A Brief Overview on Probiotics: The Health Friendly Microbes

Sanjukta Mishra and Swastik Acharya

1 Department of Biochemistry, Kalinga Institute of Medical Science, KIIT University, Bhubaneswar, Odisha, India.
2 Department of Medicine, Kalinga Institute of Medical Science, KIIT University, Bhubaneswar, Odisha, India.
*Corresponding Author E-mail: drmsanjukta@gmail.com

Probiotics are defined as non-pathogenic live microorganisms that, when administered in adequate amounts, confer health benefits on the host. Association of probiotics with human beings has a lot of history. Well known as 'health-friendly bacteria', they are widely used commercially as a functional food. The popularity of probiotics has gone exponentially high due to an increasing number of clinical trials, supporting their beneficial effects. Several in vivo and in-vitro experimental evidence supports strain-specific and disease-specific probiotic efficacy to prevent and ameliorate antibiotic-associated diarrhoea, traveller's diarrhoea, ulcerative colitis, and many more. Besides, numerous recent studies have reported that probiotics could have a significant effect in alleviating various metabolic, lifestyle and diet-related disorders like obesity, type 2 diabetes, metabolic syndrome, irritable bowel syndrome. Strains of Bifidobacterium, Lactobacillus and Saccharomyces boulardii are the most commonly used as probiotics. Safety, efficacy, pathogenicity, infectivity, intrinsic property, virulence factors are to be addressed during probiotic selection. The underlying mechanisms of probiotics effects are still not fully elucidated and have been under intensive research. Numerous diverse, strain-specific probiotic mechanisms have been proposed, which include early colonization of perturbed microbes, competitive exclusion of pathogens, short-chain volatile fatty acid production, alteration of gut pH, immunomodulation and many more. Considering the remarkable influence on human health, probiotics seem to be alluring attractive agents to promote human health conditions and to improve the quality of life against several diseases. This review discusses the current documentation and recent advances on probiotics and their possible health attributes, in scientific literature, focusing on diverse, heterogeneous, and strain-specific mechanisms of action. Randomised human controlled clinical trials are needed to reconfirm its safety and beneficial effects.

Keywords: Bifidobacteria; Health; Lactobacillus; Microorganism; Probiotics; Saccharomyces.
and composition are studied to be related to chronic diseases like obesity, type 2 diabetes mellitus, oxidative stress-related diseases, non-alcoholic fatty liver disease, cardiovascular disease and immune-mediated diseases.\textsuperscript{6,7} Due to the emergence of bacterial resistance against antibiotics, the therapeutic use of medicines would provide limited efficacy. In this regard, probiotics and their relationship with human health have been an area of interest in recent years. Probiotics can be defined as non-pathogenic live microorganisms that exert health benefits to host upon ingestion. Probiotics exhibit this unique ability to promote human health by colonization and normalization of a perturbed intestinal microbial community. Moreover, they should be able to express their activities against pathogens and should be able to stimulate the immune system.\textsuperscript{8} They are being implicated clinically as co-adjuvants for the elite properties like anti-diabetic, anti-obesity, anti-inflammatory, anti-angiogenic activities.\textsuperscript{9,10} Most of the probiotics are available commercially as foodstuff or drugs containing live microbes. Therefore, consideration of the safety assessment of probiotics is of utmost importance before use.\textsuperscript{11} Looking at the long list of health benefits, it may be considered as a biotherapeutic agent. A comprehensive review of the relevant literature was performed to reiterate the factual findings. Present review article provides a current understanding of different aspects of probiotics, highlighting the historical prospectus, compliance to the global scientific definition, criteria for safety selection, brief mechanism of action, and its role towards human health. This may result in establishing validation of probiotic therapies in application to human beings.

**Origin and Historical perspectives**

Etymologically, the term “Probiotic” comes from the Greek word “pro-bios” which means “for life”. It has long been integral since ancient times when fermented products had been used for nutritional and therapeutic purposes. A century ago, the journey of probiotics was started when scientist Henry Tessler (1899), Pasteur Institute of Paris, discovered \textit{Bifidobacterium} in the intestine of breastfed infants and found it useful for diarrhoeal episodes in those infants.\textsuperscript{12}

However, Nobel laureate Russian scientist Elie Metchnikoff (1907), first introduced the hypothesis of using microorganisms for health benefit by replacement of gut flora with useful ones.\textsuperscript{13} In the early 1930s, Shirota reported the survival of intestinal bacteria through the gut passage. He developed fermented milk containing \textit{Lactobacillus acidophilus} Shirota, which is still popular today as Yakult.\textsuperscript{14} Lilly and Stillwell (1965) then first introduced the term “Probiotic” to describe a substance which stimulates the growth of other micro-organisms.\textsuperscript{15} Next supporting evidence came from Parker (1974), who gave a new definition to probiotics as “microorganism and substances responsible for intestinal microbial homeostasis.”\textsuperscript{16} Following which, many scientists widened the definition of probiotics, including health benefits of the host.\textsuperscript{17,18,19} Subsequently, Food and agricultural organization of United Nations and World Health Organisation [FAO/WHO,2002], explained probiotics as “live micro-organisms which when administered in adequate amounts, confer health to the host”.\textsuperscript{20} This recommended definition and guidelines have been popularly adopted and proven to be useful to researchers. Since then, research in the field of probiotics has grown exponentially high, and it has been strengthened considerably to understand the role of a wide range of probiotics in enhancing or preventing chronic diseases.

**Microbial species as probiotics**

Contemporary probiotics research aims at the characterization and composition of gut microbiota, which functions as a microbial ecosystem. It is worth mentioning here that probiotic effects are strain specific. So health claim is distinctive for each probiotic strain, and probiotic prospective of bacterial strains varies significantly within the same species.\textsuperscript{21,22} That is why strain identification is recommended to characterize the functions of each probiotic to the specific strain. This could be achieved by genetic recognition using molecular approaches like DNA-DNA hybridization, 16SRNA sequencing, and pulsed-field gel electrophoresis for strain typing.\textsuperscript{23,24} That apart polymerase chain reaction(PCR) method can come up with fast quantitative and qualitative information on the constitution of the intestinal microbiome.\textsuperscript{25} It is also reported that several probiotic products contain more than one strain. A single strain may exhibit different benefits when used individually and in combination.\textsuperscript{26,27}
Every individual is bestowed with exclusive gut microbiota that take part in distinctive functions like nutrient metabolism, continuance of structural coherence of gut mucosal barrier, and immunomodulation. Traditionally, the term probiotics are more related to most popular strains of Lactobacillus and Bifidobacterium (Table-1), but it can be extended to other microorganisms like Streptococcus, Saccharomyces (yeast strain), Enterococcus and Bacillus.28,29,30 Many of these probiotics strains have been preferred based on selection criteria.31

Some bacteria that do not normally colonize the intestinal tract, may also come under the category of probiotics that include Lactobacillus bulgaricus, streptococcus thermophilus, and Leuconostoc species. Neither these bacteria colonize nor exert any significant effect on intestinal microbial balance.32 But they do play an important role in the food industry. There are several studies in progress to recognize the futuristic genre and new strains for probable use as probiotics. These new strains need to be appraised and analyzed based on accepted and confirmed selection criteria before implication.

**Requisites for selection of safe and effective probiotics**

Eighteen years before, scientific definition of probiotics was conceived, along with the guidelines warranting pertinent use of them. The aim of administering live microbes can assist therapeutic function is achieving precedence. Most of the probiotics are promoted as foodstuff or drugs (tablets, powder, and other formulations) containing live microbes. The variety of food products accommodating probiotic strain is wide such as fermented milk, cheese, ice cream, buttermilk, milk powder, yogurt, and many more. The viability and feasibility of probiotics is a fundamental parameter for developing probiotic food, as probiotics are certainly very fragile to many environmental burdens such as acidity, oxygen, heat, etc.33 Probiotic food products are widened worldwide due to never ending steady generation of research confirmations, indicating their likely health benefits to consumers. Consideration of safety of probiotics and compatibility of the product with the microbes are very important because of the frequent isolation of widely used bacteria (Table-1) from clinical infection sites. This has raised debate over their infectiveness and safety. However, it is unlikely that they require generalized infectivity as their separation is the result of opportunistic infection, which might be caused by chronic diseases, skin injury, cancer, or drug induced abnormality.34 Practically, lactobacillus and Bifidobacterium are an infrequent cause of infection to humans. This lack of pathogenicity perpetuates all age groups and also to the immunosuppressed individual.35 Assessment of the safety of probiotics from various angles is not a simple task. However, it is relatively easy for an in vitro study of several factors. Several such studies in animal and human beings have been proposed to assess the safety standards of probiotics by studying on an intrinsic property of the strain, the pharmacokinetics of the strain (survival, activity in intestine, faecal and mucosal recovery) and interaction between strain and host.36 But the values of these parameters are under debate due to discrepancies and lack of standardization of operating procedures. So, the best-proposed approach should be the target population and function-specific studies. Although, many probiotic strains are well described as safe, risk-free and reports of harmful effects to the host are rare, the following factors need to be evaluated to assess its safety and effectiveness:

1. Identified genetically at genus, species and strain level [whole genome strain characterisation]37
2. Non-pathogenic, non-infective.38,39,40
3. Should not carry transferable antibiotic resistance gene.41
4. Non toxic [no formation of any harmful substances like ammonia, indole, phenol, amines]42
5. Able to survive in adequate number during intestinal transit [acid, bile tolerant]43
6. Bile salt hydrolase activity [deconjugation of biliary salt, prevents carcinogenesis].44,45
7. Antimicrobial activity [able to adhere to the mucosal epithelium, able to colonize and competitive exclusion of pathogen]46
8. Able to antagonize pathogenic bacteria [in vitro culture study depends on microbial cell mass, buffer component, fermentation span, and growth medium]47
9. Stable and capable of remaining viable under storage condition [potentiates gut adherence, immunomodulation and can lower gut permeability]48
10. Clinically documented and validated health
effects [strain to be tested in randomized controlled human trial]49
11. Designated strain-specific for human use and animals49

That apart, several other determinants that must be described during the analysis of safety are Platelet aggregation activity and mucus degradation activity. Harry et al. could isolate different strains of *L. Rhamnosus* from infective endocarditis, which is having higher activity than laboratory strains.50 This suggests that they may have an infective property in contributing to the progression of endocarditis. Mucous degradation activity is because of the production of enzymes glycosidase and protease, which might break intestinal mucous glycoproteins, so causing infective endocarditis.51 Ruserler et al. in his study lactobacillus and *bifidobacterium* did not find the efficacy of this proposed mechanism.52 Therefore, it is critical to establish the infectivity related to the outer layer structure containing glycoproteins and lectins.

**Mechanism of action of probiotics**

Probiotics are safe microbes that confer beneficial effects to the host when administered in an adequate dose and at an appropriate period. The consequences of probiotics on host well-being have been communicated in many reports, articles, reviews, systematic meta-analysis, though many studies lack insight into the potential mechanism of action.53,54,55 The underlying mechanism on why and how the bacterial strains work to achieve such effect, has been under intensive study. Numerous probiotic mechanisms have been proposed, which are diverse, heterogeneous, and strain-specific such as modulation of host defence, antagonist to pathogenic bacteria, and effect through microbial toxins.56 After a thorough comprehensive search of relevant literature, elaborated mechanisms from in vivo and in vitro studies are given below:

1. Colonization and normalization of the perturbed intestinal microbes.57
2. Competitive exclusion of pathogens.58
3. Enzyme activity [beta galactosidase, beta glucuronidase].59,60
4. Production of bacteriocin, mucin and volatile fatty acid.60
5. Cell adhesion and cell antagonism.61
6. Modulation of immune system.62
7. Interaction of brain-gut axis.63,64,65

Currently, it is accepted that early colonization of probiotic strain and normalization of the perturbed intestinal microbial community is the key mechanism that confers health benefits to the host. Normally intestinal microflora exhibits colonization resistance or barrier effect, an indigenous mechanism to inhibit colonization of harmful enteric pathogen, which is attained by complex interactions among the bacterial community.66,67 Adhesion of bacteria to host surfaces prevents mechanical clearing of pathogens. The anti-pathogenic activity of probiotics has been a topic of research as a wide variety of such compounds (bacteriocin, ethanol, organic acid, hydrogen peroxide, acetaldehyde, peptides, etc) are produced by them.68 Some *lactobacillus* and *bifidobacterium* produce bacteriocin, which prevents proliferation by competitive exclusion of selected pathogen and can increases membrane permeability, that leads to depolarisation of membrane potential.69 Enzymatic activity of probiotic specifically beta-glucuronidase hydrolyses glucuronidated metabolite in their toxic form, causing intestinal damage. More so it has been linked to an early pre-neoplasticism marker for colon carcinoma.70 Agreeing with in vitro and in vivo study information, volatile fatty acids have been documented to have numerous biochemical, physiological and molecular effects. It is a useful source of energy for enterocytes and it acts as a key signalling molecule for maintenance of gut health.25

**Evidence for probiotic effectiveness [in vivo & in vitro studies]**

The association between lifestyle, diet, and well-being has increased the requirement for products, which can build up health beyond rendering basic nourishment. The conglomeration of probiotics on human health goes back to the long past when people were using fermented milk for their well-being.71 The detailed review of literature by WHO/FAO illustrated a comparatively small number of areas in which probiotics have shown their positive effect, which will be presented below.

**Probiotics for newborn and children**

Intestinal infection in neonates is very frequent and is the leading cause of death in developing countries.72 Necrotizing enterocolitis is a devastating intestinal condition, mostly seen in preterm infants, where intestinal microbiota will be dominated by many pathogens like *Enterococcus faecalis*, *E.Coli*, *Staphylococcus epidermidis,*
Klebsiella pneumonia etc. However, the study has indicated a low incidence of the said condition if premature infants were given breast milk, which may allow non-pathogens like lactobacillus and bifidobacterium to organize within the premature intestine. Recent meta-analysis has identified the specific strain *Lactobacillus rhamnosus* GG ATCC53103 or combination of *Bifidobacterium infantis* Bb-02, *Bifidobacterium lactis* Bb-12, and *Streptococcus thermophilus* TH-4 in order to reduce necrotizing enterocolitis. This suggests a correlation between the reduction in *Lactobacillus* and the increased risk of necrotizing enterocolitis. That apart, in a review on mucosal immunity starting at birth, Walker outlined a correlation between the normal intestinal microbiome, early intestinal colonisation, and subsequent defence from several disorders. In another meta-analysis, the author briefly discussed the effect of probiotic and conventional oral rehydration therapy, which reduces the extent of acute diarrhoea in one day in the case of little ones under 5 years of age. Cochrane review involving infant and children also reported beneficial effects of probiotics as the reduced duration of diarrhoea and diminished stool frequency.

**Probiotics for Antibiotic-associated diarrhoea and Traveller’s diarrhoea**

There is considerable evidence to encourage probiotic use in GIT illness like acute diarrhoeal disease and amelioration of antibiotic linked diarrhoea. Treatment and improvement of infectious diarrhoea are presumably the most comprehensively accepted health asset of probiotic microorganisms. Rotavirus is the commonest source, which replicates in the highly differentiated absorptive columnar cells of the small intestine. Evidence suggests the effectiveness of *L. Rhamnous, B. animalis, L. Casei Shirota* in diminishing the span of acute rotavirus infection by immunomodulation, competitive hindrance of receptor sites, and by yielding substances that inactivated viral particle. Moreover Rotavirus protein NSP1 may be linked to inhibition of interferon production by stimulating the degradation of interferon regulatory factor. Recent systematic review and meta-analysis explained the positive effect exerted by probiotics *Lactobacillus rhamnosus* GG in reducing the duration of acute rotavirus diarrhea. Randomised control trial by Allen et al, to assess the probiotic efficacy in proven acute infectious diarrhoea showed the reduced mean duration of diarrhoea and reduced stool frequency after the intervention. Several incidents of diarrhoea are the usual after-effects of antibiotic therapy. This is due to suppressing GI microflora that encourages overgrowth of opportunistic infections like clostridium difficile. A meta-analysis by Hempel et al have evaluated the evidence of probiotic administration in reducing the risk of the condition. The majority of traveller’s diarrhoea is triggered by bacteria E.Coli and rest by virus and Protozoa. The 2017 guidelines for prevention of traveller’s diarrhoea (TD) by International society of travel medicine proposed inadequate affirmation to suggest the use of probiotics for treatment. A meta-analysis of randomised control trials by Jong-Myon Bae showed statistically significant efficacy in prevention of TD. Another study by Hilton et al on randomised American tourists with

| Commonly used probiotic microorganism |
|--------------------------------------|
| *Lactobacillus*                      |
| *Bifidobacterium*                    |
| *Bacillus*                           |
| *Lactococcus*                        |
| *Saccharomyces*                      |
| *Streptococcus*                      |
| *Enterococcus*                       |
| *Pedicoccus*                         |
| *Bacteroids*                         |
| Others                               |
an intake of a probiotic placebo showed a reduced daily risk of developing diarrhea.\textsuperscript{87} Interpreting the details from several blinded, randomised, placebo-controlled trials, sazawal et al. established that the use of probiotics in antibiotic-associated diarrhoea decreases the probability of diarrhea by 52%, traveller’s diarrhoea by 8%.\textsuperscript{88} Furthermore, numerous other study results have indicated contradictory findings owing to the difference in the study population and species of probiotic being used.\textsuperscript{89,90}

**Probiotics for Inflammatory Bowel Disease (IBD)**

Ulcerative colitis and Chron’s disease are the two important bowel diseases, where a change in normal intestinal flora has been associated with gut microbial genetic susceptibility and its ambience. Change in the normal intestinal flora and subsequent breaking in the uniformity between intestinal immune status and microbiome may lead to IBD.\textsuperscript{91} It is worth mentioning here that Probiotics are progressively known for its potentiality to impede and handle intestinal disorders and enhance the immune system in both in vitro and animal model research. Several clinical review articles demonstrated the efficacy of probiotics in IBD.\textsuperscript{92,93} Though the exact mechanism of action is not known, probiotics are thought to utilise their effect by modulating and harmonising intestinal flora and intestinal immune response.\textsuperscript{93} Enteric bacteria may alter the balance of pro-inflammatory and anti-inflammatory cytokine levels (secreted by T helper cells-1 and T- helper cells-2 respectively) of the intestine that predisposes for intestinal disorders.\textsuperscript{94} These two are important in maintaining the homeostasis of the immune system in the intestinal barrier. A preliminary study investigating the efficacy of probiotics suggests that a high dose of a combination of strains may alleviate symptoms of a disease, as compared to placebo.\textsuperscript{95} This improvement in the severity of the disease might be due to a decrease in inflammation. But still, there are inadequate confirmations to conclude about the potency as there is the fear of opportunistic by modulating inflammatory status.\textsuperscript{96} Several animal trials also conducted to investigate the effects of probiotics on IBD showing its anti colitis effects via downregulation of TNF-alpha, COX-2, and upregulating anti-inflammatory cytokines.\textsuperscript{97,98,99}

Although probiotic treatment improves the severity of disease by diminishing inflammation; it did not treat the source. So definitely more clinical trials of longer duration studies are required to understand safety, effectiveness and to prove sustainability of the positive results.

**Probiotics for Hypercholesterolemia**:\textsuperscript{100,101,102,103}

Specific strains of Probiotic like *b. adolescentis* have been claimed to exhibit possible therapy for reducing cholesterol levels. The possible mechanisms include:

i. Bile salt hydrolase activity, which is considered by many scientists to be a prerequisite for the selection of probiotics.

ii. Deconjugation of bile salt in enterohepatic circulation that makes it less soluble, so can be excreted via feces. This mechanism exhibited by *Lactobacillus* has drawn attention

iii. The accumulation of cholesterol into bacterial cell membranes. *E. faceium* CRL 183 strain has already been experimented to reduce lipid parameters, so it could prevent atherosclerosis development in rabbit with induced hypercholesterolemia\textsuperscript{104}

Much work has already been accomplished using bile salt deconjugation by *Lactobacillus* to treat hypercholesterolemia.\textsuperscript{105} Another study by Lye et al also reported experimental evidence of cholesterol-reducing property of *Lactobacillus*, where cholesterol was found to get converted into coprostanol with the help of cholesterol reductase produced by the probiotic strain.\textsuperscript{106} Probiotics may also produce short-chain fatty acids, which can inhibit HMG CoA activity and subsequently can decrease the transformation of primary to secondary bile acid due to colonic acidification.\textsuperscript{100,107}

**Probiotics for Cancer**

In vivo and in vitro experimental data supported the anti-carcinogenic effect of probiotics, which may be attributed to pro-inflammatory, anti-inflammatory response.\textsuperscript{33,108} *Lactobacillus, Bifidobacterium* and *E.Coli strain of Nissle* have shown antimutagenic activity in-vitro due to inactivation of the mutagenic compound.\textsuperscript{109} Roller et al. in his animal study on rats could correlate inhibition of carcinogenesis with a change in immune activity on probiotic consumption.\textsuperscript{110} Precise mechanism remains unclear due to a lack of human experimental evidence. The proposed
mode of action includes immunomodulation, production of antimutagenic substances, which alter the physicochemical and metabolic effect. Other health benefits of probiotics

Apart from these conventional beneficial effects, the role of probiotics in diabetes, inflammation, allergy, cardiovascular diseases, and neurodegenerative diseases has been a fascinating area of research. It has been reported that probiotics by improving mucosal barrier function, might help to protect against allergies. They are found to have cardiovascular protection via antihypertensive action. Accumulating pieces of evidence prove the beneficial dermal effects of probiotics such as a wound, scar healing, skin rejuvenation. Many other effects include a reduction in body and abdominals mass, lactose intolerance, periodontal infections, women’s reproductive and bladder health and modulation of the gut-brain axis. Undoubtedly, the current research progress toward healthful effects has been encouraging.

Probiotic: hope or hype

Researchers and clinicians used probiotics in a variety of medical conditions, taking into account safety guidelines and scientific requirements. Different new technologies like microencapsulation, cell immobilisation have been developed to enhance its stability and viability in functional food. That apart, molecular technology is already being tried to manipulate Lactobacillus by replacing it with its active ingredient or metabolite to produce new improvised products, which are clinically proven safe. It is suggested that these new ways of handling gut microbe-host interaction offer hope for the therapeutic effects of probiotics. Consumption of probiotics as dietary supplements may potentiate health benefits beyond the traditional nutritional functions. Safe and health-friendly bacterial species come under the probiotics category. Association of probiotics with human beings has a long history. Probiotics have become increasingly popular as there is documented evidence of health benefits. The capability of probiotics to ameliorate different health aspects with utmost safety is the basis of the selection of probiotics. Safety assessment should be the screening tool to identify potential probiotics. Lactobacillus and Bifidobacterium genera are reported to be used widely as probiotic food supplements due to their therapeutic benefits. Recent research explorations suggest that probiotics can modify the composition and few metabolic activities of the microbiota. Probiotic clinical effects are still controversial, as several results obtained are heterogeneous. So, sustainability of the desired results is a matter of conflict. Despite the strong scientific evidence of various health benefits of probiotics, further intensive research with well-designed randomised clinical trials is needed to justify the safety and efficacy.

CONCLUSION

Probiotics may be considered as a functional food as they provide health benefits beyond the traditional nutritional functions. Safe and health-friendly bacterial species come under the probiotics category. Association of probiotics with human beings has a long history. Probiotics have become increasingly popular as there is documented evidence of health benefits. The capability of probiotics to ameliorate different health aspects with utmost safety is the basis of the selection of probiotics. Safety assessment should be the screening tool to identify potential probiotics. Lactobacillus and Bifidobacterium genera are reported to be used widely as probiotic food supplements due to their therapeutic benefits. Recent research explorations suggest that probiotics can modify the composition and few metabolic activities of the microbiota. Probiotic clinical effects are still controversial, as several results obtained are heterogeneous. So, sustainability of the desired results is a matter of conflict. Despite the strong scientific evidence of various health benefits of probiotics, further intensive research with well-designed randomised clinical trials is needed to justify the safety and efficacy.
REFERENCES

1. Dreyer J.L., Liebl A.L. Early colonization of the gut microbiome and its relationship with obesity. *Human Microbiome Journal;* **10**(1):1-5 (2018).

2. Bäckhed F., Ley R.E., Sonnenburg J.L., Gordon J.I. Host-bacterial mutualism in the human intestine. *Science;* **307**(5717):1915-1920 (2005).

3. Guarner F., Malagelada J.R. Gut flora in health and disease. *Lancet;* **361**(9356):512-519 (2003).

4. Tsai Y.L., Lin T.L., Chang C.J., et al. Probiotics, prebiotics and amelioration of diseases. *J Biomed Sci;* **26**(1):372-377 (2016).

5. Jandhyala S.M., Talukdar R., Subramanyam C., Vuyyuru H., Sasikala M., Nageshwar Reddy D. Role of the normal gut microbiota. *World J Gastroenterol;* **21**(29):8787-8803 (2015).

6. Qin J., Li Y., Cai Z., et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature;* **490**(7418):55-60 (2012).

7. Selvanantham T., Lin Q., Guo C.X., et al. Lactobacillus strains in the human intestinal microbiota: from probiotics to gastrointestinal anti-infectious biotherapeutic agent. *Clinical Microbiology reviews;* **27**(2):167-199 (2014).

8. Moal V.L., Servin A.L. Anti-infective activities of *Lactobacillus strains* in the human intestinal microbiota: from probiotics to gastrointestinal anti-infectious biotherapeutic agent. *Clinical Microbiology reviews;* **27**(2):167-199 (2014).

9. Le Barz M., Anhê F.F., Varin T.V., et al. Probiotics as Complementary Treatment for Metabolic Disorders. *Diabetes Metab J;* **39**(4):291-303 (2015).

10. Palumbo V.D., Romeo M., Marino Gammazza A., et al. The long-term effects of probiotics in the therapy of ulcerative colitis: A clinical study. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub;* **160**(3):372-377 (2016).

11. Ishibashi N., Yamazaki S. Probiotics and safety. *Am J Clin Nutr;* **73**(2 Suppl):465S-470S (2001).

12. Tissier H. Traitement des infections intestinales par la methode de la flore bacterienne de l’intestin. 1906.; *C. R. Soc. Biol. 60*:359-361.

13. Podolsky S.H. Metchnikoff and the microbe. *Lancet;* **380**(9856):1810-1811 (2012).

14. Lactobacillus casei strain Shirata., Yakult Honsha Co. Ltd., Yakult Central Institute for Microbiological Research, Tokyo, Japan (1998).

15. Lilly D.M., Stillwell R.H. Probiotics: Growth-promoting factors produced by microorganisms. *Science;* **147**(3659):747-748 (1965).

16. Parker R.B. Probiotics: the other half of the antibiotic story. *Anim Nutr. Health;* **29**:4-8 (1974).

17. Fuller R. Probiotics in human medicine. *Gut;* **32**(4):439-442 (1991).

18. Salminen S., van Wright A. Current probiotics-safety assured?. *Microbial Ecology in Health Dis;* **10**(2):68-77 (1998).

19. Salminen S., Ouwehand A., Benno Y., Lee Y.K. Probiotics: how should they be defined? *Trends in Food Science and Technology;* **10**(3):107-110 (1999).

20. FAO/WHO. Report on Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria, (2001).

21. Arslan S., Erbas M. Probiotic cereal-based fermented functional foods. *Fermented foods, part 1.:* 211-27 (2015).

22. Ramos C.L., Thorsen L., Schwan R.F., Jespersen L. Strain-specific probiotics properties of *Lactobacillus fermentum, Lactobacillus plantarum* and *Lactobacillus brevis* isolates from Brazilian food products. *Food Microbiology;* **36**:22-29 (2013).

23. Kechagia M., Basoulis D., Konstantopoulou S., et al. Health benefits of probiotics: a review. *ISRN Nutr;* 2013:481651 (2013).

24. de Magalhães J.T., Uetanabaro A.P., de Moraes C.A. Identification of *Lactobacillus* UFV H2B20 (probiotic strain) using DNA-DNA hybridization. *Braz J Microbiol;* **39**(3):542-546 (2008).

25. Isolauri E., Salminen S., Ouwehand A.C. Microbial-gut interactions in health and disease. *Probiotics. Best Pract Res Clin Gastroenterol;* **18**(2):299-313 (2004).

26. Pandey K.R., Naik S.R., Vakil B.V. Probiotics, prebiotics and synbiotics- a review. *J Food Sci Technol.;* **52**(12):7577-7587 (2015).

27. Isolauri E., Salminen S., Ouwehand A.C. Microbial-gut interactions in health and disease. *Probiotics. Best Pract Res Clin Gastroenterol;* **18**(2):299-313 (2004).

28. Fijan S. Microorganisms with claimed probiotic properties: an overview of recent literature. *Int J Environ Res Public Health;* **11**(5):4745-4767 (2014).

29. Kechagia M., Basoulis D., Konstantopoulou S., et al. Health benefits of probiotics: a review. *ISRN Nutr;* 2013:481651 (2013).

30. Dionisio D., Valassina M., Uberti M., Fabbri C., Parri F., Saffi E.G. Mycoplasma pneumoniae non-pulmonary infection presenting with pharyngitis, polyarthritis and localized exanthem.
Scandinavian J infect dis.; 33(10):782-3 (2001).
31. Havenaar R., Ten Brink B., Huis J.H. Selection of strains for probiotic use. In Probiotics Springer., Dordrecht.1992 (pp. 209-224).
32. Messina M. Western soy intake is too low to produce health effects. Am J Clin Nutr.; 80(2):528-530 (2004).
33. Soccol C.R., Vandenberghe L.P., Spier M.R., Medeiros A.B., Yamagushi C.T., Lindner J.D., Pandey A., Thomaz-Soccol V. The potential of probiotics: a review. Food Technology and Biotechnology.; 48(4):413-34 (2010).
34. Kothari D., Patel S., Kim S. Probiotic supplements might not be universally effective and safe: A review. Biomedicine and Pharmacotherapy.; 111:537-547 (2019).
35. Borriello S.P., Hammes W.P., Holzapfel W., et al. Safety of probiotics that contain lactobacilli or bifidobacteria. Clin Infect Dis.; 36(6):775-780 (2003).
36. Donohue D.C., Salminen S. Safety of probiotic bacteria. Asia Pac J Clin Nutr. 5(1):25-28 (1996).
37. Ansari J.M., Colasacco C., Emmanouil E., Kohlhepp S., Harriot O. Strain-level diversity of commercial probiotic isolates of Bacillus, Lactobacillus, and Saccharomyces species illustrated by molecular identification and phenotypic profiling. PLoS One. 14(3):e021384 (2019).
38. Hill C., Guerner F., Reid G., Gibson G.R., Merenstein D.J., Pot B., Morelli L., Canani R.B., Flint H., Salminen S., Calder P.C. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nature Rev Gastro Hep.; 11(8):506-14 (2014).
39. Kechagia M., Basoulis D., Konstantopoulou S., et al. Health benefits of probiotics: a review. ISRN Nutr.; 2013:481651 (2013).
40. Lenoir-Wijnkoop I., Gerlier L., Bresson J.L., Le Pen C., Berdeaux G. Public health and budget impact of probiotics on common respiratory tract infections: a modelling study. PLoS One. 10(4):e0122765 (2015).
41. Gueimonde M., Sanchez B., Margolleas A. Antibiotic resistance in probiotic bacteria. Front Microbiol.;4:202 (2013).
42. Sanders M. E., Akkermans L. M., Haller D., Hammerman C., Heimbach J., Hörmannsperger G., Huys G., Levy D. D., Lutgenhorff F., Mack D., Photheirath P., Solano-Aguilar G., & Vaughan E. Safety assessment of probiotics for human use. Gut microbes.; 1(3):164–185 (2010).
43. Corcoran B.M., Stanton C., Fitzgerald G.F., Ross R.P. Survival of probiotic lactobacilli in acidic environments is enhanced in the presence of metabolizable sugars. Appl Environ Microbiol.; 71(6):3060-3067 (2005).
44. Patel A.K., Singhania R.P., Pandey A., Chincholkar S.B. Probiotic bile salt hydrolase: current development and perspectives. Appl Biochem Biotechnol.; 162(1):166-88 (2010).
45. Pavlović N., Stankov K., Mikov M. Probiotics-interactions with bile acids and impact on cholesterol metabolism. Appl Biochem Biotechnol.; 168(7):1880-1895 (2012).
46. Woo J., Ahn J. Probiotic-mediated competition, exclusion and displacement in biofilm formation by food-borne pathogens. Lett Appl Microbiol.; 56(4):307-313 (2013).
47. Monteagudo-Mera A., Rastall R.A., Gibson G.R., Charalampopoulos D. et al. Adhesion mechanisms mediated by probiotics and prebiotics and the potential link with infective endocarditis. J Appl Bacteriol.; 129(12):2945-2951 (1993).
48. Hill C., Guerner F., Reid G., Gibson G.R., Merenstein D.J., Pot B., Morelli L., Canani R.B., Flint H., Salminen S., Calder P.C. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nature Rev Gastro Hep.; 11(8):506-14 (2014).
49. Reid G., Gadir A.A., Dhir R. Probiotics: Reiterating What They Are and What They Are Not. Front Microbiol.;10:424 (2019).
50. Harty D.W., Patrikakis M., Hume E.B., Oakey H.J., Knox K.W. The aggregation of human platelets by Lactobacillus species. J Gen Microbiol.;139(12):2945-2951 (1993).
51. Oakey H.J., Harty D.W., Knox K.W. Enzyme production by lactobacilli and the potential line with infective endocarditis. J Appl Bacteriol.;78(2):142-148 (1995).
52. Ruseler-van Embden J.G., van Lieshout L.M., Gesselin M.J., Mareau P. Inability of Lactobacillus casei strain G.G. L. acidophilus, and Bifidobacterium bifidum to degrade intestinal mucus glycoproteins. Scand J Gastroenterol.;30(7):675-680 (1995).
53. Didari T., Solki S., Mozaffari S., Nikfar S., Abdollahi M. A systematic review of the safety of probiotics. Expert Opin Drug Saf.;13(2):227-239 (2014).
54. Hempel S., Newberry S.J., Maher A.R., et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. JAMA.; 307(18):1959-1969 (2012).
55. Plaza-Díaz J., Ruiz-Ojeda F.J., Vilchez-Parijal L.M., Gil A. Evidence of the Anti-Inflammatory Effects of Probiotics and Symbiotics in Intestinal
Chronic Diseases. 

6. Oelschlaeger T.A. Mechanisms of probiotic actions - A review. Int J Med Microbiol. 2010; 300(1):57-62.

7. Yang L., Corwin E.J., Brennan P.A., Jordan S., Murphy J.R., Dunlop A. The Infant Microbiome: Implications for Infant Health and Neurocognitive Development. Nurs Res.; 65(1):76-88 (2016).

8. Zoumpopoulou G., Tsakalidou E., Thomas L.V. An Overview of Probiotic Research: Human and Mechanistic Studies. Probiotic Dairy Products.:293-357 (2017).

9. Plaza-Diaz J., Ruiz-Ojeda F.J., Gil-Campos M., Gil A. Mechanisms of Action of Probiotics. Adv Nutr.:10(suppl_1):S49-S66 (2019).

10. Mayrhofer S., van Hoek A.H., Mair C., et al. Antibiotic susceptibility of members of the Lactobacillus acidophilus group using broth microdilution and molecular identification of their resistance determinants. Int J Food Microbiol.; 144(1):81-87 (2010).

11. Ribet D., Cossart P. How bacterial pathogens colonize their hosts and invade deeper tissues. Microbes Infect.; 17(3):173-183 (2015).

12. Hevia A., Delgado S., Sánchez B., Margolles A. Molecular Players Involved in the Interaction Between Beneficial Bacteria and the Immune System. Front Microbiol.; 6:1285 (2015).

13. Vuong H.E., Yano J.M., Fung T.C., Hsiao E.Y. The Microbiome and Host Behavior. Annu Rev.; 1285 (2015).

14. Tillisch K., Labus J., Kilpatrick L., et al. Consumption of fermented milk product with probiotic modulates brain activity. Gastroenterology; 144(7):1394-1401 (2013).

15. Bonaz B.L., Bernstein C.N. Brain-gut interactions in inflammatory bowel disease. Gastroenterology; 144(1):36-49 (2013).

16. Zamora N., Elvin E. Personalized gut mucosal colonization resistance to Empiric Probiotics Is associated with Unique host and Microbiome features. Cell.; 174:1388-1405 (2018).

17. Papadimitriou K., Zoumpopoulou G., Foliagne B., et al. Discovering probiotic microorganisms: in vitro, in vivo, genetic and omics approaches. Front Microbiol.; 6:58 (2015).

18. Figueroa-González I., Quijano G., Ramirez G., Cruz-Guerrero A. Probiotics and prebiotics—perspectives and challenges. J Sci Food Agric.; 91(8):1341-1348 (2011).

19. Kumar M., Nagpal R., Verma V., et al. Probiotic metabolites as epigenetic targets in the prevention of colon cancer. Nutr Rev.; 71(1):23-34 (2013).

20. Hendler R., Zhang Y. Probiotics in the Treatment of Colorectal Cancer. Medicines (Basel). 5(3):101 (2018).

21. Gismondo M.R., Drago L., Lombardi A. Review of probiotics available to modify gastrointestinal flora. Int J Antimicrob Agents. 12(4):287-292 (1999).

22. Ugboko H.U., Oyewale J. Childhood diarrhoeal disease in developing countries. Helioyn. e03690 (2020).

23. Xiong T., Maheshwari A., Neu J., El-Saie A. et al. An overview of systematic reviews of Randomised controlled trials for preventing Necrotizing Enterocolitis in preterm infants. Neonatology.; 117:46-56 (2020).

24. HP van den Akker C., B van Goudoever J., Shamar R., Domellof M., Embleton N.D., Hojsak I. et al. Probiotic and preterm infants: A position paper by the European society for paediatric gastroenterology Hepatology and nutrition committee on nutrition and European society for paediatric gastroenterology Hepatology and Nutrition working group for probiotics and prebiotics. J Pediatr Gastroenterol Nutr. 70(5):664-680 (2020).

25. Nanthakumar N.N., Fusunyan R.D., Sanderson I., Walker W.A. Inflammation in the developing human intestine: A possible pathophysiological contribution to necrotizing enterocolitis. Proc Natl Acad Sci U S A.; 97(11):6043-6048 (2000).

26. Allen S.J., Martinez E.G., Gregorio G.V., Dans L.F. Probiotics for treating acute infectious diarrhoea. Cochrane Database Syst Rev. 2010(11):CD003048 (2010).

27. Guo Q., Goldenberg J.Z., El Dib R. Probiotic for prevention of pediatric antibiotic associated diarrhoea. Cochrane Database syst Rev; 4(4): CD004827 (2019).

28. McFarland L.V. Meta-analysis of probiotics for the prevention of traveler’s diarrhoea. Travel Med Infect Dis.; 5(2):97-105 (2007).

29. Hickson M., D’Souza A.L., Muthu N., et al. Use of probiotic Lactobacillus preparation to prevent diarrhoea associated with antibiotics: randomised double blind placebo controlled trial. BMJ.; 335(7610):80 (2007).

30. Pillai G., Nelson R. Probiotics for treatment of Clostridium difficile-associated colitis in adults. Cochrane Database Syst Rev. 1 :CD004611 (2008).

31. Ouwehand A.C., Salminen S., Isolauri E. Probiotics: an overview of beneficial effects. Antonie Van Leeuwenhoek. 82(1-4):279-289 (2002).

32. Gonzalez-Ochoa G., Flores-Mendoza L.K., Tamez-Guerra P. Modulation of rotavirus severe gastroenteritis by the combination of probiotics and prebiotics. Archives of Microbiology.
199-953-961 (2017).

83. Ahmadi E., Alizadeh-Navaei R., Rezai M.S. Efficacy of probiotic use in acute rotavirus diarrhoea in children: A ayastematic review and meta-analysis. Caspian J Intern Med. 6(4):187-195 (2015).

84. Allen S.J., Martinez E.G., Gregoria G.V., Dans L.F. Probiotics for treating acute infectious diarrhoea. Sao Paulo Medical Journal.; 129(3):185 (2011).

85. Hempel S., Newberry S.J., Maher A.R., et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhoea: a systematic review and meta-analysis. JAMA. 307(18):1959-1969 (2012).

86. Bae J.M. Prophylactic efficacy of probiotics on traveller’s diarrhoea: an adaptive meta-analysis of randomised controlled trials. Epidemiol Health. 40:e2018043 (2018).

87. Briand V., Buffet P., Genty S., Lacombe K. et al. Absence of efficacy of nonviable Lactobacillus acidophilus for the prevention of traveller’s diarrhoea: a randomised, double blinded controlled study. Clin Infect Dis. 43:1170-75 (2006).

88. Katelaris P.H., Salam I., Farthing M.J. Lactobacilli to prevent traveler’s diarrhoea?. N Engl J Med. 333(20):1360-1361 (1995).

89. Sazawal S., Hiremath G., Dhingra U., Malik P., Deb S., Black R.E. Efficacy of probiotics in prevention of acute diarrhoea: a meta-analysis of masked, randomised, placebo-controlled trials. Lancet Infect Dis. 6(6):374-382 (2006).

90. Marteau P., Seksik P., Jian R. Probiotics and intestinal health effects: a clinical perspective. Br J Nutr. Suppl 1:S51-S57 (2002).

91. Khor B., Gardet A., Xavier R.J. Genetics and pathogenesis of inflammatory bowel disease. Nature. 474(7351):307-317 (2011).

92. Ng S.C., Hart A.L., Kamm M.A., Stagg A.J., Knight S.C. Mechanisms of action of probiotics: Recent Advances. Inflamm Bowel Dis. 15(2):300-310 (2009).

93. Derwa Y., Gracie D.J., Hamlin P.J., Ford A.C. Systematic review with meta analysis: the efficacy of probiotics in inflammatory bowel disease. Alimentary pharmacology and therapeutics. 46:4 (2017).

94. Shi L.H., Balakrishnan K., Thiagarajah K., Mohd Ismail N.I, Yin O.S. Beneficial Properties of Probiotics. Trop Life Sci Res. 27(2):73-90 (2016).

95. Gionchetti P., Rizzello F., Venturi A., et al. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. Gastroenterology. 119(2):305-309 (2000).

96. Butterworth A.D., Thomas A.G., Akobeng A.K. Probiotics for induction of remission in Crohn’s disease. Cochrane Database Syst Rev; 2008(3):CD006634 (2008).

97. Duary R.K., Rajput Y.S., Batish V.K., Grover S. Assessing the adhesion of putative indigenous probiotic lactobacilli to human colonic epithelial cells. Indian J Med Res. 134(5):664-671 (2011).

98. Chen Y.P., Hsiao P.J., Hong W.S., Dai T.Y., Chen M.J. Lactobacillus kefranofaciens M1 isolated from milk kefir grains ameliorates experimental colitis in vitro and in vivo. J Dairy Sci.; 95(1):63-74 (2012).

99. Zocco M.A., dal Verme L.Z., Cremonini F., et al. Efficacy of Lactobacillus G.G in maintaining remission of ulcerative colitis. Aliment Pharmacol Ther. 23(11):1567-1574 (2006).

100. Huang C.C., Nam M.K., Tsai Y.T., Tsai C.C. Safety evaluation for multispecies probiotics in a 28-day feeding study in Sprague-Dawley rats. African J Biochem Res. 8(7):127-36 (2014).

101. Ahn Y.T., Kim G.B., Lim K.S., Baek Y.J., Kim H.U. Deconjugation of bile salts by Lactobacillus acidophilus isolates. International Dairy J.;13:303-311 (2003).

102. Kimoto H., Ohnomo S., Okamoto T. Cholesterol removal from media by lactococci. J Dairy Sci. 85(12):3182-3188 (2002).

103. Park J.W., Jeong J.S., Lee S.I., Kim I.H. Effect of dietary supplementation with a probiotic (Enterococcus faecium) on production performance, excreta microflora, ammonia emission, and nutrient utilization in ISA brown laying hens. Poult Sci. 95(12):2829-2835 (2016).

104. Cavallini D.C., Abdalla D.S., Vendramini R.C., et al. Effects of isoflavone-supplemented soy yogurt on lipid parameters and atherosclerosis development in hypercholesterolemic rabbits: a randomized double-blind study. Lipids Health Dis. 8(40) (2009).

105. Jones M.L., Tomaro-Duchesneau C., Martoni C.J., Prakash S. Cholesterol lowering with bile salt hydrolase-active probiotic bacteria, mechanism of action, clinical evidence, and future direction for heart health applications. Expert Opin Biol Ther. 13(5):631-642 (2013).

106. Lye H.S., Rusul G., Liow M.T. Removal of cholesterol by lactobacilli via incorporation and conversion to coprostanol. J Dairy Sci.; 93(4):1383-1392 (2010).

107. Wong J.M., de Souza R., Kendall C.W., Emam A., Jenkins D.J. Colonic health: fermentation and short chain fatty acids. J Clin Gastroenterol.; 40(3): 235-243 (2006).

108. Commane D., Hughes R., Shortt C., Rowland I. The potential mechanisms involved in the anticarcinogenic action of probiotics. Mutat Res.;
109. Geier M.S., Butler R.N., Giffard P.M., Howarth G.S. Lactobacillus fermentum B.R11, a potential new probiotic, alleviates symptoms of colitis induced by dextran sulfate sodium (DSS) in rats. *Int J Food Microbiol.; 114*(3):267-274 (2007).

110. Roller M., Pietro Femia A., Caderni G., Rechkemmer G., Watzl B. Intestinal immunity of rats with colon cancer is modulated by oligofructose-enriched inulin combined with Lactobacillus rhamnosus and Bifidobacterium lactis. *Br J Nutr.; 92*(6):931-938 (2004).

111. Hirayama K., Rafter J. The role of lactic acid bacteria in colon cancer prevention: mechanistic consideration. *Antonie Van Leeuwenhoek. 76*(1-4):391-394 (1999).

112. Isolauri E., Sütas Y., Kankaanpää P., Arvilommi H., Salminen S. Probiotics: effects on immunity. *The American journal of clinical nutrition.; 73*(2):444s-50s (2001).

113. Erdman S.E., Poutahidis T. Probiotic ‘glow of health’: it’s more than skin deep. *Benef Microbes.; 5*(2):109-119 (2014).

114. Guéniche A., Bastien P., Ovigne J.M., et al. Bifidobacterium longum lysate, a new ingredient for reactive skin. *Exp Dermatol.; 19*(8):e1-e8 (2010).

115. Lew L.C., Liong M.T. Bioactives from probiotics for dermal health: functions and benefits. *J Appl Microbiol.; 114*(5):1241-1253 (2013).

116. Tanida M., Shen J., Maeda K., et al. High-fat diet-induced obesity is attenuated by probiotic strain Lactobacillus paracasei S.T11 (NCC2461) in rats. *Obes Res Clin Pract.; 2*(3):1-11 (2008).

117. Levi K.M, Ketvertis K, Deramo M, Merenstein J.H, D’Amico F. Do probiotics reduce adult lactose intolerance? A systematic review. *J Fam Pract.; 54*(7):613-620 (2005).

118. Cildir S.K., Germec D., Sandalli N., et al. Reduction of salivary mutants streptococci in orthodontic patients during daily consumption of yoghurt containing probiotic bacteria. *Eur J Orthod.; 31*(4):407-411 (2009).

119. Masdea L., Kulik E.M., Hauser-Gerspach L, Ramseier A.M., Filippi A., Waltimo T. Antimicrobial activity of Streptococcus salivarius K12 on bacteria involved in oral malodour. *Arch Oral Biol.; 57*(8):1041-1047 (2012).

120. Reid G., Bruce A.W., Fraser N., Heinemann C., Owen J., Henning B. Oral probiotics can resolve urogenital infections. *FEMS Immunol Med Microbiol.; 30*(1):49-52 (2001).

121. Reid G., Jass J., Sebulsky M.T., McCormick J.K. Potential uses of probiotics in clinical practice. *Clin Microbiol Rev.; 16*(4):658-672 (2003).

122. Grenham S., Clarke G., Cryan J.F., Dinan T.G. Brain-gut-microbe communication in health and disease. *Front Physiol.; 2*:94 (2011).

123. Neufeld K.M., Kang N., Bienenstock J., Foster J.A. Reduced anxiety-like behavior and central neurochemical change in germ-free mice. *Neurogastroenterol Motil.; 25*(3):255-e119 (2011).

124. Lazar V., Ditu L., Pir-calabioru G.G., Gheorghe I., Curutiu C., Holban A.M., Picu A. et al. Aspects of Gut Microbiota and Immune system Interactions in infectious diseases. *Immunopathology, and Cancer. Front Immunol. (2018). https://doi.org/10.3389/fimmu.2018.01830*

125. Lerner A., Shoenfeld Y., Matthias T. Probiotics: If It Does Not Help It Does Not Do Any Harm. Really?. *Microorganisms.; 7*(4):104 (2019).

126. Wang Y., Jiang Y., Deng Y. et al. Probiotic Supplements: Hope or Hype?. *Front Microbiol. 11*:160 (2020). Published 2020 Feb 28.

127. Imperial I.C., Iban A. Addressing the Antibiotic Resistance Problem with Probiotics: Reducing the Risk of Its Double-Edged Sword Effect. *Front Microbiol. 7*:1983 (2016).