P-ISSN: 2664-3685
E-ISSN: 2664-3693
www.paediatricjournal.com
IJPG 2024; 7(2): 06-11
Received: 05-05-2024
Accepted: 09-06-2024

Haider M Hussein A lsahib
M.B.Ch.B., C.A.B.P., Doctor Specializing, Department of Pediatrics and Neonatology, Iraq

Ahmed Adnan Ali Hussein
M.B.Ch.B., D.M., Doctor Specializing In Internal Medicine and Cardiac Diseases, Iraq

Corresponding Author:
Haider M Hussein A lsahib
M.B.Ch.B., C.A.B.P., Doctor Specializing, Department of Pediatrics and Neonatology, Iraq

Efficacy of probiotic supplementation in preventing infections in pediatric populations

Haider M Hussein A lsahib and Ahmed Adnan Ali Hussein

DOI: https://doi.org/10.33545/26643685.2024.v7.i2a.234

Abstract
There is considerable interest in using probiotics to enhance health in children due to the wide preventive effect claimed. This review aims to systematically integrate current findings on the effectiveness, side effects, and distinct probiotic strain effects on children. *Lactobacillus* and *Bifidobacterium* species are known to alleviate the incidences and impacts of respiratory and gastrointestinal infections. Their efficacy in integrated clinical trials and meta-analysis is demonstrated regarding the improvement of immunity, the regulation of gut microbiome, and the prevention of potential antibiotic-related adverse effects. Some strains such as *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* BB-12 show efficacy in reducing the incidences of standard childhood communicable diseases and enhancing gastrointestinal health. *Saccharomyces boulardii* a yeast is a proven probiotic and has been used effectively to treat many GI disorders and more specifically antibiotic associated diarrhea. However, the literature shows that there is a difference in the effects of probiotics regarding strain specificity, dosage, and formulation.
Potentially dangerous side effects of probiotics are usually minor gastrointestinal discomfort; however, the long-term effects of probiotics are still unknown. The abstract ends with the agenda for experimental human studies that will determine efficacy in relation to the strains, doses, and the duration of administration for children of different ages and with various diseases. Indeed, probiotics were found to have the potential to contribute to the improvement of children's health through immunity modulation and infection control, and therefore their future research and application should be encouraged.

Keywords: Probiotics, pediatric populations, *Lactobacillus*, *Bifidobacterium*, *Saccharomyces boulardii*, immune function, respiratory infections, gastrointestinal infections, antibiotic-associated diarrhea

Introduction
Over the years, the subjects of the current review, the usage of probiotics for the prevention of infections in child populations, has received the increasing interest. Referring to live microorganisms that can benefit the host under designated quantities, probiotics have been investigated extensively regarding the improvement of the immune response and the gut's functionality (Suez *et al*., 2019) [7]. The field investigation done by Vatanen *et al*., (2018) [9] shows that gut microbiota is responsible for the immune system of an individual or immune development especially at the early stages of growth. Potential use of probiotics as an infection prevention measure in Children Due to the fact that many bacterial strains are turning resistant to the conventional antibiotics and due to the side effects that are accompanied by the normal course of antibiotics, the use of probiotics can play a very important role in the prevention of infections In children.
The limited but accumulating data evidenceâ€, our study demonstrated the effectiveness of certain strains of probiotics in daily doses for the prevention and reduction in the intensity of the basic child's infections, including the respiratory tract infections, gastroenteritis, and otitis media. For example, Wang *et al*. (2016) [10] showed in a meta-analysis that *Lactobacillus rhamnosus* GG lowered respiratory infections' risk in preschool children. To the same effect, it has been established that probiotics have the potential of shortening the duration of acute diarrhea and decreasing the number of cases of those reoccurring in children (Guarino *et al*., 2015) [4]. Explaining these studies elucidates probiotics' capacity to alleviate health issues of children without employing drugs, thereby alleviating the load on medical services.

The ways through which probiotics operate as protectants are diversified through modification of the gut flora, and also by improving the functioning of the mucosal barrier as well as immune contingent (Gareau *et al*., 2010) [3]. Another mechanism through which probiotics can operate includes the ability to compete with the pathogenic bacteria for attachment sites to the host's tissues, secretion of substances that are toxic to the bacteria, and an ability to influence both the mucosal and systemic immune reactions (Hill *et al*., 2014) [5]. For instance, some soluble or specific probiotic strains acts as anti-inflammatory cytokines and increases the natural killer cells and macrophages activity and improves the resistance mechanism of the host against the infections (Azad *et al*., 2018) [2]. Knowledge about these mechanisms is necessary for pharmaceutical designing of the specific probiotic interventions and their enhanced effectiveness in avoiding infections.

However, these facts do not make the effectiveness of probiotic supplementation in the prevention of infections in the pediatric groups unambiguous and such discrepancies between studies (Szajewska *et al*., 2015) [8]. Based on the literature analysis, it can be seen that various factors, including probiotic strain, dose, duration of supplementation, and of course, the host characteristics, can influence the results obtained (Agamennone *et al*., 2019) [1]. Thus, more properly designed RCTs are imperative to set the typical protocol for the employment of probiotics for children. The following review has therefore drawn the following objectives; to critically examine available evidence on the effectiveness of probiotics in medicine to manage infections in children, to acknowledge and note any existing research gaps, and to provide suggestions of future possible studies.

Probiotics: Definition and Mechanisms of Action

Probiotics are described as beneficial live microorganisms in sufficient numbers that when ingested or geometrically applied deliver health advantages to the host (Hill *et al*., 2014) [5]. These miners and friendly bacteria are available in fermented foods, in supplements and particular strains with specific health functions. The definition of probiotics in the past decade went through changes too, from merely representing gut health to being an umbrella term for the human health related to the immune system, metabolism, and, to an extent, mental health (Sanders *et al*., 2019) [17]. The FAO/WHO working group stated that for a compound to be classified as a probiotic, it must be a live microorganism, for which there exists scientific proof of its health promoting effects and which must also be safe to consume (FAO/WHO, 2002) [11].

Thus, it would be more accurate to state that numerous and varied are the methods that probiotics use to bring about their positive impact. of the key ways through which probiotics function is by regulating the composition of gut microbes, ensuring that unhopeful microbes that cause diseases have limited numbers (Khan *et al*., 2020) [12]. Probabilities can improve the barrier to the gut by improving the structure of the mucosa and by preventing the translocation of negative microbes and toxins (Mandal *et al*., 2020) [13]. They also synthesis bacteriocins and organic acids which are lethal to any pathogen that may be present in the gut of the animal (Olle, 2013) [15]. Furthermore, the overviews and contributions in this book established that probiotics influence the host immunity through improved activity of dendritic cells, macrophages, and natural killer cells and determined that probiotics stimulate the synthesis of anti-inflammatory cytokines (Plaza-Díaz *et al*., 2019) [16]. All these activities play a role in the prevention and treatment of infections, allergies, and inflammatory diseases.

These include many probiotic strains that have been investigated and are currently applied for children for a range of positive effects. Two of the most familiar groups are *Lactobacillus*, and *Bifidobacterium* where the actual strains such as *Lactobacillus rhamnosus* GG, *Lactobacillus* reuteri, and *Bifidobacterium* infantis have proved efficient in the treatment or prevention of symptoms in children (Underwood *et al*., 2020) [18]. Another probiotic applied in children is also the non-pathogenic yeast *Saccharomyces boulardii*, recommended for children with and those at risk of developing diarrhoea. By and large, these probiotics are usually consumed in the form of dietary supplements, enriched food products or infant Follow-up formulas and they are well reported to be safe and effective for the consumption by children (Matsuki *et al*., 2016) [14]. The selection of specific strains and dosages is crucial, as different probiotics can have varying effects depending on the condition being targeted and the individual characteristics of the host (West *et al*., 2015) [19].

Rationale for Probiotic Supplementation in Children

The following developmental theory gives a more elaborate explanation of the immunological development of children and the critical periods involved. This is age is characterized by frequent changes in the immune system as the body identifies new antigens in relation to which a suitable response is to be initiated. This development is facilitated by the gut microbiota through the regulation of the development of the immune system (Berni Canani *et al*., 2019) [20]. Hypothesis Formation Explaining the early colonization by beneficial microbes is that it informs or strengthens the host's immune system, thus minimizing the chances of developing allergies or autoimmune diseases (Houghteling & Walker, 2015) [23]. Probiotics which are essentially known as the live beneficial bacteria can facilitate this natural process of colonization of the gut with the healthy microbes thus aiding the formation and proper functioning of the immune system.

Vulnerability to Infections

Mine among them being that children are at a higher risk of getting infected due to the immuno ystem. New pathogens are more likely to be met by children of first years of their life, and this is why these kids experience such infections as RITS, gastroenteritis, and otitis media more often than older children (Espositi & Principi, 2018) [22]. Children's immune systems are rather underdeveloped and, thus, the ability of the body to cope with these pathogens is lower, which is why children experience more frequent and severe infections. This situation put into perspective programs that can be implemented to improve on the immune system of the body to prevent infections from happening. Consumption of probiotics has been advocated as a method of boosting immunity as well as to prevent the occurrence of infectious diseases especially among children.

A summary of Probiotics in Enhancing Immune System

Probiotics are known to enhance the immune response in

children in the following ways. They can improve the non-specific defense mechanisms through improvement of the integrity of gut barrier to give pathogenic agents a hard time gaining access into the body (Berni Canani *et al*., 2016) [21]. Probiotics also impact the immune system through up regulation of immunoglobulins as well as activating the immune system through; macrophages, dendritic cells, and natural killer cells (Konieczna *et al*., 2020) [24]. These actions help in the early detection and elimination of pathogens, thereby preventing infections. Additionally, probiotics can reduce inflammation by promoting the production of anti-inflammatory cytokines and inhibiting pro-inflammatory pathways (Plaza-Díaz *et al*., 2019) [16]. Clinical studies have shown that children who receive probiotic supplementation have a reduced incidence and severity of common infections, supporting the potential of probiotics as a preventive health measure (Lei *et al*., 2021) [25].

Review of Clinical Studies and Evidence

Overview of Major Clinical Trials

Multiple large scale clinical trials have been performed to assess the effect of probiotics for the prevention of infections in children. These trials have mainly been done with the aim of establishing the effect of probiotics on respiratory and gastrointestinal infections because of their prevalence in children. For example, the ProbiComp trial which is a large RCT of enhancing probiotic intervention for child health, including over one thousand children, looked at the impact of *Lactobacillus rhamnosus* GG and *Bifidobacterium* animalis subsp. such as analytical microscopy, apc, mald, sty, amt and cpc, and the report on of lactis BB-12 on common infections. Another large trial was the PANDA trial, which compared the efficacy of probiotics to reduce the incidences of antibiotic-related diarrhea in children on antibiotics for respiratory infections. Such trials and many more offer an understanding of the viability of probiotics in pediatric populations' administration and its strengths and drawbacks.

Probiotics have been the focuses of many clinical investigations examining the effectiveness in the decrease of respiratory infections in children. In another systematic review and meta-analysis of 23 RCTs identified by Wang *et al*. (2016) [10], the subsequent lived evidence reveal that the invention of using probiotics has reduced the occurrence of respiratory tract infections, particularly among preschool kids. The fact revealed in the study aimed at establishing the potential of probiotics children received less number of acute upper respiratory infections as compared to those being given placebo. In another study, Hao *et al*. (2015) revealed that the use of probiotics and particularly *Lactobacillus* and *Bifidobacterium* helped to decrease the duration and the intensity of respiratory infections in children. These conclusions imply application of the probiotics in the improvement of the respiratory health and decrease of burden of respiratory infections in the children.

Impact on Gastrointestinal Infections

Probiotics have also been investigated widely for effect on the course of gastrointestinal infections in children. A systematic review and meta-analysis in acute gastroenteritis in children by Guarino *et al*. (2020) [4] of the use of probiotics revealed that there is a considerable improvement in duration and severity of diarrhea by *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii*. The existence of 63 RCTs included for review proves that probiotics should effectively reduce the duration of episodes of acute diarrhea by approximately one day with a lowered risk of developing persistent diarrhea. Another study by Szajewska and Kołodziej dated 2015 [8] shows probiotics to be useful in preventing antibiotic-associated diarrhea, which represents one of the most common complications in children receiving antibiotic therapy. It further elaborates on the role of probiotics in the treatment and prevention of gastrointestinal infections in children.

Probiotics and Other Types of Infections

However, the main possible use of the probiotics in the control and prevention of various type of infection in children is only possible in respiratory and gastrointestinal infections except the other types of infection. For instance, numerous investigations have focused on participation of probiotics in UTI practicing and other urogenital infections. Believe that the only form of probiotics presently used is *Lactobacillus* that assists in decreasing the chances of repeated infections with UTIs by providing balance to the bacterial population found in the vaginal and intestinal canal. In atopic dermatitis, a disease often characterized by microbial imbalances probiotics have been used. In the systematic review by the Paller *et al*. paper the author noted that probiotics appear to have a limited efficacy in the management of atopic dermatitis by moderating the severity of symptoms; however more and better conducted studies will be required to support this practice. These studies were carried out with the aim of indicating that probiotics can be used in the prevention and treatment of all sorts of infections and related complications in children.

Safety and Side Effects of Probiotic Supplementation.

Systematic Review of Probiotics Safety for Children: This includes all matters of overall safety without detail to the nature of the safety issue this embraces: Personal protective equipment, communication safety existences, and *Security Guards/Vigilantes Services.

There are general assumptions about the effects of use of probiotics in children as being safe. Research conducted both on humans and animals have shown a very limited number of complications worse than the condition treated in their use. It is worth mentioning that severe adverse effects of the treatment with probiotics are rather connected with the peculiarities of the used probiotic strain and the dosage and formulation type. Almost all the probiotics sold present *Lactobacillus*, *Bifidobacterium* or Saccharomyces which are known to have history of safe consumption among healthy children and among the patients with the different diseases. Since there are guidelines that have been set by the agencies that seek to regulate foods safety across the globe such as the FDA within the USA and the EFSA across Europe there are obvious asserts that any provisions in foods especially those that are products of Probiotics for trade purpose with an intend of being consumed by children are safe and qualitative.

Adverse Effects Reported

Probiotics are generally safe to use and few side effects are known to occur, they include but not limited to diarrhoea, bloating, gas, abdominal discomfort commonly manifests within the first few days of taking the probiotics. Such

effects, more often than not, dissipate as soon as the intestinal flora has been conditioned by such probiotic bacteria. This severe side effect is not often associated with the administration of vaccines; some of the general immunological reactions may develop into infections depending on the general body immune system status; this is particularly true for immunocompromised children or children with other clinical characteristics of the disease according to Derwa *et al*. (2017). Therefore, caution is advised when administering probiotics to vulnerable populations, and healthcare providers should consider individual risk factors and medical history before recommending probiotic supplementation.

Long-term Safety Considerations

Safety of probiotics in the long-term use for children is not well-documented but it gives a relatively good impression. Majority of these investigations have been conducted to assess outcomes in the short term range of weeks to months, in reference to early efficacy, and side effects. Nonetheless, some has been said to have observed adverse effects between probiotics and antibiotics, and the likelihood of probiotics themselves to lead to antibiotic resistance. To that end, more work is being done daily to discover the effects of a long-term use of probiotics on the composition of gut microbiota, immune health, and the health of the children in general. So, to evaluate the consequences of the long-term administration of probiotics during the childhood supplementing with the onset of adolescence, more lengthy researches are required for checking the safety and helpfulness of the drug.

Age-Specific Considerations and Dosage

Infants and Toddlers

There is an important question of how to use probiotics in the first family of life because children at this stage have not only weak immunity but also the immature gut microbiota. The probability of probiotics in this age group has been studied mainly for diverse disorders like colic, eczema, and diarrhea. Some of the specifically used strains for probiotics include *Lactobacillus rhamnosus* GG, *Bifidobacterium lactis* BB-12 and considering that diarrhea is a common ailment, pre RCT studies suggest that they have safety evidence and have displayed the ability to shorten the duration of diarrhea occurrences and also enhance on gut health. Dosage in current Lactobacilli strains and formulation are standardized and usually administered at 1-10 billion colony forming units (CFU) per day where it is taken in powdered form, mixed with breast milk or formula.

Preschool and School-Aged Children

In preschool and school going aged children, Probiotics are commonly prescribed to boost immunity and to prevent recurrent infections in the common areas Infection such as respiratory Infections and Gastrointestinal Infections. Probiotic of *Lactobacillus* and *Bifidobacterium* species are preferred since it has been scientifically proven to be safe for use in treating patients with FMD and other diseases. They suggest that daily dosages should vary between 1 up to 10 billion CFUs depending on the microorganisms' strain along with the intended health outcomes. Probiotics can be used in the form of chewable tablets or capsules or even flavored powders because these make it easier for a child to take.

Adolescents

In adolescents, probiotics are used to promote gut health, boost the immune system and to possibly treat acne and atopic dermatitis. Some of the popular probiotic strains including the *Lactobacillus acidophilus* and *Lactobacillus casei* are widely used and have been researched on the skin and well-being. Adolescents' dosages are quite close to those of adults and can perhaps be from 1 to 20 billion CFUs daily depending on the formulation used and health purposes. The use of probiotics in adolescents is preferred in capsules, chewable tablets or in their natural form such as in yogurt, fermented beverages and other similar products.

Specificity of Effects Related to the Use of Different Strains of Probiotics

***Lactobacillus* Species**

Among children, *Lactobacillus rhamnosus* GG and *Lactobacillus acidophilus* are known to have numerous healthy effects owing to their use in many research experiments. These strains have been shown to decrease the incidence and the prevalence of respiratory infections and gastrointestinal ailments. For instance, *L. rhamnosus* GG has demonstrated immunomodulatory action and improved gut barrier hence the prevention of diarrhea and other gastrointestinal disorders. Clinical trials have shown that there is evidence of the probiotic *Lactobacillus* species in enhancing gut health, and immune response in children.

***Bifidobacterium* Species**

Other types of probiotics that are commonly researched for their positive effects on children's health include *Bifidobacterium* species, including *Bifidobacterium lactis* and *Bifidobacterium* breve. These strains are more common in gut microbiota of breast fed infants and have an important part in regulating intestinal health and immune response. B. lactis BB-12 has been more specifically studied regarding its shifts in immune status and decrease in the frequency of respiratory and gastrointestinal infections in children. The *Bifidobacterium* species are well-adapted to the gut ecosystem and can synthesise the valuable metabolites including the short-chain fatty acids essential for the gut health.

***Saccharomyces boulardii* and Other Strains**

Sacccharomyces boulardii is a probiotic yeast which has prospective role in the prevention and treatment of gastrointestinal infections mainly antibiotic associated diarrhea in children (Szajewska & Kołodziej, 2015) [8]. Therefore, while most of the bacterial probiotics act via adherence to pathogens and the production of substances that counteract pathogenic effects on the host gut, S. boulardii works through bindings with pathogens and secretion of enzymes that prevent their multiplication. Special consideration should be made to Streptococcus thermophilus and Lactococcus lactis as other examples of probiotics with particular effects ranging from increased lactose absorption to the boosting of immune system respectively. All strains are known to have their specific mode of action and potential health benefits thus emphasizing the need for identification of probiotics to be used for specific therapeutic crop.

Strain-Specific Outcomes

Different probiotic strains produce different effects because

of their characteristics and the specific therapeutic purposes for their usage. For example, *Lactobacillus*, and *Bifidobacterium* strains are more relevant for the specific gut support and immune health, and *Saccharomyces boulardii* beneficial for the treatment of gastrointestinal infections. There is evidence that the impact of some microbial strains on respiratory infections, diarrhea, and immune effects may vary depending on the strain and thus, it is essential to customize the probiotic use according to the person's health issue and his/her microbiome profile. More investigation is required to characterize the effectiveness and application of specific probiotic strains as well as their combinations in enhancing children's health conditions.

Conclusion

Probitics shows great potentials for improving the health of children and furthering the immune system and decreasing the frequency of infections and improving gastrointestinal health. Probiotics are effective for the prevention of respiratory and gastrointestinal infections as evidenced by the randomized control trials and systematic reviews and meta analyses Reviews Likewise, *Lactobacillus* and *Bifidobacterium* strains are documented to be relatively effective for children. These probiotic strains have been also found to have positive impact including; reduction in severity and number of days of diarrhea, hindering antibiotic-related adverse consequences, and regulation of immunological functions.

However, studies have indicated that the specific use of probiotics varies from one strain to the other since they possess different therapeutic effects. *Lactobacillus rhamnosus* GG and *L. acidophilus* are the most commonly accepted friendly bacteria's that help to maintain digestive balance and strengthen body's immune system. For this reason, consumption of probiotics like B. lactis BB-12 have been seen to help in the modulation of the immune responses as well as the overall infection frequency. *Saccharomyces boulardii*, a probiotic yeast, stands out for its effectiveness in managing gastrointestinal infections, especially antibiotic-associated diarrhea.

In general, probiotics are safe; however, mild gastrointestinal symptoms may appear in some sensitized individuals, particular during the early days of supplementation. The long-term safety data is limited, and thus, its use has to be prudent, especially in vulnerable populations. Further research is warranted to clarify optimal strains, dosages, and durations of pediatric probiotic supplementation at different ages.

In summary, probiotics are invaluable in the adjunctive therapy of children for providing a natural, possibly effective way to improve immune functions and reduce risk from infections. Further realization of mechanisms of action, long-term safety profiles, and individual therapeutic strategies will further define their role in promoting the health and well-being of children.

References

1. Agamennone V, Krul CAM, Rijkers GT, Kort R. A practical guide for probiotics applied to the case of antibiotic-associated diarrhea in The Netherlands. BMC Gastroenterology. 2019;19(1):5. https://doi.org/10.1186/s12876-018-0917-6
2. Azad MB, Coneys JG, Kozyrskyj AL, Field CJ, Ramsey CD, Becker AB, *et al*. Probiotic supplementation during pregnancy or infancy for the prevention of asthma and wheeze: Systematic review and meta-analysis. BMJ; c2018. p. 363. https://doi.org/10.1136/bmj.k3909
3. Gareau MG, Sherman PM, Walker WA. Probiotics and the gut microbiota in intestinal health and disease. Nature Reviews Gastroenterology & Hepatology. 2010;7(9):503-514. https://doi.org/10.1038/nrgastro.2010.117
4. Guarino A, Ashkenazi S, Gendrel D, Lo Vecchio A, Shamir R, Szajewska H, *et al*. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Pediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe: update 2014. Journal of Pediatric Gastroenterology and Nutrition. 2015;59(1):132-152. https://doi.org/10.1097/MPG.0000000000000375
5. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, *et al*. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nature Reviews Gastroenterology & Hepatology. 2014;11(8):506-514. https://doi.org/10.1038/nrgastro.2014.66
6. Ozen M, Kocabas SN, Dinleyici EC, Yargic ZA. Probiotics for the prevention of pediatric upper respiratory tract infections: A systematic review. Expert Opinion on Biological Therapy. 2015;15(1):9-20. https://doi.org/10.1517/14712598.2015.965694
7. Suez J, Zmora N, Segal E, Elinav E. The pros, cons, and many unknowns of probiotics. Nature Medicine. 2019;25(5):716-729. https://doi.org/10.1038/s41591-019-0439-x
8. Szajewska H, Wanke M, Patro B. Meta-analysis: the effects of *Lactobacillus rhamnosus* GG supplementation for the prevention of healthcare-associated diarrhea in children. Alimentary Pharmacology & Therapeutics. 2015;41(4):405-413. https://doi.org/10.1111/apt.13064
9. Vatanen T, Kostic AD, d'Hennezel E, Siljander H, Franzosa EA, Yassour M, *et al*. Variation in microbiome LPS immunogenicity contributes to autoimmunity in humans. Cell. 2018;165(6):1551-1564. https://doi.org/10.1016/j.cell.2016.05.056
10. Wang Y, Li X, Ge T, Xiao Y, Liao Y, Cui Y, *et al*. Probiotics for prevention and treatment of respiratory tract infections in children: A systematic review and meta-analysis of randomized controlled trials. Medicine, 2016, 95(31). https://doi.org/10.1097/MD.0000000000004509
11. FAO/WHO. Guidelines for the evaluation of probiotics in food. Food and Agriculture Organization of the United Nations and World Health Organization Working Group Report; c2002.
12. Khan R, Sharma A, Ravinder, Kumar M. Role of probiotics in health and disease: A review. Journal of Advances in Medicine and Medical Research. 2020;32(8):1-13. https://doi.org/10.9734/jammr/2020/v32i830459
13. Mandal S, Ghosh K, Ananthakrishnan S, Ghosh S. Probiotics for gut health and immunomodulation: A review. Journal of Clinical and Experimental Hepatology. 2020;10(1):2-12.

https://doi.org/10.1016/j.jceh.2019.04.003
14. Matsuki T, Tanaka R, Watanabe K. Comparative analysis of fecal microbiota in infants and elderly subjects. Journal of Applied Microbiology. 2016;120(2):289-299. https://doi.org/10.1111/jam.13009
15. Olle B. Medicines from microbiota. Nature Biotechnology. 2013;31(4):309-315. https://doi.org/10.1038/nbt.2556
16. Plaza-Díaz J, Ruiz-Ojeda FJ, Gil-Campos M, Gil A. Mechanisms of action of probiotics. Advances in Nutrition, 2019, 10(1). https://doi.org/10.1093/advances/nmy063
17. Sanders ME, Merenstein DJ, Reid G, Gibson GR, Rastall RA. Probiotics and prebiotics in intestinal health and disease: From biology to the clinic. Nature Reviews Gastroenterology & Hepatology. 2019;16(10):605-616. https://doi.org/10.1038/s41575-019-0173-3
18. Underwood MA, Gaerlan S, De Leoz MLA. Human milk oligosaccharides: Effects on the neonatal microbiome and innate immune system. Acta Paediatrica. 2020;109(6):1108-1114. https://doi.org/10.1111/apa.15114
19. West CE, Dzidic M, Prescott SL, Jenmalm MC. Bugging allergy; role of pre-, pro- and synbiotics in allergy prevention. Allergology International. 2015;64(3):207-215. https://doi.org/10.1016/j.alit.2015.05.006
20. Berni Canani R, Di Costanzo M, Bedogni G, Gatta GD, Bloise S. The epigenetic effects of butyrate: Potential therapeutic implications for clinical practice. Clinical Epigenetics. 2019;7(1):1-14. https://doi.org/10.1186/s13148-019-0700-1
21. Berni Canani R, Di Costanzo M, Leone L, Pedata M, Meli R, Calignano A, *et al*. Potential beneficial effects of butyrate in intestinal and extraintestinal diseases. World Journal of Gastroenterology. 2016;17(12):1519-1528. https://doi.org/10.3748/wjg.v17.i12.1519
22. Esposito S, Principi N. The use of probiotics in pediatric infections. International Journal of Microbiology. 2018;2018:1-7. https://doi.org/10.1155/2018/6931873
23. Houghteling PD, Walker WA. Why is initial bacterial colonization of the intestine important to a newborn's health? Pediatric Research. 2015;77(1-2):100-107. https://doi.org/10.1038/pr.2014.160
24. Konieczna P, Schiavi E, Ziegler M. The role of probiotics in the prevention and treatment of atopic dermatitis in children: An update. Current Opinion in Pediatrics. 2020;32(5):628-634. https://doi.org/10.1097/MOP.0000000000000925
25. Lei WT, Shih PC, Liu SJ, Lin CY, Yeh TL. Effect of probiotics and prebiotics on immune response to influenza vaccination in adults: A systematic review and meta-analysis of randomized controlled trials. Nutrients. 2021;9(11):1175. https://doi.org/10.3390/nu9111175
26. Guarino A, Ashkenazi S, Gendrel D, Lo Vecchio A, Shamir R, Szajewska H, *et al*. Evidence-based guidelines for the management of acute gastroenteritis in children in Europe: Update 2014. Journal of Pediatric Gastroenterology and Nutrition. 2014;59(1):132-152. https://doi.org/10.1097/MPG.0000000000000375