



Modulation Gut Microbiota In Aging: Current Insights And Strategies

¹Viren V. Chavhan, ²Bhagyashri A. Borade, ³Sachin J. Dighade

¹Student, ²Assistant Professor, ³Principle

¹Department of B. Pharmacy.

¹Institute of Pharmacy and Research Badnera, Amaravati, India

Abstract: The gut microbiota, a complex microbial ecosystem comprising bacteria, archaea, fungi, and viruses, plays an integral role in maintaining human health by supporting digestion, immune modulation, and metabolic processes. With advancing age, the diversity and functionality of gut microbiota decline, a phenomenon linked to various age-related diseases, including cardiovascular disorders, metabolic syndrome, and neurodegenerative conditions. Dysbiosis, characterized by microbial imbalance, exacerbates systemic inflammation, gastrointestinal disorders, and reduced short-chain fatty acid (SCFA) production. Emerging strategies to restore microbial balance include dietary interventions, probiotics, prebiotics, and fecal microbiota transplantation. Diets rich in fiber and low glycemic index foods, such as the Mediterranean diet, have demonstrated beneficial effects in maintaining microbial diversity and SCFA production. Probiotics and prebiotics further enhance gut health by promoting the growth of beneficial microbes and modulating immune responses. Additionally, synbiotics, combining probiotics with prebiotics, exhibit potential anti-inflammatory and anti-aging effects. Understanding the interplay between gut microbiota, diet, and aging presents opportunities for developing personalized interventions to improve health outcomes and promote longevity. Further research integrating metagenomics and metabolomics is critical to advancing therapeutic approaches for healthy aging.

Index Terms - gut microbiota, aging, dysbiosis, probiotics, prebiotics, SCFAs, Mediterranean diet, inflammation.

I. INTRODUCTION

The human gastrointestinal tract harbors approximately 100 trillion microorganisms primarily bacteria, fungi, viruses, and an insignificant number of Archaea. This heterogenic population is at least ten times the host cells and participates in nearly all our physiological processes. "Gut microbiota" is a term used to describe microorganisms that live in the gut, and "gut microbiome" describes the genes of these organisms.

It recently became apparent that gut microbiota plays a central role in digestion by breaking down complex carbohydrates in the form of dietary fibers and SCFAs that are critical sources of energy and nutrients. They also contribute to the integrity of the gut lining, regulation of the immune system, and defense against pathogens. Each person has his or her bacterial profile in the gut and this can be affected by diet, age, and health. A diverse population of microbes is healthy for the gut and has been associated with favorable health risks. On the other hand, when microbial richness is low, the multitude of bacteria brings about dysbiosis, a condition commonly linked to obesity, autoimmune diseases, and gastrointestinal diseases. The gut microbiota is usually described as a virtual organ since it is much more abundant genetically, with some 3 million genes on record while the human body has only 23,000. [1]

Bacteria are members of the human endogenous microbiota; the number of bacterial cells equals that of human cells and 10 bacterial cells to one human cell. Altogether they are called the 'microbiota' that consist of numerous bacteria, viruses, and eukaryotic organisms. Gut bacteria are a necessity in the lives of humans as they interfere with most of the body's activities and diseases. Due to modern genetics and metagenomics, the

association between intestinal bacteria and other diseases such as inflammatory bowel disease, inflammatory bowel disease, gastric ulcers, cardiovascular diseases, metabolic diseases, autoimmune diseases, and mental illness is well established.[2] It is believed that there are at least bacteria and archaea, with an estimated 1100 species, or about 160 species per human. Microbial communities exist in and on each human and these microbial communities are 150 times more gene-rich than the human genome hence they are relevant in drug discovery structure and function of PPIs, and metformin. While the role of gut microbiota in health and disease is gradually being discovered, the link between host and microbial diversities is still not clear. This review aims to review the studies of the relationship between gut microbiota and human health and to identify the conceptual problems regarding the connection between metabolic syndrome and gut microbiota.[3]

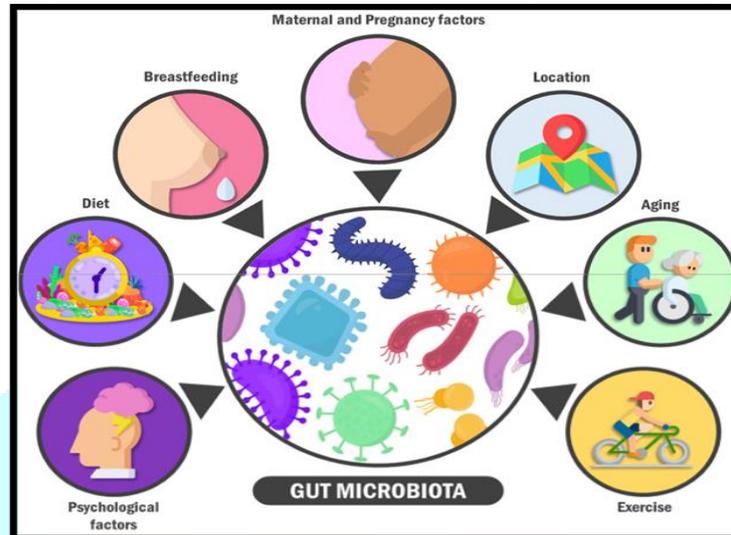


Figure no. 01: Gut microbiota modifiers. [4]

The intricate relationship between the gut microbiome and human health

The human gut microbiome (GM) is a population of microorganisms living in an environment and depends on other inhabitants of the ecosystem; each of them is important and able to regulate its activity according to the signals coming from the human host. The components of the GM reflect individual and population factors and environmental factors such as age, gender, genetic profile, route of feeding; breastfeeding or formula feeding, antibiotic exposure, immunological lifetime, ethnicity, culture, and diet. The fact that the GM is flexible to fine-tune immune and metabolic pathways and pathways to need is therefore very significant in determining health and disease. The GM has been defined as a viable community that can adjust the structure and role of the environment in which the human host resides given the fluctuations in demand on host metabolism. Thus, flexibility benefits the GM to strike a thin line between enhancing the health of the host and preventing diseases. A key function of the GM is regulating immune responses and metabolism, thus, acting as an essential regulator of homeostasis and health and being implicated in the pathogenesis of a wide array of diseases, including IBD, obesity, and T2D. The relations between the GM, immune system, and metabolism need to be understood to define specific strategies for health and disease prevention.[5]

From the health and experimental characteristics of the intestine, it was ascertained that the effect of intestinal microbiota on the health of adults and humans is enormous due to the discovery of Intestinal microbial culture. In the long run, this microbial community serves numerous functions for the homeostasis of metazoans. It aids in digestion, supports the integrity and function of the epithelial tissue of the small intestine, 'freezes' the immune system of the small intestine, and prevents pathogenic bacteria from emerging in the intestines. This could be attributed to the fact that the intestine and the body are linked with the microbiota where their metabolites interact with one or more biological processes. It helps digestion, maintains the healthy structure and function of the epithelial layer of the small intestine, "freezes" the immune system of the small intestine, and prevents the development of pathogenic bacteria in the intestine. This can be seen as due to the relationship between the microbiota in the intestine and the body, where metabolites produced by the microbiota affect one or more biological processes. [6] Similar studies conducted by researchers studying nutrition, the intestinal microbiome, and the immune system have important implications regarding the ineffectiveness of providing nutrients such as ham and immunity in adults. For example, intestinal bacteria use fermentation to produce short-chain fatty acids as substances that regulate the microbial environment of the intestine and the immune system. This good behavior of the intestines raises the question of what is the function of microbial interaction to determine what can improve the quality of life in the elderly. Therefore, it is necessary to protect healthy cells to promote a healthy state and eliminate aging diseases. [7]

Spiritual Benefits of Fasting:

Fasting has been considered a practice by many religions for many years and has always been seen as a form of spiritual elevation and development of the virtue of self-control. On the other hand, today's civilization does not accept this approach and therefore a situation arises where there is no good and healthy food. This change has been associated with an increase in non-communicable diseases such as obesity, diabetes, and heart disease due to the increase in malnutrition and sedentary lifestyle, for many purposes. It can help people get closer to God, especially when praying or meditating. Since fasting is a form of surrender, it helps to gain strength from God rather than food. It also encourages harmony so that one does not stray from the right path or destroy the soul. Fasting as a practice also gives one more reason to be thankful because when one does not have food or other blessings, one is not busy preparing food. Leadership allows doctors to experience hunger so that they can identify the needs of society. Fasting also has been around for hundreds of years and is often linked with religious spiritual growth and enhanced virtues of temperance. On the other hand, today's developed civilizations have let go of this practice, and thus there is constant eating without proper healthy food. This has been said to have been due to a rise in non-communicable diseases such as obesity, diabetes, and cardiovascular diseases that are a result of poor diet and increased cases of immobility. [8]

Fasting, in these religious contexts, has been used for so many occasions. It helps people to become closer to God, as they are praying and thinking. Fasting is a kind of submission, it helps to derive strength from God rather than food. It also encourages temperance so that people follow the straight rules of conduct without yielding to pleasures that can derail them. Moreover, fasting increases a person's opportunities to say thank you because not having food and other blessings is most noticeable when one is not busy eating. Nonetheless, fasting is also social because the limited feeding of the body helps the practitioners to feel the plight of needy individuals. It's not just the fasting but it is the fasting to feast more with the Lord and have fellowship with Him. Based on the study's findings, religious fasting seems to have positive spiritual and health implications, enhance the positive alteration of lifestyles, and may in some way help address other social health issues. Therefore, the principles of renewed fasting in modern society are still valuable and help people to obtain a new vision and direct their consciousness to others. [9]

The Importance of the Gut Microbiota for Human Health

The human gut microbiota is a complex community of microorganisms that co-evolved with us and reside in the gastrointestinal tract. This co-evolution with human cells was done in the context of many changes, including lifestyle, such as medications, urbanization, and dietary habits. The gut microbiome includes bacteria, archaea, relatively less-known fungi, and viruses. Bacteria are well-surveyed and are the focus of our review. The development of high-throughput DNA and RNA sequencing technologies, along with advanced computational methodologies, has allowed scientists to catalog microorganisms comprehensively in an unprecedented manner. Various body habitats host distinct microbial communities and microbiomes that vary in microbial composition and function, including metabolic modules and pathways. We now know that each body site has its distinct composition of microbial communities depending on the physiological characteristics of the body niche. Poor diet, antibiotic use, infections, and stress can lead to dysbiosis, characterized by a loss of beneficial microbes, microbial diversity, and the appearance of harmful bacteria. [10]

The biogeography of the gut compartments (small and large intestines) affects the composition of the microbiota. Following the upper digestive tract, like the oral cavity and esophagus, the duodenum and jejunum have lower diversity than the ileum or the proximal colon. The small intestine is predominantly populated by Gram-positive Firmicutes, including genera such as *Streptococcus*, *Veillonella*, and *Clostridium*. In contrast, the colon hosts different dominant bacterial groups, especially strict anaerobes. At the genus level, *Prevotella*, *Clostridium*, *Lactobacillus*, *Ruminococcus*, or *Odoribacter*, as well as *Roseburia*, *Faecalibacterium prausnitzii*, *Bacteroides vulgatus*, or *Fusicatenibacter saccharivorans*, are reduced in colon cancer and important anti-inflammatory taxa of the distal gut. Various intestinal bacteria transform simple sugars into organic acids like lactate, acetate, propionate, and butyrate (short-chain fatty acids (SCFAs), which impact the proliferation and virulence of pathogens. For instance, acetate produced by *Bifidobacterium* spp. can suppress the virulence of Shiga-like toxins from verotoxigenic *E. coli*. Dysbiosis has been implicated in several gastrointestinal disorders, including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and other problems including *Clostridioides difficile* infections. For instance, patients with IBD often show reduced levels of beneficial bacteria like *Faecalibacterium prausnitzii* and increased levels of pro-inflammatory microbes. Beyond the gut, dysbiosis is linked to systemic conditions such as obesity and even neurological disorders like depression and anxiety, and often, dietary changes and probiotic consumption help improve mood and overall health. [11,12]

Diet and Aging

According to Kirkwood's disposable soma theory of aging, organisms age because of an evolutionary trade-off between resources needed for cellular maintenance, development and reproduction because they have limited access to resources. Aging is a plastic process that can be influenced by dietary habits. Nutrition affects gene expression and metabolism of the host and gut microbiota, representing a link between the two symbionts.

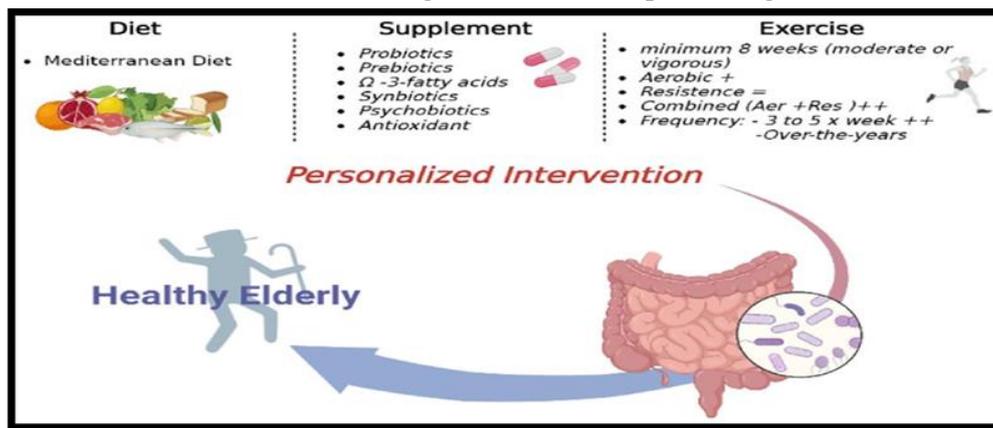


Figure no. 02: Personalized Interventions on microbiota to support healthy aging.

There are numerous signaling pathways involved in the alteration of gut microbiota and its metabolites, the short-chain fatty acids (SCFAs), which can disturb the host's normal physiological functions. Significantly, many of these processes happen to be controlled by the mammalian target of rapamycin (mTOR). [13]

The SIR1 also promotes autophagy by upregulating AMPK in a positive feedback loop through acylating and activating LKB1. In an elderly population (aged 65 years), where subjects were fed low fat and high fiber diets, greater diversity in bacterial microbiota profiles were observed, while those with "moderate to high" levels of fat and "low" fiber intakes had the least diverse microbiota. Collectively, these studies show that intake of dietary fiber influences the diversity of intestinal microbiota and the dominant species, suggesting that a richly diverse microbiota may be beneficial in, for example, protecting against and excluding enteric pathogens that cause intestinal diarrhea-associated diseases. The Med diet can greatly affect senescence and related aspects, acting on cellular and molecular hallmarks of aging. However, other mechanisms remain to be discovered; to this regard, several authors have discovered that modifications to gustatory or olfactory neurons, or even treatment of animals with diet-derived scents, can influence lifespan in *Caenorhabditis elegans* and *Drosophila melanogaster*. [14]

Exploring the Role of Diet and Gut Microbiota in Healthy Aging

With the increase in evidence directly linking diet and health, several plants and plant extracts (e.g., fruit extracts, leaf extracts, root and tuber extracts) have emerged as possessing potential health benefits. In general, differences in the composition of the gut microbiota have been reported between older and younger adults; Actinobacteria, particularly Bifidobacterium and Firmicutes, appear to decline with age, whereas Bacteroidetes and Proteobacteria, particularly Enterobacteriaceae and Clostridia, appear to increase. We describe the preventive and therapeutic attributes of phytochemicals such as polyphenols, probiotic microbes and omega-3-fatty acids in influencing the emerging nexus of immune senescence, cellular senescence and SC during aging. Outstanding questions and nutraceuticals-based pro-longevity and niche research areas have been deliberated. Further research using integrative approaches is recommended for developing nutrition-based holistic immunotherapeutic strategies for 'healthy aging'.

Probiotics

According to Hill's definition, probiotics are "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host". Probiotics may be helpful for treating and preventing gastrointestinal diseases, irritable bowel syndrome, blood pressure and depressive symptoms, according to recent meta-analyses of randomized controlled trials (RCTs) in adult populations. [15]

Inflammation Reduction: Probiotics like *B. subtilis* CU1 have shown increased immune markers and reduced respiratory infections among older adults during winter months, indicating their role in combating age-related inflammation.

Gut Microbiota Modulation: A recent study highlighted that a 6-month probiotic diet improved gut microbiota composition in seniors, increasing beneficial Lactobacilli and Bifidobacteria while decreasing harmful Proteobacteria.

Clostridium difficile Prevention: Probiotic combinations have been effective in reducing the risk of *C. difficile* infections in elderly patients post-surgery, suggesting their importance in managing gut health during recovery periods.

Overall, while probiotics show great promise for improving health outcomes in the elderly by modulating gut microbiota and enhancing immune function, variability in study results emphasizes the need for controlled parameters in future research to better understand their efficacy and mechanisms of action. [16]

Prebiotics

Prebiotics are defined as non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and activity of beneficial gut bacteria, such as Bifidobacteria and Lactobacilli. They must meet three criteria: resistance to gastric acidity and digestion, fermentation by intestinal microbiota, and selective stimulation of health-associated bacteria. Research shows that prebiotics like xylooligosaccharides (XOS) and galacto-oligosaccharides (GOS) can enhance gut microbiota, improve immune function, and support gastrointestinal health in older adults. [17]

Synbiotics

As already reported in the previous paragraphs, the effect of probiotic administration varies according to factors such as sex, age and lifestyle, and often the selected strains are found in fecal samples for a limited time. For this reason, probiotics and prebiotics working synergistically are often administered in a single product. The International Scientific Association for Probiotics and Prebiotics (ISAPP) in 2019 updated the definition of a synbiotic to “a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host”, emphasizing that a synergistic synbiotic is a synbiotic for which the substrate is designed to be selectively utilized by the co-administered microorganisms. [18]

Factors Affecting the Gut Microbiota in the Elderly

- **Dietary Changes:** Aging often leads to significant dietary shifts due to factors like loss of taste and difficulty in chewing, resulting in increased consumption of sugars and fats while decreasing intake of plant-based foods. This shift negatively impacts gut microbiota diversity.
- **Healthy Food Diversity (HFD):** The HFD concept emphasizes the importance of a diverse diet rich in healthy foods. Studies, such as those by the ELDERMET consortium, have shown that lower HFD scores correlate with reduced microbial diversity in older adults.
- **Impact of Living Situations:** Research indicates that dietary habits vary significantly between community-dwelling elderly individuals and those in long-term care facilities, affecting gut microbiota composition. Institutionalized individuals often have less diverse diets, leading to decreased microbiota diversity.
- **Additional Factors:** Besides diet, factors such as increased frailty, inflammatory markers, health impairments, residence location, and antibiotic use also influence gut microbiota composition in the elderly. For instance, community-dwelling individuals on antibiotics showed higher Bifidobacteria levels compared to those in long-term care.
- **Microbial Composition:** Studies indicate that the gut microbiota of older adults is often dominated by the phylum Bacteroidetes and shows a decline in beneficial microorganisms like Faecalibacterium and Rumino coccus. There is also an increase in facultative anaerobes such as Escherichia coli with aging. [19]

Gut Microbiota and Aging

Microbial colonization of the human body begins before birth, and increases after delivery when the baby comes in contact with several microbial communities, including mother fecal, vaginal and skin microbiota. Then, the composition of the gut microbiota is influenced by age, sex, development of the immune system and environmental factors, becoming more stable between 6 and 36 months of age. Thereafter, it is possible to distinguish a constant endogenous flora, which is considered the “core microbiota”, and bacteria that are still provisional, highly sensitive to external perturbations. The age-related changes of the intestinal flora begin after a genetically and environmentally determined age, depending on individual characteristics related to race and ethnicity, drugs, life style and diet habits. [40]

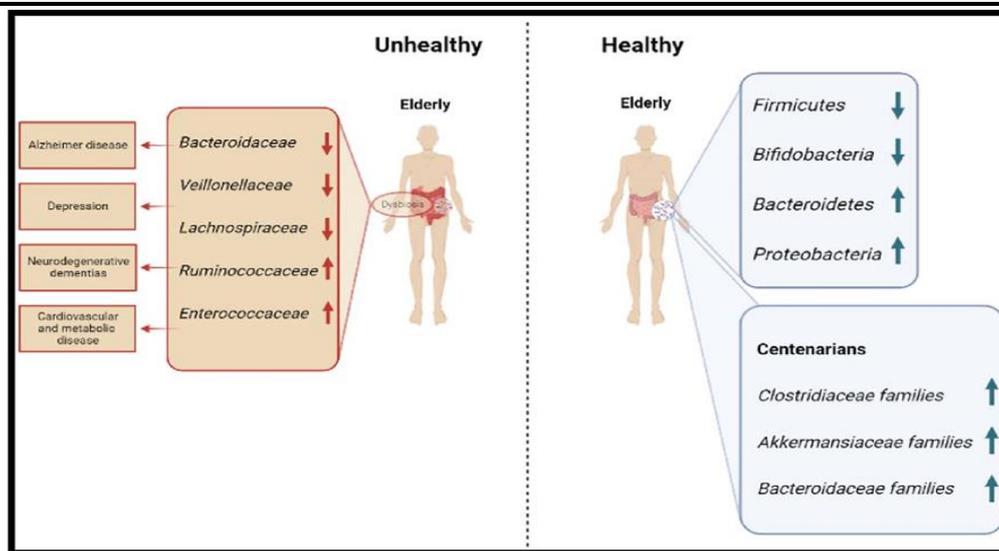


Figure No. 04: Microbial communities commonly found in unhealthy and healthy elderly, with a focus on centenarians. [20]

Gastrointestinal physiologic changes in aging led to a decrease in colonic transit and an increase in intestinal permeability associated with a local inflammation. Elevated expression of inflammatory cytokines can decrease expression of tight junction proteins (e.g., zonulin and claudins), which increases permeability and could act to perpetuate inflammation. The gut microbiota composition in the elderly is characterized by decreased diversity, a reduced abundance of butyrate-producing species, and the presence of potential pathogens, particularly in centenarians. These changes are linked to increased frailty due to alterations in short-chain fatty acid (SCFA) production, which plays a crucial role in modulating gut health and systemic inflammation.

Key Characteristics

Diversity Reduction: Elderly individuals often exhibit lower microbial diversity, with dominant phyla being Bacteroidetes and Firmicutes. However, the relative proportions of Firmicutes subgroups shift, showing a decrease in beneficial *Clostridium* cluster XIVa and an increase in Bacilli and Proteobacteria, which includes potential pathogens.

SCFA Production: SCFAs like acetate, propionate, and butyrate help maintain gut health by lowering pH, inhibiting pathogen growth (e.g., *Escherichia coli*), and promoting beneficial bacteria from the Firmicutes phylum. They also have systemic effects such as modulating insulin response and influencing inflammation.

Specific Changes in Centenarians: Studies reveal that centenarians have unique gut microbiota compositions, including lower levels of beneficial butyrate producers like *Faecalibacterium prausnitzii* while showing increased levels of potentially pathogenic bacteria. Notably, co-housing with centenarian parents correlates with higher occurrences of opportunistic pathogens among their offspring.

Implications for Health:

The alterations in gut microbiota are associated with chronic low-grade inflammation and metabolic issues prevalent in aging populations. The presence of pro-inflammatory microbes can exacerbate conditions like frailty, highlighting the importance of maintaining a healthy gut microbiome for longevity and overall health in older adults. [21]

Beneficial gut microbiota for healthy aging

The composition and functionality of the gut microbiota play crucial roles in maintaining health and preventing diseases, particularly in elderly individuals. Several factors influence this microbiota, with diet being one of the most significant. Nutritional substrates can modulate gut microbiota diversity, which tends to decrease with age due to reduced intake of fibrous foods, often linked to diminished taste and olfactory senses in older adults. This decline negatively impacts beneficial species like *Bifidobacteria*.

Vitamin D is another critical nutrient for the elderly, as its biosynthesis decreases with age. Vitamin D deficiency can disrupt calcium absorption and may also alter gut microbiota, leading to immune system irregularities.

To support gut health, the consumption of prebiotics and probiotics is encouraged. Prebiotics, such as inulin and fructo-oligosaccharides, act as substrates for beneficial bacteria, promoting their growth and activity. Studies indicate that prebiotic intake can enhance *Bifidobacteria* abundance and reduce inflammation markers

56. Probiotics, which are live microbial supplements, also show potential in restoring microbial balance in aging populations.

However, the effectiveness of probiotics is limited by their survival through the gastrointestinal tract's harsh conditions. Research into novel probiotics and their delivery systems is essential for maximizing health benefits in elderly individuals. Overall, dietary interventions targeting gut microbiota could significantly improve health outcomes during aging. [22]

Modulation of Gut Microbiota for Health

A. Diet and Gut Microbiota:

- Diet significantly influences the establishment and development of stable gut microbiota, aiding in its modulation.
- Older adults often experience malnutrition, making dietary manipulation crucial for gut health.
- A decline in short-chain fatty acid (SCFA) production in older adults is linked to shifts in bacterial composition and malnutrition, leading to reduced anti-inflammatory responses and increased infection rates.
- High-fiber diets are recommended for older adults as they enhance SCFA production and lower intestinal pH, which helps reduce pathogenic bacteria colonization.
- Conversely, high-fat diets with certain polyunsaturated fatty acids (omega-3-PUFA) can increase Firmicutes and Actinobacteria while decreasing Bacteroidetes.

B. Therapies for Dysbiosis:

- Various therapies, including prebiotics, probiotics, and synbiotics, have been proposed to treat dysbiosis.
- Prebiotics alone can also improve gut microbiota and SCFA production.

C. Antibiotic Use:

- Broad-spectrum antibiotics can effectively treat infections but may result in the loss of beneficial commensal bacteria.
- Caution is advised in antibiotic use across all ages; narrow-spectrum or targeted therapies are preferred to minimize microbiota disruption.[23]

CONCLUSION

The extensive review of modulation gut microbiota in aging, highlighting how this complex microbial ecosystem influences human health. It discusses how diet, probiotics, prebiotics, and symbiotic can modulate gut microbiota composition to promote healthy aging, reduce inflammation, and improve immune responses. Key insights include the beneficial effects of short-chain fatty acids (SCFAs) produced by gut bacteria and how dysbiosis (microbial imbalance) contributes to age-related diseases. Therapies like dietary interventions and fecal microbiota transplants (FMT) are explored as promising methods to restore gut health. The conclusion reinforces the importance of maintaining a balanced gut microbiota for aging populations to enhance overall health, emphasizing that diet and microbiota modulation strategies can positively impact aging and prevent disease.

REFERENCES

1. Vich Vila, A., Imhann, F., Collij, V., Jankipersadsing, S.A., Gurry, T., Mujagic, Z., Kurilshikov, A., Bonder, M.J., Jiang, X., Tigchelaar, E.F. and Dekens, J., 2018. Gut microbiota composition and functional changes in inflammatory bowel disease and irritable bowel syndrome. *Science translational medicine*, 10(472), p.eaap8914.
2. Forslund, K., Hildebrand, F., Nielsen, T., Falony, G., Le Chatelier, E., Sunagawa, S., Prifti, E., Vieira-Silva, S., Gudmundsdottir, V., Krogh Pedersen, H. and Arumugam, M., 2015. Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. *Nature*, 528(7581), pp.262-266.
3. Chu, H. and Mazmanian, S.K., 2013. Innate immune recognition of the microbiota promotes host-microbial symbiosis. *Nature immunology*, 14(7), pp.668-675.
4. Coelho, G.D.P., Ayres, L.F.A., Barreto, D.S., Henriques, B.D., Prado, M.R.M.C. and Passos, C.M.D., 2021. Acquisition of microbiota according to the type of birth: An integrative review. *Revista latino-americana de enfermagem*, 29, p.e3446.
5. Baothman, O.A., Zamzami, M.A., Taher, I., Abubaker, J. and Abu-Farha, M., 2016. The role of gut microbiota in the development of obesity and diabetes. *Lipids in health and disease*, 15(1), pp.1-8.
6. Lagier, J.C., Khelaifia, S., Alou, M.T., Ndongo, S., Dione, N., Hugon, P., Caputo, A., Cadoret, F., Traore, S.I., Seck, E.H. and Dubourg, G., 2016. Culture of previously uncultured members of the human gut microbiota by culturomics. *Nature microbiology*, 1(12).
7. Clemente, J.C., Ursell, L.K., Parfrey, L.W. and Knight, R., 2012. The impact of the gut microbiota on human health: an integrative view. *Cell*, 148(6), pp.1258-1270.
8. Xavier, R.J. and Podolsky, D., 2007. Unravelling the pathogenesis of inflammatory bowel disease. *Nature*, 448(7152), pp.427-434.
9. Clemente, J.C., Ursell, L.K., Parfrey, L.W. and Knight, R., 2012. The impact of the gut microbiota on human health: an integrative view. *Cell*, 148(6), pp.1258-1270.
10. Dominguez-Bello, M.G., Godoy-Vitorino, F., Knight, R. and Blaser, M.J., 2019. Role of the microbiome in human development. *Gut*, 68(6), pp.1108-1114.
11. Indiani, C.M.D.S.P., Rizzardi, K.F., Castelo, P.M., Ferraz, L.F.C., Darrieux, M. and Parisotto, T.M., 2018. Childhood obesity and Firmicutes/Bacteroidetes ratio in the gut microbiota: a systematic review. *Childhood obesity*, 14(8), pp.501-509.
12. Guo, Y., Xie, J.P., Deng, K., Li, X., Yuan, Y., Xuan, Q., Xie, J., He, X.M., Wang, Q., Li, J.J. and Luo, H.R., 2019. Prophylactic effects of *Bifidobacterium adolescentis* on anxiety and depression-like phenotypes after chronic stress: A role of the gut microbiota-inflammation axis. *Frontiers in Behavioral Neuroscience*, 13, p.126.
13. Kim, S. and Jazwinski, S.M., 2018. The gut microbiota and healthy aging: a mini- review. *Gerontology*, 64(6), pp.513-520.
14. Kawano, Y., Edwards, M., Huang, Y., Bilate, A.M., Araujo, L.P., Tanoue, T., Atarashi, K., Ladinsky, M.S., Reiner, S.L., Wang, H.H. and Mucida, D., 2022. Microbiota imbalance induced by dietary sugar disrupts immune-mediated protection from metabolic syndrome. *Cell*, 185(19), pp.3501-3519.
15. Fang, X., Yue, M., Wei, J., Wang, Y., Hong, D., Wang, B., Zhou, X. and Chen, T., 2021. Evaluation of the anti-aging effects of a probiotic combination isolated from centenarians in a SAMP8 mouse model. *Frontiers in immunology*, 12, p.792746.
16. Salvesi, C., Silvi, S., Fiorini, D., Scortichini, S., Sagratini, G., Palermo, F.A., De Leone, R., Egidi, N., Fatone, L., Cifani, C. and Amedei, A., 2022. Impact of a probiotic diet on well - being of healthy senior: THE PROBIOSNIOR PROJECT. *Journal of Applied Microbiology*, 133(5), pp.2941-2953.
17. Muthyala, S.D.V., Shankar, S., Klemashevich, C., Blazier, J.C., Hillhouse, A. and Wu, C.S., 2022. Differential effects of the soluble fiber inulin in reducing adiposity and altering gut microbiome in aging mice. *The Journal of Nutritional Biochemistry*, 105, p.108999.

18. Cicero, A.F., Fogacci, F., Bove, M., Giovannini, M. and Borghi, C., 2021. Impact of a short-term synbiotic supplementation on metabolic syndrome and systemic inflammation in elderly patients: a randomized placebo-controlled clinical trial. *European journal of nutrition*, 60, pp.655-663.
19. Fransen, F., Van Beek, A.A., Borghuis, T., Aidy, S.E., Hugenholtz, F., van der Gaast– de Jongh, C., Savelkoul, H.F., De Jonge, M.I., Boekschoten, M.V., Smidt, H. and Faas, M.M., 2017. Aged gut microbiota contributes to systemical inflammaging after transfer to germ-free mice. *Frontiers in immunology*, 8, p.1385.
20. Paone, P. and Cani, P.D., 2020. Mucus barrier, mucins and gut microbiota: the expected slimy partners. *Gut*, 69(12), pp.2232-2243.
21. Petursdottir, D.H., Nordlander, S., Qazi, K.R., Carvalho-Queiroz, C., Ahmed Osman, O., Hell, E., Björkander, S., Haileselassie, Y., Navis, M., Kokkinou, E. and Lio, I.Z.L., 2017. Early-life human microbiota associated with childhood allergy promotes the T helper 17 axis in mice. *Frontiers in immunology*, 8, p.1699.
22. Devkota, S., Wang, Y., Musch, M.W., Leone, V., Fehlner-Peach, H., Nadimpalli, A., Antonopoulos, D.A., Jabri, B. and Chang, E.B., 2012. Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in *Il10^{-/-}* mice. *Nature*, 487(7405), pp.104-108.
23. Carasi, P., Racedo, S.M., Jacquot, C., Romanin, D.E., Serradell, M.A. and Urdaci, M.C., 2015. Impact of kefir derived *Lactobacillus kefir* on the mucosal immune response and gut microbiota. *Journal of immunology research*, 2015(1), p.361604.

