may be added to other food products, and also available as dietary supplements or as drugs. Probiotic microorganisms from commercial providers come in a variety of forms, including powders, pills, liquid suspensions, and food products.

Microorganisms selected for probiotic use should exhibit the following characteristics:

- Adhere to the intestinal mucosa of the host
- Be easily cultured
- Be nontoxic and nonpathogenic to the host
- Exert a beneficial effect on the host
- Produce useful enzymes or physiological end products that the host can use
- Remain viable for a long time
- Withstand HCl in the host's stomach and bile salts in the small intestine

Health Benefits of Probiotics

Numerous clinical trials have proven the health benefits of probiotics but the exact mechanisms of the health benefits are not fully understood. Gut health is the most important target for probiotics. Prevention and treatment of different forms of diarrhea is one of the most successful and best-documented health benefits of probiotics.



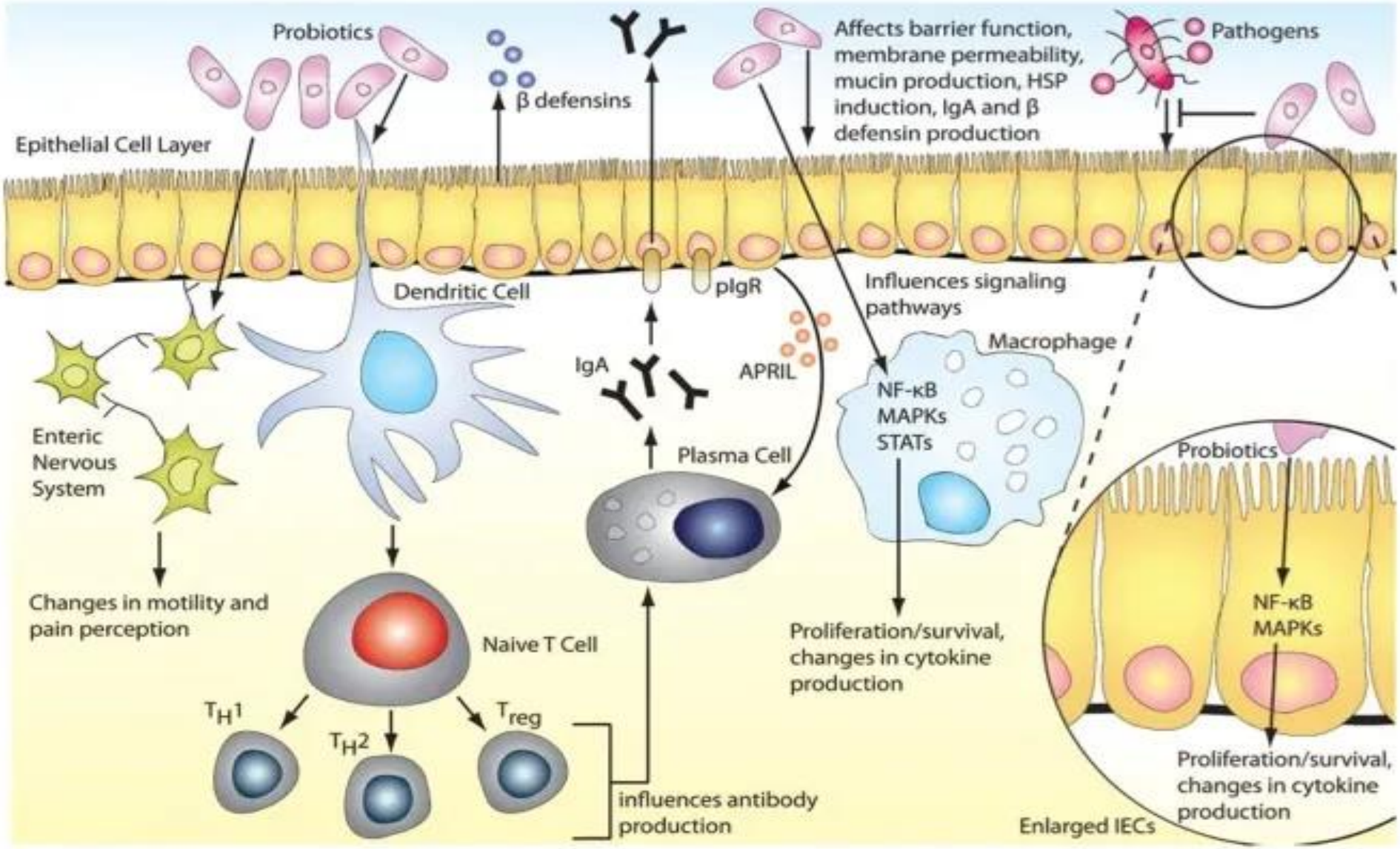
Health benefits of probiotics (Image source)

Proven potential benefits of probiotics include:

- Anticarcinogenic activity
- Control of intestinal pathogens
- Improvement of lactose use in individuals who have lactose intolerance
- Reduction in the serum cholesterol concentration
- Reduction of the risk of antibiotic-induced diarrhea

- Probiotics are live microorganisms that are supposed to have health benefits when consumed or applied to the body in adequate amounts. Scientific evidence suggests that specific strains of probiotic microorganisms confer health benefits on the host and are safe for human use. Healthy individuals are using probiotics with the intended benefits of promoting gastrointestinal health and immunity and preventing urogenital infections, allergies, and even cancers.
- *Lactobacillus*, *Bifidobacterium*, *Escherichia*, *Enterococcus*, and *Saccharomyces* are some of the most widely used probiotic microorganisms.
- There are several possible explanations of how probiotic microorganisms displace pathogens and enhance the development and stability of the microbial balance in the large intestine.

Mechanisms


Probiotics
β defensins
Affects barrier function, membrane permeability, mucin production, HSP induction, IgA and β defensin production
Pathogens
Epithelial Cell Layer
Dendritic Cell
pIgR
Influences signaling pathways
Macrophage
IgA
APRIL
NF-κB
MAPKs
STATs
Enteric Nervous System
Plasma Cell
Probiotics
Changes in motility and pain perception
Naive T Cell
Proliferation/survival, changes in cytokine production
NF-κB
MAPKs
T_H1
T_H2
T_{reg}
influences antibody production
Proliferation/survival, changes in cytokine production
Enlarged IECs

Competition with pathogens for nutrients and adhesion sites

The beneficial bacteria prevent the colonization of pathogenic microorganisms by competitive inhibition for microbial adhesion sites. For example, *Lactobacillus casei* and *Lactobacillus plantarum* competitively inhibit the attachment of enteropathogenic *Escherichia coli*.

Inactivation of pathogenic bacterial toxins or metabolites

Some members of the intestinal microbiota influence the onset of carcinogenesis by producing enzymes, such as glycosidase, azoreductase, nitroreductase, and β-glucoronidase, which transform pre-carcinogens into active carcinogens. Human studies have shown that the ingestion of *L. acidophilus* or *Lactobacillus casei* results in reduced levels of the above enzymes in the stools of volunteers. It's not yet confirmed that consumption of these probiotic microorganisms actually reduces the incidence of cancer.

Production of substances that inhibit pathogen growth

Probiotic microorganisms produce organic acids, fatty free acids, ammonia, hydrogen peroxide, and **bacteriocins**, all of which have antimicrobial activity. For example, *L. casei* produces a low-molecular-weight antibacterial substance that is inhibitory to both Gram-positive and Gram-negative enteric bacteria. Probiotics suppress the growth of pathogens also by inducing the host's production of β-defensin and IgA.

Stimulation of nonspecific immunity

Oral administration of different probiotics have shown adjuvant-like effects on intestinal and systemic immunity. Enhanced phagocytic activity against intracellular pathogens and enhanced immunoglobulin A (IgA) responses against pathogenic viruses have been demonstrated in several studies. Probiotics may be able to fortify the intestinal barrier by maintaining tight junctions and inducing mucin production.

In-vitro and in-vivo studies suggest that probiotics may modulate the immune response by promoting endogenous host defense systems. Probiotic bacteria can modify various immune parameters, including humoral, cellular, and nonspecific immunity

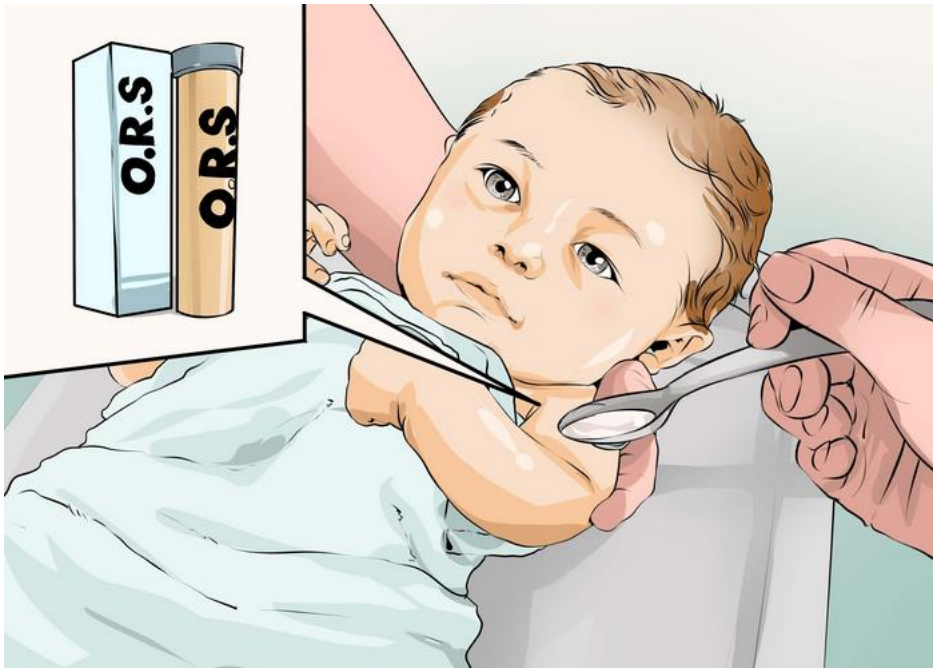
- Enhance the activity of natural killer cells in the elderly
- Induces mucus production
- Activate macrophage by lactobacilli signaling
- Stimulate secretory IgA and neutrophils
- Inhibit release of inflammatory cytokines, etc.

Prevention of Dirrhea

Consumption of probiotics microorganisms such as *Lactobacillus rhamnosus* GG, *Bifidobacterium lactis* BB-12 and *Lactobacillus reuteri* SD2222 has shown a significant reduction in incidence or duration of certain diarrheal illnesses such as rotavirus diarrhea. Prophylactic use in hospitalized children has also resulted in a reduction in the risk of acquiring nosocomial diarrhea.

Mechanisms that have been proposed for this protective effect include competitive blockage of receptor sites (resulting in inhibition of virus adherence and invasion), enhancement of the host immune system, and production of substances that inactivate virus particles.

توجه



در موارد اسهال حاد با دزیدراتاسیون شدید و متوسط به هیچ وجه پروبیوتیک جایگزین مایع درمانی مناسب نخواهد شد

Kids and Diarrhea

- Some of the best proof that probiotics work comes from studies of diarrhea in children, especially when it's caused by rotavirus. Probiotics might cut bouts of infectious diarrhea by half a day to about 2 days.
- Some research shows that the bacteria strains most likely to help are *Lactobacillus reuteri*, *Lactobacillus rhamnosus*, and the probiotic yeast *Saccharomyces boulardii*, although other strains might be useful. A mix of a few different probiotics may also treat this type of diarrhea.

Main results

Cochrane Database Syst Rev. 2010 Nov; 2010(11): CD003048.
Published online 2010 Nov 10. doi: 10.1002/14651858.CD003048.pub3

Probiotics for treating acute infectious diarrhoea

- Sixty-three studies met the inclusion criteria with a total of 8014 participants. Of these, 56 trials recruited infants and young children. The trials varied in the definition used for acute diarrhoea and the end of the diarrhoeal illness, as well as in the risk of bias. The trials were undertaken in a wide range of different settings and also varied greatly in organisms tested, dosage, and participants' characteristics. No adverse events were attributed to the probiotic intervention.
- Probiotics reduced the duration of diarrhoea, although the size of the effect varied considerably between studies.
- The average of the effect was significant for mean duration of diarrhoea (mean difference 24.76 hours; 95% confidence interval 15.9 to 33.6 hours; n=4555, trials=35) diarrhoea lasting ≥4 days (risk ratio 0.41; 0.32 to 0.53; n=2853, trials=29) and stool frequency on day 2 (mean difference 0.80; 0.45 to 1.14; n=2751, trials=20).

- The differences in effect size between studies was not explained by study quality, probiotic strain, the number of different strains, the viability of the organisms, dosage of organisms, the causes of diarrhoea, or the severity of the diarrhoea, or whether the studies were done in developed or developing countries.

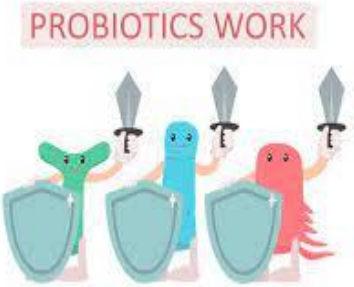
Authors' conclusions

- Used alongside rehydration therapy, probiotics appear to be safe and have clear beneficial effects in shortening the duration and reducing stool frequency in acute infectious diarrhoea. However, more research is needed to guide the use of particular probiotic regimens in specific patient groups.

BMJ

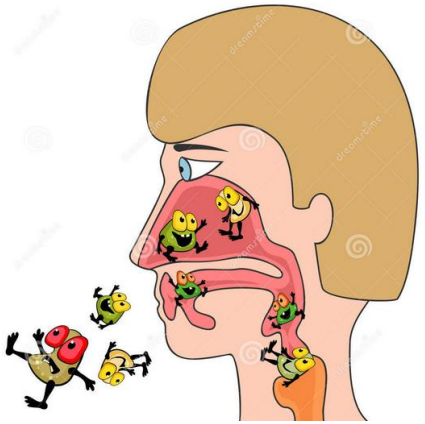
- To compare the efficacy of five probiotic preparations recommended to parents in the treatment of acute diarrhoea in children. Design Randomised controlled clinical trial in collaboration with family paediatricians over 12 months. Primary care. Children aged 3-36 months visiting a family paediatrician for acute diarrhoea. Children's parents were randomly assigned to receive written instructions to purchase a specific probiotic product: oral rehydration solution (control group); Lactobacillus rhamnosus strain GG; Saccharomyces boulardii; Bacillus clausii; mix of L delbrueckii var bulgaricus, Streptococcus thermophilus, L acidophilus, and Bifidobacterium bifidum; or Enterococcus faecium SF68. Primary outcomes were duration of diarrhoea and daily number and consistency of stools. Secondary outcomes were duration of vomiting and fever and rate of admission to hospital. Safety and tolerance were also recorded. 571 children were allocated to intervention. Median duration of diarrhoea was significantly shorter (P<0.001) in children who received L rhamnosus strain GG (78.5 hours) and the mix of four bacterial strains (70.0 hours) than in children who received oral rehydration solution alone (115.0 hours). One day after the first probiotic administration, the daily number of stools was significantly lower (P<0.001) in children who received L rhamnosus strain GG and in those who received the probiotic mix than in the other groups. The remaining preparations did not affect primary outcomes. Secondary outcomes were similar in all groups. Not all commercially available probiotic preparations are effective in children with acute diarrhoea. Paediatricians should choose bacterial preparations based on effectiveness data.

Decrease in Genitourinary Tract Infections



Absence of vaginal lactobacilli increases the risk of sexually transmitted infection and carriage of Neisseria gonorrhoeae and Chlamydia trachomatis. A couple of studies has shown that oral intake of probiotic lactobacilli reduces the risk of urinary tract infection, bacterial vaginosis, and candidiasis. Though the exact mechanism is not known, it has been suggested that ingested lactobacilli could ascend from the rectal skin to the vagina, or alternatively, prevent the ascent of pathogens.

Probiotics for prevention and treatmen of respiratory tract infections in childre



Respiratory tract infections (RTIs) remain one of the leading causes of global morbidity and mortality among children at different ages. Most children younger than 2 years experience several RTIs during the first year of life, and one-quarter suffer from recurrent or prolonged infections in developed countries.[1,2] RTIs are a major cause for parental concern and medical visits in preschool and elementary school children, leading to school absenteeism and hospitalizations. They also lead to inappropriate prescription of antibiotics in pediatric practice because antibiotics are not effective against viruses. Inappro-priate and wide use of antibiotics may lead to the development of bacterial resistance and disturb the normal balance of humanmicrobiota, facilitating the pathogen colonization and reducing availability of vaccines for viruses.

Conclusions

Taken together, the present systematic review and meta-analysis suggested that probiotic consumption may decrease the incidence and illness duration of RTI episode.

The optimal probiotic strains, dosing, administration form, time of intervention, and

long-time follow-up should be considered in future clinical trials and studies are needed to explore the mechanisms of such action of probiotics on RTI in children.

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ADDENDUM

Probiotics to prevent *Staphylococcus aureus* disease?

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ABSTRACT

There are a plethora of probiotic formulae that supposedly benefit human health on the market. However, the scientific underpinnings of the claimed benefits have remained poorly established. Scientific evidence is now increasingly being provided that explains those benefits, for example, by immune-stimulatory effects or inter-bacterial competition between beneficial and pathogenic bacteria. In our recent study (Piewngam et al. *Nature* 2018), we show that *Bacillus* colonization of the human intestine is negatively correlated with that of the human pathogen, *Staphylococcus aureus*. This type of colonization resistance is achieved by secretion of a class of lipopeptides by *Bacillus* species that inhibits *S. aureus* quorum-sensing signaling, which we found is crucial for *S. aureus* intestinal colonization. Here, we discuss what these findings imply for the general role of *S. aureus* intestinal colonization, the role of quorum-sensing in that process, and potential alternative ways to control *S. aureus* infection.

ARTICLE HISTORY
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KEYWORDS
Staphylococcus aureus; Bacillus subtilis; quorum-sensing; probiotics; colonization resistance

Introduction

It is now widely acknowledged that the ensemble of microorganisms that colonize human epithelial surfaces, the human microbiota, has a key role in determining human health. The number of microorganisms in the human gut exceeds by far that on any other body part, and intestinal colonization has, therefore, received the most attention.[1] Some of the bacteria that colonize the human gastrointestinal tract are of considerable benefit to the host, while others may cause severe infections.[2] A major reason for the expansion of pathogenic

The contribution of the microbiota to host defense against pathogen colonization and overgrowth is called "colonization resistance" and it has been suggested to exploit mechanisms of colonization resistance by next-generation probiotics consisting of beneficial commensal bacteria.[5,6] However, there are no FDA-approved colonization resistance-based therapies as of yet, which is mostly due to the fact that the mechanisms underlying bacterial interactions that lead to such resistance have remained poorly understood. Generally, the marketing and use of probiotics have far outpaced the scientific investigation of

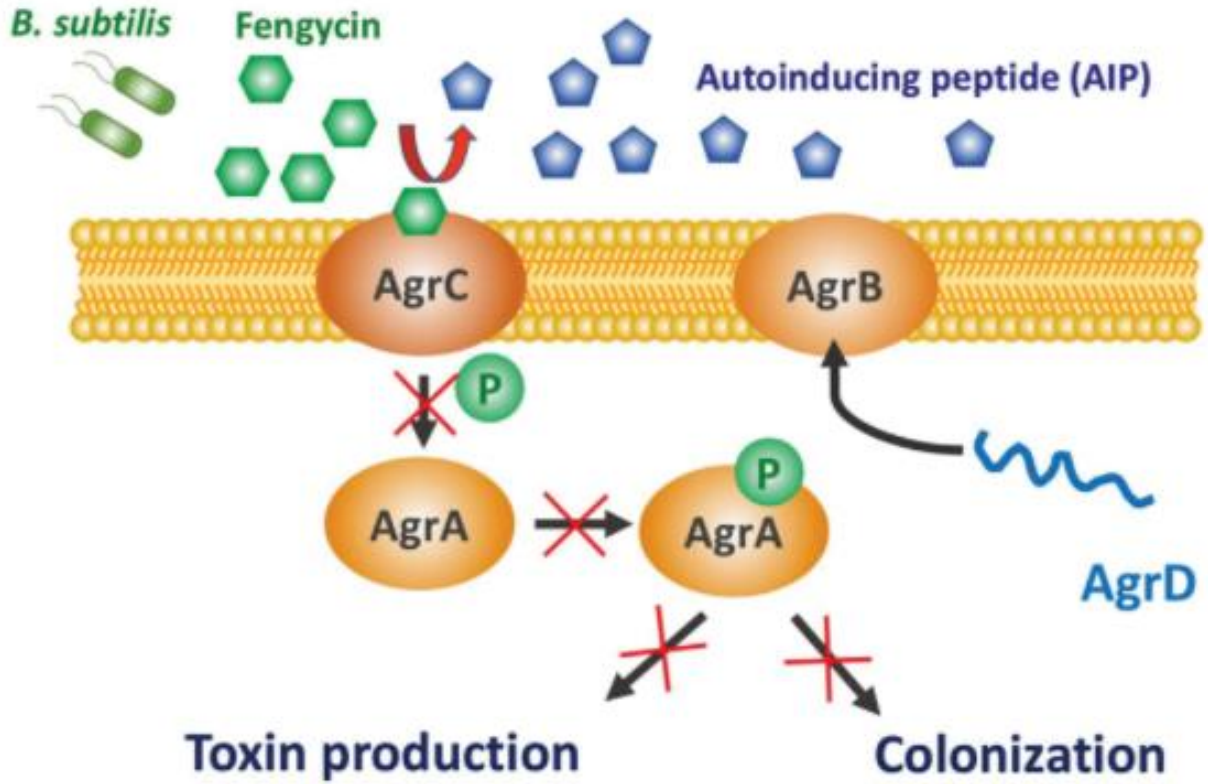

Figure 1. Inhibition of Agr quorum-sensing in *S. aureus* by *Bacillus*. *Bacillus* ssp. produce fengycin lipopeptides, which resemble the Agr auto-inducing peptide (made from the AgrD precursor by AgrB) and compete with the AIP for binding to the AgrC receptor, part of the AgrC-AgrA two-component system. This blocks signal transduction, which is dependent on AgrA phosphorylation and binding of AgrA to specific promoters, which include that driving *agrABCD* expression in an auto-regulatory fashion and toxin gene promoters in a direct or indirect manner. As a consequence, there is a diminished capacity to produce toxins and colonize the intestinal tract.

Side Effects

People are using probiotic microorganisms from ancient times to prepare various fermented foods and there are no reports of adverse side effects. Probiotics are generally assumed to be safe in healthy people, though in some people they may cause gas. taste disturbance. fever.

There have been some reports of probiotics causing problems among vulnerable patients. Saccharomyces fungemia secondary to the use of the probiotic has been described for critically ill patients. To ensure patient safety, proper assessment of risk versus benefit of probiotics administration must be made and probiotics should be properly handled during administration


Thank you